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Neuroprotective Effects of Cardiorespiratory Fitness on White Matter Integrity and Cognition Across the Adult Lifespan

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Abstract

Objective: Cardiorespiratory fitness (CRF) is associated with decreased risk for cognitive decline. Accumulating evidence has linked CRF to more conserved white matter (WM) integrity and better cognitive performance in older adults. Additional research is needed to determine: (1) which WM tracts are most strongly related to CRF, (2) whether CRF-related benefits on WM translate to enhanced executive functioning (EF), and (3) if the neuroprotective effects of CRF are age-dependent. This study aimed to evaluate CRF as an intervention for modulating decreased WM integrity and EF in aging. **Method:** Participants were community-dwelling adults (N = 499; ages 20-85) from the open-access Nathan Kline Institute – Rockland Sample (NKI-RS) with CRF (bike test), self-report of physical activity, diffusion tensor imaging (DTI), and EF data. Mixed-effect modeling tested the interaction between CRF and age on WM integrity (global and local microstructure). Significant WM tracts were retained for structural equation modeling to determine whether enhanced microstructure mediated a positive relationship between CRF and EF. **Results:** Among older participants (age ≥ 60), CRF was significantly related to stronger whole-brain (*z*-score slope = 0.11) and local WM integrity within five tracts (*z*-score slope range = 0.14 – 0.20). In support of the age-dependent hypothesis, the CRF–WM relationship was comparably weaker (*z*-score slopes ≤ 0.11) and more limited (one WM tract) in younger adults. CRF was more consistently related to WM than self-report of physical activity. Although CRF was linked to enhanced WM integrity, its potential benefits on EF were not directly observed. **Conclusion:** The findings highlight the importance of positive lifestyle factors, such as physical activity, in maintaining brain health in senescence. CRF may selectively preserve a collection of anterior and posterior WM connections related to visuomotor function.

Keywords: exercise, brain health, white matter integrity, cognition, aging

Introduction

Dementia and Mild Cognitive Impairment

As the global population ages, the prevalence of dementia and age-related cognitive impairment have been deemed a looming epidemic (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007; Larson, Yaffe, & Langa, 2013). According to the World Health Organization (2015), the worldwide prevalence of dementia is approximately 47.5 million, with an estimated 7.7 million new cases each year. The prevalence of mild cognitive impairment (MCI), conceptualized as an intermediary state between normal aging and dementia, affects an estimated 16% to 20% of adults aged 60 or older (Roberts & Knopman, 2013). Given that advancing age is the greatest risk factor for dementia and MCI (Flier & Scheltens, 2005), the global burden of dementia can be explained by the demographic growth in the "old-old" (age > 80) category (Larson et al., 2013), particularly in developing nations (Ferri et al., 2005; Wimo, Jönsson, Bond, Prince, & Winblad, 2013). Thus, the number of older adults at risk for cognitive impairment is projected to increase alongside rising life expectancies (World Health Organization, 2015).

Cost-of-illness studies have quantified the substantial societal burden imposed by dementia, via both direct (medical care) and indirect (family caregiving) costs. Worldwide, the direct total economic toll of dementia was $604 billion in 2010, with 70% of those costs absorbed by western countries (Wimo et al., 2013). The social costs of dementia are immense and difficult to quantify (Wimo et al., 2013); most individuals with dementia are cared for by the community, amounting to insurmountable unpaid informal caregiving (Langa et al., 2001). At the individual level, cognitive decline often precedes physical, psychological, and social impairment (World Health Organization, 2015). A large proportion of people with dementia or age-related cognitive impairment require varying degrees of support with activities of daily

living, both basic (e.g., bathing, feeding) and instrumental (e.g., medication management, handing finances).

Dementia is a clinical syndrome comprising progressive deterioration of neurocognitive and daily functioning (Grand, Caspar, & Macdonald, 2011). While the neuropsychiatric profile varies by etiology, dementia (classified as major neurocognitive disorders in the Diagnostic Statistical Manual – 5; DSM-5; American Psychiatric Association, (2013) involves significant decline in one or more cognitive domains that impair activities of daily living (American Psychiatric Association, 2013). MCI (subsumed under mild neurocognitive disorders in the DSM-5) is a decline from previously normal cognitive functioning with relatively intact daily functioning in the absence of dementia (Petersen et al., 1999). MCI and dementia are not monolithic syndromes, rather they stem from a variety of diseases and injuries that affect the brain. A subgroup of people with amnestic MCI are more likely to progress to Alzheimer's disease, the most common cause of dementia (Cooper, Li, Lyketsos, & Livingston, 2013). Nearly half of people with MCI develop dementia within three years–only 3% of age-matched peers convert over the same period (Tschanz et al., 2006). MCI and dementia, as pathological cognitive decline, have been conceptualized to lie on a spectrum with normative cognitive aging (see Figure 1). Examining individual differences in cognition in subclinical samples provides an opportunity to better understand both healthy aging and the underlying mechanisms that may precede MCI or dementia. (Figure 1 here)

Cognitive aging

Gradual late-life decreases in cognitive performance expected in older non-clinical populations (i.e., in the absence of neuropathology) is known as normal cognitive aging (Grady, 2008). There is considerable inter-individual variability in the rate of decline for some cognitive

domains (Wisdom, Mignogna, & Collins, 2012). “Crystalized” abilities (using knowledge that is overlearned), such as vocabulary and semantic memory, are preserved with cognitive aging (Salthouse, 2012). Crystalized abilities may remain stable or slightly improve by 0.02 to 0.003 standard deviations per year in the sixties and seventies; fluid abilities are expected to peak in the thirties and then decline by approximately -0.02 standard deviations per year until the end of the lifespan (Salthouse, 2012). Age-related declines have been well-documented for “fluid” cognitive abilities (the capacity to solve novel problems): processing speed, executive functioning (EF), conceptual/perceptual reasoning, and memory (Harada, Natelson Love, & Triebel, 2013; S. Lockhart, DeCarli, & Fama, 2014). In a large lifespan sample, Salthouse (2011) found the following age correlations with the fluid cognitive abilities: -0.63 for processing speed, -0.46 for reasoning, -0.45 for visuospatial, and -0.44 for memory (see Figure 2). (Figure 2 here)

Structural and functional brain changes associated with the developmental of underlying neurodegenerative disease may start up to 10–20 years prior to symptom onset (Beason-Held et al., 2013). Identifying intermediate phenotypes, characteristics correlated with MCI and dementia measurable in both unaffected and affected individuals, may elucidate differential effects of normal aging and pathological cognitive decline (Gottesman & Gould, 2003). Subtle individual differences in cognitive and functional abilities coupled with atrophy or cortical disconnection on neuroimaging may confer risk for future MCI and dementia (Chen et al., 2017). Measures of memory and EF may be used to predict cognitive decline among healthy individuals (Belleville, Fouquet, Duchesne, Collins, & Hudon, 2014; Reitz & Mayeux, 2009). Differences in several brain regions and white matter (WM) tracts may also represent preclinical characteristics of dementia and MCI (Bennett & Madden, 2014; Reitz & Mayeux, 2009). This suggests that some brain regions may be more important than others for understanding aging and pathological

processes. Such intermediate phenotypes are thought to account for per-person year progression from normal aging to MCI, which has been estimated to range from 5% among community-dwelling elders to 30% in patient cohorts (Chen et al., 2017).

Aging and Neuroimaging

Neuroimaging studies have been critical for non-invasively studying structural brain changes in cognitive aging. High dimensional neuroimaging markers may inform early detection of age-related cognitive and functional decline that precede clinical diagnosis of cognitive impairment (Amieva et al., 2005; Grober et al., 2008; Jedynak et al., 2012). As clarified below, changes in brain structural morphology identified on neuroimaging are associated with age-related differences in cognition over the lifespan (DeCarli et al., 2005; Head, Rodrigue, Kennedy, & Raz, 2008; N Raz et al., 2005a).

Diffusion tensor imaging (DTI) is a powerful and relatively newer neuroimaging technique for in-vivo characterization of microstructural changes (Alexander, Lee, Lazar, & Field, 2007). DTI can provide estimates of connectivity patterns of cerebral WM, which largely consist of densely packed myelinated neuronal axons, by mapping three-dimensional diffusion or movement of water molecules within each tract. Water diffusion occurs more rapidly along the length of the axon (rather than perpendicularly) due to restraints imposed by axonal cell membranes, myelin sheaths, and microfilaments (Beaulieu, 2002). The integrity of WM is vital for transmission of signals between gray matter and integrating brain structures into functional networks to support cognitive functioning (Kennedy & Raz, 2009; Liston et al., 2006; Perry et al., 2009; Tuch et al., 2005; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). Consequently, the disconnection hypothesis posits that disruptions in the connectivity of such neural networks, due to aging (Davis et al., 2009; Anders M. Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2017;

Kennedy & Raz, 2009; O'Sullivan et al., 2001) or neurodegeneration (Head et al., 2004; Salat et al., 2010), may underlie decline in fluid cognitive abilities with old age (Bartzokis, 2004; Bennett & Madden, 2014). Fractional anisotropy (FA) is a commonly reported DTI scalar (range = 0 – 1) of overall microstructural integrity. FA measures the degree of anisotropy (i.e., directional dependence) along the length of WM axons (Bennett & Madden, 2014). Lower FA values (i.e., approaching 0) indicate more isotropic or unrestricted diffusion associated with age-related degradation of WM microstructure integrity (Burzynska et al., 2014).

Neuroimaging studies have consistently identified changes in brain structural morphology across the lifespan. Aging predicts smaller gray matter brain volume and thinner cortices (A. M. Fjell et al., 2010; N. Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; N Raz et al., 2005a). In healthy lifespan sample (N = 434, age 8 – 85), Fjell et al. (2010) estimated that the greatest acceleration of age-related decrease in brain volume occurred at age 49; hippocampal volume was estimated to decline by -2.19 to -2.15 (z-scores) from age 60 to 85. Aging is also associated with reduced WM volume and increased severity of WM lesions (Bennett & Madden, 2014; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; N Raz et al., 2005a). Age-related decreases in WM volume accelerate in the sixth or seventh decade of the lifespan (Dennis & Cabeza, 2008; Westlye et al., 2010).

DTI studies show widespread decreases in integrity of WM microstructure with increasing age (Bennett & Madden, 2014; Gunning-Dixon et al., 2009; Head et al., 2004; O'Sullivan et al., 2001; Sullivan & Pfefferbaum, 2006; Yang, Tsai, Liu, Huang, & Lin, 2016). Loss of axon and myelin integrity in aging has been linked to reduced FA (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Burzynska et al., 2010). As depicted in Figure 3, the non-linear trajectory of WM integrity suggests a three-phasic lifespan model: FA development peaks

in the third decade, exhibits a small yet stable linear decline until the sixth decade, followed by steeper decline until end of life (Westlye et al., 2010). Westlye et al. (2010) found that most WM tracts fell below 50% of peak FA values by the sixth decade of the lifespan. Reduced integrity of WM observed in cognitive aging may either underpin gray-matter atrophy or coincide with such differences (Andrews-Hanna et al., 2007; Sullivan & Pfefferbaum, 2007). Tissue volume and DTI measures may in fact provide unique indices of WM health (Westlye et al., 2010). (Figure 3 here)

Age-related changes in brain macrostructure appear to be regionally specific. Decreased brain gray matter volume in aging has been most consistently localized in frontal lobe, medial temporal, and hippocampal gray matter regions for older adults (Buckner, 2004; DeCarli et al., 2005; A. M. Fjell et al., 2014; Head et al., 2008; N. Raz et al., 2010), which are critical substrates for memory and EF, respectively (S. Lockhart et al., 2014). In a sample of middle-age and older healthy adults, Raz et al. (2010) observed significant shrinkage (gray matter volume) of the hippocampus, entorhinal cortex, orbital-frontal cortex, and cerebellum over a 15-month period. Significant shrinkage of the caudate nucleus, prefrontal subcortical WM, and the corpus callosum only appeared after 30-month follow-up, whereas other regions (e.g., visual cortices) did not exhibit significant reductions in volume (N. Raz et al., 2010).

DTI studies also indicate that age-related microstructural alterations in WM differ by region (Westlye et al., 2010). Age-related decline in FA has been identified in the corpus callosum, fornix, and corona radiata, which are involved in projection, association, and commissural fibers of the brain (Bennett & Madden, 2014; Yang et al., 2016). The strongest age-related decline in WM integrity have been consistently localized in the prefrontal cortex (Davis et al., 2009; Head et al., 2004; Salat et al., 2005; Sullivan, Rohlfing, & Pfefferbaum, 2010).

Several studies have identified an overall anterior–posterior pattern of lower FA values observed with aging suggesting primary disruption of WM connections with frontal regions (Burzynska et al., 2010; Hayes, Salat, Forman, Sperling, & Verfaellie, 2015). Decreased integrity of anterior WM is associated with decline in processing speed and EF in cognitive aging (Charlton et al., 2006; Madden, Bennett, & Song, 2009) and neurodegeneration (Nowrangi et al., 2015). Of note, Westlye et al. (2010) found that the corticospinal tract was among the earliest WM tracts to deteriorate while forceps major and the dorsal cingulum bundles were among the last, which did not support an inverse ontogenetic pattern of WM decline in aging. Nevertheless, regional differences in WM changes identified by tract-wise and voxel-based DTI studies (N Raz et al., 2005a; Westlye et al., 2010) suggest the presence of neuroprotective effects that are age-dependent and vary across people.

Modifiable risk factors

There is strong evidence for genetic liability in dementia, such as the apolipoprotein-E epsilon 4 (APOE-ε4) allele as a candidate gene for late-onset Alzheimer's disease (J. C. Smith et al., 2016). However, genes do not account for all of the variance in risk for dementia (Bird, 2008; Reitz & Mayeux, 2009). APOE is thought to account for approximately 20% to 50% of risk of late onset Alzheimer's disease (Ashford & Mortimer, 2002; Slooter et al., 1998). This suggests the presence of environmental factors that contribute to disease progression (J. C. Smith et al., 2016). Indeed, observational and population-based studies have identified a host of lifestyle risk factors for developing neurodegenerative diseases (Xu et al., 2015). Nearly half of Alzheimer's disease cases globally and in the United States may be attributable to these non-genetic risk factors (Barnes & Yaffe, 2011). In the absence of robustly disease and genetically modifying treatments for MCI and dementia (Cooper et al., 2013; Raina et al., 2008; Sink, Holden, & Yaffe,

2005), researchers are increasingly focused on identifying understand risk and protective factors for brain disease (Cooper et al., 2013; World Health Organization, 2015).

Brain health has been defined as "the development and preservation of optimal brain integrity and neural network functioning for a given age" (Cattaneo et al., 2018; Gelfo, Mandolesi, Serra, Sorrentino, & Caltagirone, 2018; Gorelick et al., 2017). Neuroplasticity, the nervous system's ability to adapt to internal and external environmental demands (Alvaro Pascual-Leone et al., 2011), is the hypothesized mechanism by which lifestyle factors impact brain health. Exercise, socialization, weight management, blood pressure control, mental health, cognitive stimulation, Mediterranean diet, good sleep quality, and a meaningful life are positively associated with brain health with aging and may reduce the incidence of brain disease (Livingston et al., 2017; Xu et al., 2015). Although brain health remains sensitive to environmental factors even in old age, diminished neuroplasticity is associated with the development of disease and disability (A. Pascual-Leone, 2006).

Given that cerebrovascular and cardiovascular health are highly interrelated, heart disease, smoking, hypertension, high cholesterol, obesity, and diabetes are significantly associated with age-related cognitive decline, including risk for MCI and dementia (Barnes & Yaffe, 2011; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005; Xu et al., 2015). Figure 4 illustrates age-specific prevalence of individual cardiovascular risk factors from (S. N. Lockhart & DeCarli, 2014). These cardiovascular risk factors contribute to atherosclerosis that underlies cardiovascular disease (i.e., heart disease), an umbrella term for linked pathologies that affect the heart or blood vessels. Advancing age predicts greater risk for cardiovascular disease (Halter et al., 2014); greater than one in three (85.6 million) Americans have at least one cardiovascular disease, over half of which are adults aged 60 or older (Mozaffarian et al., 2016). As depicted in

Figure 5, aging may be linked to cardiovascular disease through musculoskeletal, metabolic, and vascular paths (Nair, 2005). Cardiovascular burden accumulated over the lifespan further accelerates the age-associated degradation of brain structure and function (Bherer, Erickson, & Liu-Ambrose, 2013; N. Raz et al., 2010). (Figure 4 and Figure 5 here)

Cardiovascular injury and neurodegenerative diseases commonly co-occur (Carmichael, 2014). Cardiovascular risk factors are thought to exacerbate cognitive decline through the accumulation of silent brain injury in the form of small lesions, tissue loss, and neural dysfunction (Carmichael, 2014; Debette & Markus, 2010). The incidence of cerebrovascular disease and stroke are highest among older adults (Mozaffarian et al., 2016); Neuroinflammatory and oxidative stress are central pathologic processes that occur during cerebral ischemia (Di Napoli & Shah, 2011). The neuroinflammatory response has been associated with cognitive decline and delirium, particularly in older stroke patients (Rothenburg et al., 2010; Whitehead, Cheng, Hachinski, & Cechetto, 2007). A composite of cardiovascular risk is significantly associated with indicators of poor brain health, such as lower volume and WM hyperintensities (Glodzik et al., 2011; Raji et al., 2012), decreases in cognitive performance over time (Jefferson et al., 2015), and progression from MCI to dementia (Viticchi et al., 2015). In a dose dependent fashion, the presence of one to four cardiovascular risk factors in midlife is associated with a 1.27- and 2.37-fold increase of dementia, respectively (Whitmer et al., 2005). For comparison, genotypes linked to Alzheimer's disease APOE-ε4 and APOE-ε3 are associated with 1.2-fold and 1.7-fold greater risk for developing dementia, respectively (Slooter et al., 1998).

Many of these cardiovascular risk factors are modifiable to some degree; therefore, there is a growing optimism in their role for preventing cognitive decline and promoting healthy aging. According to the World Health Organization (2016), 80% of premature cardiovascular disease

and stroke cases are preventable and mitigating risk factors can alleviate healthcare burden. An estimated 10-25% reduction in cardiovascular risk factors could prevent up to 1.1 to 3.0 million dementia cases globally (Barnes & Yaffe, 2011). Reduction of and treatments for cardiovascular risk factors effectively decrease major adverse health outcomes such as heart attacks and stroke, which in turn reduce the burden of cognitive impairment (Carmichael, 2014). In fact, recent survey and population-based studies suggest that the incidence of new dementia cases and age-specific cognitive impairment may be declining (Langa et al., 2001; Larson et al., 2013; Schrijvers et al., 2012). According to US long-term care survey data from 1982 to 1999, rates of dementia decreased from 5.7% to 2.9% (Manton, Gu, & Ukraintseva, 2005). Schrijvers et al. (2012) examined two older adult sub-cohorts in 1990 (n = 5,727) and 2000 (n = 1,769) and found that the younger group developed fewer cases of dementia, had significantly greater brain volumes, less cerebral injury on neuroimaging, lower rates of hypertension and obesity.

Cardiorespiratory fitness (CRF)

Cardiorespiratory fitness (CRF) is the ability of the circulatory, respiratory, and muscular systems to supply the body with oxygen during sustained physical activity (D. Lee, Artero, Xuemei Sui, & Blair, 2010). According to the American Heart Association, "CRF is directly related to the integrated function of numerous systems, and is thus considered a reflection of total body health" (Ross et al., 2016). Approximately 50% of the variance in CRF may be explained by heritable factors, which align with heritability for other cardiovascular disease risk factors such as blood pressure, lipoproteins, and insulin (Bouchard et al., 1999). The remaining variance in CRF is promoted or maintained by regular and sustained aerobic physical activity sufficient to increase heart rate and need for oxygen (Ahlskog, Geda, Graff-Radford, & Petersen, 2011). CRF is typically expressed as maximal oxygen uptake (VO_2 max) during peak exercise, with higher

values indicating greater CRF. CRF is widely considered a sensitive and reliable measure of a person's habitual physical activity (American College of Sports Medicine, 1998; Jackson, Sui, Hébert, Church, & Blair, 2009; Wang et al., 2010).

CRF is also a useful prognostic indicator of overall health in patients and non-patients (Gibbons et al., 1997; Gulati et al., 2005; Myers et al., 2002). CRF is so critical to health outcomes that the American Heart Association has argued for its use as a clinical vital sign in a recent scientific statement (Ross et al., 2016). Yet, it has been traditionally overlooked in clinical practice relative to the presence of cardiovascular risk factors, such as smoking, hypertension, hyperlipidemia, and type 2 diabetes mellitus (Mark & Lauer, 2003). Mounting epidemiological and clinical evidence suggest that poor CRF strongly predicts adverse health outcomes (Ross et al., 2016). Poor CRF is consistently linked to increased risk for cardiovascular disease, all-cause mortality, and cancer-related deaths (Blair et al., 1989; Gulati et al., 2005; D. Lee et al., 2010; Myers et al., 2002; Sui, LaMonte, & Blair, 2007). There is a strong consensus on effectiveness of CRF in the primary and secondary prevention of cardiovascular disease and associated risk factors (Stewart, Manmathan, & Wilkinson, 2017; Warburton, 2006), which otherwise converge to cause brain damage and neurodegeneration (Cotman & Berchtold, 2002; Profenno, Porsteinsson, & Faraone, 2010). While the health benefits of CRF are wide-ranging (Ross et al., 2016), the role of CRF in brain and cognitive health are the focus herein.

A growing body of literature has implicated physical inactivity (i.e., low CRF) in risk for developing Alzheimer's disease and other causes of dementia. Physical inactivity has been identified as the 3rd largest contributor to Alzheimer's disease cases globally and is considered the largest cause in the US (Barnes & Yaffe, 2011). An estimated 13% (4.3 million) of Alzheimer's disease cases, including 21% (> 1.1 million) cases in the US, may be attributed to

physical inactivity (Barnes & Yaffe, 2011). In a meta-analysis of prospective studies, midlife overweight body mass index (BMI; 1.26 to 1.35 times) and obesity (1.64 to 2.04 times) were associated with increased risk for Alzheimer's disease and related dementias (Anstey, Cherbuin, Budge, & Young, 2011). These figures are staggering when considering the high global prevalence of physical inactivity and that sedentariness increases with age. Approximately 17% of adults in a 51-country survey were physically inactive (Guthold, Ono, Strong, Chatterji, & Morabia, 2008). CRF is expected to decline with advancing age in healthy adults; Fleg et al. (2005) reported that VO_2 max decreased 3% to 6% per decade in the 30s and 40s and >20% per decade after age 70. Burns et al. (2008) found that CRF was modestly reduced in patients with Alzheimer's disease compared to controls; In early AD, higher fitness was associated with greater brain volume after controlling for age, sex, dementia level, and frailty. From a public health standpoint, a 10% or 25% reduction in the prevalence of physical inactivity could prevent greater than 380,000 (90,000 US cases) or 1 million Alzheimer's disease cases (230,000 in the US), respectively (Barnes & Yaffe, 2011).

Human and animal research has consistently demonstrated broad and direct beneficial health effects of CRF on brain structure and function (Cotman, Berchtold, & Christie, 2007; Voss et al., 2013) that may combat late-life cognitive decline (Ahlskog et al., 2011; Santos et al., 2017). Increased CRF was significantly associated with higher WM integrity, which in turn was related to better EF performance in MCI patients (K. Ding et al., 2018). Findings from population-based studies suggest that increased mid-life CRF reduces the odds of MCI (Geda et al., 2010) and dementia (Andel et al., 2008; Hamer & Chida, 2009) in late-life. A systematic meta-analysis representing 163,797 older adults without dementia and 3,219 cases of dementia at follow-up found that the risks associated with physical inactivity yielded increased odds for all-

cause dementia (1.39) and Alzheimer's disease (1.82) (Hamer & Chida, 2009). DeFina et al. (2013) found that participants in the highest quartile for midlife CRF had a 36% lower risk of developing dementia compared to those in the lowest quartile (median follow-up of 25 years) in a large community-dwelling sample (N = 19,459). In a separate longitudinal sample of community adults aged 20 to 88 at baseline (women; *n* = 14,811, men; *n* = 45,078; *M* follow-up = 17 years), Liu et al. (2012) found that for each 1-Metabolic Equivalent of Task (MET) increase in CRF, adjusted risk for dementia mortality decreased by 14%. In their review of cross-sectional, longitudinal, and intervention research, Bherer et al. (2013) concluded that "physical exercise is a promising nonpharmacological intervention to prevent age-related cognitive decline and neurodegenerative diseases."

CRF and Brain Macrostructure

Higher physical activity and fitness is linked to CRF improved gray matter status and cognitive functioning in older adults (Bherer et al., 2013; Erickson, Leckie, & Weinstein, 2014). In the community-based Framingham Sample (*N* = 2,354), accelerometer-derived measurements of light-intensity physical activity were incrementally associated with larger gray matter volume, which was interpreted as less brain aging (Spartano et al., 2019). A review of cross-sectional studies concluded that higher CRF was consistently related to greater gray matter volume in the prefrontal cortex and hippocampus, with less routinely observed correlations in other regions (Erickson et al., 2014). Erickson et al. (2010) found that greater physical activity (blocks walked per week) among older adults (N = 299, *M* age = 78) predicted greater prefrontal, temporal, entorhinal, and hippocampal gray matter volume at 9-year follow-up. Enhanced gray matter attributed to physical activity was associated with two-fold reduction in risk for cognitive impairment (Erickson et al., 2010). Weinstein et al. (2012) showed that the significant

association between higher CRF and greater performance on EF tasks was mediated by frontal gray matter volumes (right inferior frontal gyrus, precentral gyrus, and dorsolateral prefrontal cortex) in an older adult sample (N = 142, *M* age = 66.6 years). This suggests that CRF may improve cognitive function among healthy older adults by reducing regional neuronal loss (Weinstein et al., 2012).

In addition to gray matter, neuroimaging research has evidenced a significant link between physical fitness and improved WM structure in the aging brain (Sexton et al., 2016; Tian, Studenski, Resnick, Davatzikos, & Ferrucci, 2016). Three of the five cross-sectional MRI studies reviewed by Sexton et al. (2016) did not find a significant relationship between global WM volume and CRF; however, greater CRF was associated with larger global WM volume in the two largest studies (Benedict et al., 2013; Gow et al., 2012), with an overall effect size of 0.22 (Cohen's *d*). The effect size for WM lesions was smaller (*d* = 0.17), with ten of 14 studies surveyed by Sexton et al. (2016) yielding non-significant findings. The CRF–WM association has been localized most consistently in the frontal lobe (Sexton et al., 2016). Higher physical fitness has been linked to greater volumes of prefrontal WM tracts cross-sectionally (Erickson et al., 2007) and in exercise interventions (S. J. Colcombe et al., 2006; Voss et al., 2013). In a recent longitudinal study of community-dwelling adults (N = 146), Tian et al. (2016) found a significant relationship between midlife CRF and greater middle temporal gyrus and perirhinal cortex WM volumes. Higher late-life CRF was significantly associated with slower atrophy in the middle frontal and angular gyri, which may be attributed to the vascular watershed location of these regions (Tian et al., 2016). Measures of gray and WM status may be uniquely associated with cognitive functioning (Arvanitakis et al., 2016).

CRF and WM Microstructure

Extending the link between CRF and brain macrostructure, the integrity of WM microstructure that connects gray matter may also differ as a function of CRF. However, fewer studies have focused on microstructural effects of CRF with aging. DTI may circumvent overestimation of gray and WM volume during tissue segmentation due to hyperintensities and inflammation with aging (Burgmans et al., 2009; Levy-Cooperman, Ramirez, Lobaugh, & Black, 2008; Taki et al., 2011). DTI is well suited for investigating both aging and pathological processes because it is sensitive to subtle changes in WM microstructure within interconnected neural networks that may precede tissue loss (Alexander et al., 2007; Westlye et al., 2010). Since DTI indices are thought to reflect myelin-related processes (Alexander et al., 2007; Schmierer et al., 2007; Westlye et al., 2010), it may be used to substantiate evidence for the benefit of CRF on myelin sheath regeneration (Feter et al., 2018). Longitudinal DTI studies suggest that such WM integrity differences in aging may be detected in as little as one year within health older adults (Barrick, Charlton, Clark, & Markus, 2010; Teipel et al., 2010). Earlier detection of degradation of WM tracts may help identify age- or disease-related brain changes before they become functionally observable. Accurate measurements of brain microstructure can detect early stages of cognitive impairment (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2013). DTI indices can also be used to characterize the properties of CRF-related WM preservation in late adulthood.

FA is the most common DTI measurement reported in studies examining the CRF–WM relationship in the aging brain. Of the eight studies identified by Sexton et al. (2016), only three studies that examined mean diffusivity (MD), an index of average rate of diffusion expected to increase with age, and two were not significant (Johnson, Kim, Clasey, Bailey, & Gold, 2012; B. Marks, Katz, Styner, & Smith, 2011). Tseng et al. (2013) found lower MD in the left cingulum of the hippocampus and posterior thalamic radiation (non-overlapping with FA) in Master athlete

(life-long endurance training) older adults compared to sedentary elders. Only one study in Sexton et al. (2016) examined axial diffusivity (AD) and radial diffusivity (RD), which measure the rate of perpendicular and parallel axonal diffusion, respectively. In a sample of healthy seniors (N = 26, *M* age = 64.79 ± 2.8 years), Johnson et al. (2012) found that reductions in RD corresponded with CRF-related increases in FA. RD appears to be more sensitive to myelin in WM whereas AD relates to axonal degeneration (Song et al., 2002). FA has been found to relate more strongly to EF (range of $\eta^2 = 0.24 – 0.39$) than MD in older adults (Nowrangi et al., 2015).

There is cumulating evidence from DTI studies that individual variance in physical activity is significantly associated with differences in microstructure across multiple WM tracts (Bracht et al., 2016). Of seven cross-sectional studies on WM structure in the systematic review by Sexton et al. (2016), three found a significant relationship between CRF and increased FA. Voss et al. (2013) found that greater percent change in CRF during a one-year training intervention was associated with significant increases in prefrontal ($r = 0.51$, $p = 0.001$), parietal ($r = 0.45$, $p = 0.005$), and temporal ($r = 0.33$, $p = 0.03$) FA for older adults in the exercise group and not the control group (stretching condition). More specifically, studies have identified tracts associated with CRF: genu and body of the corpus callosum (Hayes et al., 2015; Johnson et al., 2012), anterior cingulum bundle (B. Marks et al., 2011; B. L. Marks et al., 2007; Tian et al., 2014), superior longitudinal fasciculus (Z. Liu et al., 2009; Tseng et al., 2013), arcuate fasciculus (Z. Liu et al., 2009), uncinate fasciculus (B. L. Marks et al., 2007), superior corona radiate and inferior fronto-occipital fasciculus (Z. Liu et al., 2009; Tseng et al., 2013), and inferior longitudinal fasciculus (Tseng et al., 2013). Bracht et al. (2016) found a significant association between physical activity and myelin water fraction, a proxy for myelination, in the right parahippocampal cingulum ($r = 0.48$, $p = 0.007$) in a sample (N = 33) of healthy adults (*M* age =

25.5, *SD* = 4.2 years). After accounting for demographics and depression, CRF accounted for 20% of the variance in FA within significant tracts identified by Hayes et al. (2015).

Yet, some studies on the effects of physical activity on WM microstructure have produced mixed results (Sexton et al., 2016). Using 24-hour actigraphy monitoring, physical activity was positively associated with FA in the cingulum and right superior longitudinal fasciculus (Walther et al., 2010); physical activity was negatively associated with FA in the left corticobulbar tract, right posterior corpus callosum, and left superior longitudinal fasciculus (Walther et al., 2010). Burzynska et al. (2014) did not find a significant CRF-FA relationship using whole-brain tract-based spatial statistics (TBSS); furthermore, light physical activity (e.g., housework, gardening), and not CRF was positively associated with FA in the temporal lobe (Burzynska et al., 2014). The discrepant findings suggest that the effect of exercise on WM integrity in aging may be measure- and region-specific (Burzynska et al., 2014). This highlights the need for studies that incorporate multiple CRF (e.g., questionnaire, performance-based) and WM integrity (e.g., global versus local microstructure) measurements.

CRF and Neurocognitive Functioning

Overall, cross-sectional studies have evidenced a positive relationship between CRF and improved cognitive functioning throughout the lifespan (Bherer et al., 2013; Middleton, Barnes, Lui, & Yaffe, 2010). Meta-analyses by Smith et al. (2010) and Colcombe and Kramer (2003) suggest that fitness training produced robust yet selective effects on cognition (0.50 *SD* average cognitive improvement). Evidence for the relationship between CRF and improved cognitive function among healthy adults is greatest for EF, processing speed, attention, and memory, with mild to moderate effect sizes (Ahlskog et al., 2011; S. Colcombe & Kramer, 2003; P. J. Smith et al., 2010; Tian et al., 2016). Smith et al. (2010) observed that trials with longer exercise

interventions tended to demonstrate greater improvements; cerebrovascular benefits of CRF and its potential to stave off cognitive decline may accumulate over a lifetime (Ahlskog et al., 2011; Barnes & Yaffe, 2011). Indeed, a nationally representative study in 11 European countries (N = 17,333) found that older adults who engaged in frequent physical activity, particularly vigorous intensity more than once per week, demonstrated less cognitive decline after 2.5 years ($\beta = 0.06$) compared to older adults who did not engage in frequent activity (Aichberger et al., 2010).

Less understood is the extent to which "wellness interventions" that include physical activity aimed at improving CRF impact the cognitive functioning of healthy older adults. A meta-analysis of 30 randomized control trials (N = 2,020) indicated a positive effect of physical activity interventions on CRF ($d = 0.69$) and cognitive functioning ($d = 0.57$) for older adults with MCI and dementia (Heyn, Abreu, & Ottenbacher, 2004). Six months of exercise training has been found to significantly increase hippocampal volume and memory functioning among older adults (Baker et al., 2010; Erickson et al., 2011; ten Brinke et al., 2015). Yet, other studies have more modest to no effects of fitness training in older adults with cognitive impairment (Eggermont, Swaab, Hol, & Scherder, 2009; Lautenschlager et al., 2008). Two recent meta-analyses found insufficient evidence for CRF interventions for promoting cognitive functioning and reducing cognitive decline or dementia risk in undiagnosed older adults (Brasure et al., 2018; Young, Angevaren, Rusted, & Tabet, 2015). The benefits of short-term exercise interventions may not generalize to multiple cognitive domains (Churchill et al., 2002). Bherer et al. (2013) reached the opposite conclusion: "older adults who have completed a physical activity program that produces significant increases in CRF… often show enhanced cognitive performance."

Few studies have explored whether the positive effects of physical activity on WM are associated with cognitive functioning. Wirth, Haase, Villeneuve, Vogel, and Jagust (2014)

examined the effects of cognitive (i.e., mentally challenging tasks) and physical activity on cognitive functioning in older adults (N = 92) using a path analysis involving neural integrity within the brain regions affected in Alzheimer's disease (see Figure 6). Adjusting for age, gender, and education, higher lifetime cognitive (β = -0.21) and physical activity (β = -0.20) was associated with fewer WM lesions. WM lesion volume was in turn negatively related to neural integrity of Alzheimer's disease brain regions (β = 0.27) and global cognitive functioning (β = 0.36). Conversely, CRF-related increases in prefrontal and temporal FA from a one-year exercise intervention were not significantly associated with improved working memory performance on a digit span task (Voss et al., 2013). (Figure 6 here)

CRF and Other Individual Differences

The effect of risk and protective factors that interact in the development of dementia occur at different times across the lifespan (Fratiglioni, Paillard-Borg, & Winblad, 2004). As illustrated in Figure 7, lifestyle factors such as exercise may not begin to modulate risk for dementia until middle or later age (Fratiglioni et al., 2004). Hayes, Salat, Forman, Sperling, and Verfaellie (2015) found that CRF (VO_2 max) was positively associated with WM integrity in older adults (n = 27, M age = 63.4 years) but was non-significant in young adults (n = 32, M age = 21.1 years). However, Hayes et al. (2015) acknowledged that small sample size could account for the lack of association found for younger adults (i.e., Type II error). Replication is needed with larger samples to confirm the differential effect of CRF on WM integrity between younger and older adults. MRI studies have reported that the positive effects of CRF on prefrontal cortex and hippocampal volume were greater for older adults (Bugg & Head, 2011; S. J. Colcombe et al., 2003; Erickson, Weinstein, & Lopez, 2012). In a meta-analysis investigating effects on cognitive functioning, older adults aged 66 to 80 benefitted more from physical activity

interventions than those between 55 and 65 years old (S. Colcombe & Kramer, 2003). Aerobic exercise may also produce sex-specific effects on brain health and cognition. The positive effects of CRF on WM structure has been reported to be stronger for both males (Sen et al., 2012) and females (S. Colcombe & Kramer, 2003) in separate studies. Baker et al. (2010) found that high-intensity aerobic interventions for MCI led to significantly greater performance on a range of EF for women, but only improved set-shifting for men. (Figure 7 here)

Factors that promote general health and wellbeing can also positively impact the cardiovascular system and structure of WM in older adults (N. Raz & Rodrigue, 2006). Exercise may enhance neurocognitive functioning and reduce the risk of dementia indirectly by improving psychological functioning. Adults who exercise regularly tend to endorse lower rates of depression and anxiety (Conn, 2010; Dunn, 2010; Rethorst, Wipfli, & Landers, 2009; Wipfli, Rethorst, & Landers, 2008). Physical activity is widely known to reduce chronic stress that may otherwise harm brain structure and function (Herring et al., 2010; Nakajima, Ohsawa, Ohta, Ohno, & Mikami, 2010). Both animal and human models of chronic stress reveal hippocampal damage and accompanying deficits in learning and memory (Bremner, 1999). The association between increased oxidative cerebral stress, cortisol, cognitive impairment, and hippocampal atrophy found in people with dementia suggest the role of stress adaptation failure in pathogenesis of the disease (Bremner, 1999; Deshmukh & Deshmukh, 1990). In fact, Wilson et al. (2003) found that older adults with high susceptibility to psychological distress had a two-fold greater risk for developing Alzheimer's disease and lower episodic memory (*M* follow-up = 4.9 years) compared to those low in distress proneness. Exercise training resulted in reduced stress and improved indicators of cardiovascular health in a randomized control trial of patients (N = 134) with ischemic heart disease (Blumenthal et al., 2005).

Pathological processes associated with cognitive decline may also modify CRF. Decreased level of physical activity is often included in the behavioral changes in Alzheimer's disease and related dementias, perhaps due to increased frailty and apathy (Burns et al., 2008). Indeed, greater risk for falls, mobility impairment, gait abnormality, and balance dysfunction have been observed in older adults with WM lesions (Srikanth et al., 2009; Starr et al., 2003; Wakefield et al., 2010). Long-term exercise training has been associated with significantly decreased risk for falling and injurious falling (Barreto, Rolland, Vellas, & Maltais, 2019). WM integrity may influence the ability of older adults to participate in physical activity, thereby reversing the directionality of the CRF–WM relationship (Sexton et al., 2016). Therefore, it is important that studies include sedentary older adults or participants who are unable to complete fitness tests in analyses of CRF and WM in the aging brain.

Research gaps

Tract specificity. Additional neuroimaging evidence is needed to understand the specific neuroprotective effects of CRF, particularly at the microstructural level (Tian et al., 2016). In particular, it is unclear which WM tracts are most strongly related to CRF and whether these improvements are localized in tracts that tend to degrade with aging (Bennett & Madden, 2014; Yang et al., 2016). Studies have identified several overlapping WM tracts that support the anterior-posterior patterns of age-related atrophy (Davis et al., 2009; Hayes et al., 2015; Johnson et al., 2012; R. Liu et al., 2012; Z. Liu et al., 2009; B. L. Marks et al., 2007, 2007; Tseng et al., 2013); however, replication is needed to confirm the CRF-FA relationship in disparate WM tracts. Methodological differences in neuroanatomical identification of WM tracts and measurement of physical activity also dilute our understanding of the neuroprotective effects of CRF across the lifespan from existing studies. Further, Sexton et al. (2016) indicated that few

studies have examined the influence of CRF on WM at both whole brain and regionally specific levels, despite evidence that local and global CRF-related effects are not mutually exclusive (Bennett & Madden, 2014). Information on the magnitude and specificity of the CRF-WM relationship is vital for determining the viability of aerobic exercise interventions for promoting brain health and the primary and secondary prevention of dementia.

CRF, WM, and cognition. The culmination of research on lifestyle factors, cognitive functioning, and brain health suggests complex interplay between these factors in normal aging (See Figures 4, 5, and 7). Yet, few studies have integrated measurements of CRF, structural neuroimaging, and neuropsychological functioning in analyses of compensatory processes in aging. Such analyses have the potential to elucidate the role of the physiological mechanisms in supporting brain health and cognitive functioning. I aimed to extend the Wirth et al. (2014) path analysis that lifestyle factors (physical and cognitive activity) influenced brain pathology, which in turn predict cognitive functioning (see Figure 6). The Wirth et al. (2014) findings are encouraging but are limited by several methodological features: (1) their use of indirect activity assessments (i.e., no performance-based CRF measure) are retrospective and may be biased by social desirability, (2) controlling for age precludes analyses on the role of aging or cohort effects, and (3) cognitive functioning was measured as a global composite rather than investigating the effects of physical activity and brain pathology on fluid cognitive abilities that decline with aging. While aerobic exercise offers a promising intervention for reducing or delaying deleterious effects of aging, further research is needed to determine whether CRF-related benefits on WM microstructure translate to enhanced cognitive functioning (Sexton et al., 2016). Deliniating neurocognitive effects of CRF may serve clinicians in individually tailoring wellness interventions to meet patients' specific cognitive concerns.

Mediators and moderators. Additional research is needed to understand factors that influence the neuroprotective effects of aerobic exercise (Bherer et al., 2013; Brasure et al., 2018; Kramer, Erickson, & Colcombe, 2006; Young et al., 2015). Recent research suggests that age may moderate the relationship between CRF on brain structure and cognitive functioning. Interactions with age suggest the presence of a "therapeutic window" for CRF on brain structure and function. Erickson et al. (2014) hypothesized that the timeframe may be most apparent during periods associated with greater age-related neural deterioration. Our current understanding of a potential age effect is obscured by studies that only use a young adult or elderly sample or control for age as a nuisance variable. DTI studies reveal that statistically controlling for age can obfuscate our understanding of brain-behavior relationships (Z. Liu et al., 2012; Madden et al., 2012, 2009; Tian et al., 2014). The heterogeneity of studies reporting differential effects between males and females suggest that sex should also be examined as a potential moderator in the relationship between CRF and brain structure (Sexton et al., 2016). An improved understanding of mediators in the CRF–WM relationship may enhance individualized treatment plans to reduce cognitive impairment based on modifiable risk factors.

The relationship between CRF and indices of brain health may be mediated by other risk factors for brain atrophy, such as levels of stress and BMI (Erickson et al., 2014). In their meta-analysis on the relationship between prefrontal cortex size and EF, Yuan and Raz (2014) highlighted that the exclusion of cardiovascular factors in neuroimaging studies obstructs researchers' ability to "fully describe the nature of observed structure-function associations." Vascular health factors should be included as covariates given their relationship with both aerobic capacity (Green, Maiorana, O'Driscoll, & Taylor, 2004) and neurocognitive functioning (Naftali Raz, Rodrigue, & Acker, 2003; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003;

Vicario, Martinez, Baretto, Diaz Casale, & Nicolosi, 2005). Differential relationships between individual cardiovascular risk factors and age (see Figures 4 and 7) further highlights the importance of including them in analyses of cerebrovascular health across the adult lifespan. The extent to which time courses of vascular brain injury relate to time courses of neurodegenerative brain injury are unknown (Carmichael, 2014). Sexton et al. (2016) noted that the majority of studies' findings on the CRF–WM relationship held after considering such covariates; however, Ho et al. (2011) found that the relationship between physical activity and WM volume became non-significant after controlling for BMI. These research gaps must be addressed before further conclusions are drawn regarding the potential benefits of CRF on WM and cognition with aging.

Study Overview

The principal goal of this study was to substantiate the potential neuroprotective effects of CRF. In this pursuit, I examined the relationship between CRF, integrity of WM microstructure, and EF in middle to late adulthood. This study prioritized investigating the effects of CRF and WM integrity (global and local) on EF for several reasons: (1) evidence for the relationship between CRF and improved cognitive function among healthy adults is greatest for EF relative to other cognitive domains (Ahlskog et al., 2011; S. Colcombe & Kramer, 2003; P. J. Smith et al., 2010; Tian et al., 2016), (2) The CRF–WM association has been localized most consistently in the frontal lobe (Sexton et al., 2016), (3) FA has been found to relate more strongly than MD to EF in older adults (Nowrangi et al., 2015), (4) age-related decline in EF is well-documented (Harada et al., 2013; S. Lockhart et al., 2014; Salthouse, 2011), and (5) the wide range of EF measures available in Nathan Kline Institute – Rockland Sample (NKI-RS).

The NKI-RS is well-suited to address this aim and the identified gaps in the literature. It was collected to meet the National Institute of Mental Health's call to elucidate developmental

trajectories for risk and resilience across the lifespan (Nooner et al., 2012). NKI-RS is a large-scale, open-access, cross-sectional lifespan sample of adults that includes protocol-driven neuroimaging, neurocognitive testing, psychological assessment, and physiological measures. This community sample allowed for the investigation of age-related neurocognitive changes that may differentiate normal aging and pathological cognitive decline. DTI data available in NKI-RS were used because measures of WM integrity have demonstrated sensitivity to aging and pathological processes (Alexander et al., 2007; Bigler, 2013). The NKI-RS battery of traditional neuropsychological tests and computerized cognitive neuroscience tasks allowed for comprehensive assessment of EF. NKI-RS participants completed a bike test and questionnaire of physical activity, which allowed the unique opportunity to compare performance-based CRF and self-report of physical activity.

First, mixed-effect modeling was used to investigate the extent to which CRF predicted WM integrity, as global and regionally-specific measurements of FA. This approach allowed for the simultaneous examination of nine major WM tracts of interest (TOI): anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), corpus callosum forceps minor (Fmin), corpus collosum forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC). I categorized participants as younger (ages 20 to 59) and older (60 to 85) to compare potential benefits of CRF between lifespan phases of relative neurocognitive stability (younger age) to a presumed period of more accelerated decline (older age). Second, structural equation modeling was used to investigate whether higher FA within significant TOI from the mixed-effects accounted for a positive relationship between CRF and EF. The role of other participant demographics (e.g., sex, socioeconomic status) and clinical characteristics (e.g.,

cardiovascular risk factors, depression) were also explored as covariates in the link between CRF, WM, and EF. The analyses were designed to evaluate CRF as an intervention for modulating decline in WM integrity and EF observed with aging.

Hypotheses.

H1: Global WM microstructure. I hypothesized that higher CRF would be associated with stronger global FA. This hypothesis is consistent with previous research (Gow et al., 2012) and evidence that CRF may make unique contributions to both local and global microstructure (Bennett & Madden, 2014).

H2: Local WM microstructure. I hypothesized that the CRF-FA relationship would be strongest in WM TOI that connect frontal regions (UNC, CCG, CAB, SLF, ATR, Fmin). This aligned with the differential association between CRF and WM integrity in tracts identified by similar studies (Hayes et al., 2015; Johnson et al., 2012; Z. Liu et al., 2009; B. Marks et al., 2011; B. L. Marks et al., 2007; Tian et al., 2014; Tseng et al., 2013). I also hypothesized that higher CRF will be associated with greater FA within the CST given that it connects the brain stem to the motor cortex. The remaining non-frontal WM tracts were not (Fmaj, ILF) expected to be significantly related to CRF.

H3: Age dependence. I hypothesized that the neuroprotective effects of CRF on WM integrity would interact with age, such that the association between CRF and FA would be stronger in old age (60 to 85) compared to younger (20 to 59) age. This was in line with the age-dependent hypothesis of CRF on neural architecture (Hayes et al., 2015; Hötting & Röder, 2013).

H4: Self-report of physical activity. I hypothesized that performance-based CRF more strongly predict WM integrity than self-report of physical activity. This was based on the modest relationship between the two assessment methods (Craig et al., 2003) and measurement error

often found in self-reports of physical activity (W. Brown, Bauman, Chey, Trost, & Mummery, 2004; Fogelholm et al., 2006).

H5: CRF and WM on cognition. As depicted in Figure 8, I hypothesized that higher CRF would predict stronger performance on tests of EF and that this relationship would be partially accounted for by greater WM integrity in tracts that connect frontal regions (UNC, CCG, CAB, SLF, ATR, Fmin). Partial mediation was predicted given the role of genetic, lifestyle, and medical factors not available in NKI-RS. Non-frontal WM tracts were not (Fmaj, ILF) expected to be significantly related to EF.

Methods

Sample

Data from the "Cross-Sectional Lifespan Connectomics Study" of NKI-RS were analyzed for the present study (Nooner et al., 2012). Participants were community-dwelling residents from Rockland County, New York prospectively recruited through advertisements, flyer mailings, and postings in the community. Rockland County is economically and ethnically comparable to the United States (US Census Bureau, 2010), thereby enhancing the generalizability of NKI-RS studies. Zip code-based recruitment and monitoring enrollment for key demographic variables (e.g., age, sex, ethnicity) were used to maintain adequate representation of Rockland County and prevent sampling biases (e.g., cohort effects).

NKI-RS eligibility criteria was designed for inclusivity (Nooner et al., 2012). Nearly half of recruited individuals met criteria for at least one Diagnostic Statistical Manual – 4th Edition (American Psychiatric Association, 2000) diagnosis based on a semi-structured clinical interview. Exclusionary criteria were: severe psychiatric illness (bipolar disorder, schizophrenia disorder, schizoaffective disorder), severe developmental disorders (autism spectrum disorders,

intellectual disabilities), current suicidal or homicidal ideation, severe cerebral trauma (stroke, moderate to severe traumatic brain injury, ischemic attack in the past two years), severe neurodegenerative disorders (Parkinson's disease, Huntington's Disease, dementia), a history of substance dependence in the past two years (with an exception for cannabis), a lifetime history of psychiatric hospitalization, current pregnancy, and MRI contraindications.

De-identified phenotypic and neuroimaging data from 645 NKI-RS adult participants (age 20 or older) were available at the start of this study (October, 2016). Maximum age was set at 85 to reduce the rate of comorbid chronic illness (Wolff, Starfield, & Anderson, 2002). Of the eligible NKI-RS participants, 530 had complete diffusion tensor imaging (DTI) and T1-weighted structural imaging (Magnetization-Prepared Rapid Gradient-Echo; MPRAGE) without significant artifacts. As described under quality assurance below, five NKI-RS participants with scans determined to be of poor quality after re-processing were excluded from analysis. Six NKI-RS participants were excluded for evidence of an intellectual disability as indicated by a Wechsler Abbreviated Scale of Intelligence (WASI) Full Scale IQ of 70 or below (-2 *SD*). Finally, twenty NKI-RS participants were excluded for not attempting the bike test. NKI-RS participants who attempted but were unable to complete the bike test (n = 101, 20.24%) were included for comparisons with bike test completers. The final sample for data analysis consisted of 499 NKI-RS participants. Sample demographics are presented in **Error! Reference source not found.**. (**Error! Reference source not found.** here)

Procedure

Study procedures were approved by the NKI-RS institutional review board and written informed consent was obtained from all participants. Suffolk University institutional review board approval was acquired prior to completing a data use agreement with the enhanced Nathan

Kline Institute. All participants completed a medical evaluation, psychiatric interview, self-report questionnaires, standardized battery of cognitive tests, and neuroimaging at the Nathan Kline Institute. Measurement selection emphasized empirically validated tests that could be administered across the lifespan. Participants enrolled in NKI-RS before September 15, 2015 engaged in a two-day research protocol. Since then, the participant schedule was abbreviated to a one-day protocol following an hour-long screening visit. See Nooner et al. (2012) for a complete list of assessments and the participant schedule.

Measures and Constructs

Age. Age was recorded by NKI-RS via a self-report demographics measure. It was included in study analyses both as an integer (years old) and a dichotomous grouping variable (younger versus older participants). The decision to split the sample into younger (ages 20 – 59) and older (ages 60 – 85) subgroups was informed by the following literature. Using the same WM TOIs selected in this study, Westyle et al. (2010) found that FA tends to reach 50% of peak integrity by the sixth decade, followed by more accelerated decline until end-of-life (See Figure 3). Correspondingly, performance for "fluid" cognitive abilities tends to fall below average in the sixties (see Figure 2; Salthouse 2011). Stronger WM-cognition relationships have been found in adults aged 60s or older (Au et al., 2006; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009). Figure 4 illustrates that the sixth decade also marks a substantial rise in age-specific prevalence of several cardiovascular risk factors (DeCarli et al., 2005). Taken together, this piecewise approach to age allows for the comparison of CRF effects between lifespan phases of expected neurocognitive plateau (middle age) and more accelerated decline (old age).

Cardiorespiratory fitness (CRF). Participants' aerobic fitness was estimated based on the Astrand-Ryhming test (I. Astrand, 1960; P. O. Astrand & Ryhming, 1954). The Astrand-

Ryhming test is a brief standardized cycle ergometer test commonly used for predicting VO_2 max (Jessup, Riggs, Lambert, & Miller, 1977; Wagganer et al., 2015), a measure of the maximum rate of oxygen consumption during physical exertion (Léger & Lambert, 1982). Astrand and Rhyming (1954) developed a nomogram to predict VO_2 max based on the linear relationship between heart rate during physical exertion and oxygen intake in percentage of an individual's maximum aerobic capacity. It is a predictive submaximal exercise test in that it is designed to measure individuals' aerobic capacity below the cardiovascular workload that induces angina (i.e., chest pain due to reduced blood flow to the heart) (Noonan & Dean, 2000). Compared to maximal exercise tests, submaximal exercise tests are more appropriate for individuals who have various functional limitations (e.g., pain, fatigue, abnormal gait) and older adults (Noonan & Dean, 2000).

The validity of the Astrand-Ryhming test has been studied in healthy male and female adults across a range of age groups (Noonan & Dean, 2000). Initial validation analyses evidenced a significant correlation (r = .71) between the Astrand-Ryhming test and the direct measurement of VO_2 max (I. Astrand, 1960). Since then, several researchers have reported increased predictive validity (r = .95 to .98) of estimated VO_2 max based on revised nomograms (Hartung, Blancq, Lally, & Krock, 1995; Hartung, Krock, Crandall, Bisson, & Myhre, 1993). The incorporation of age-corrections, which account for decreases in heart rate with advancing age (I. Astrand, 1960), have also enhanced the accuracy of Astrand-Ryhming test VO_2 max estimates (Noonan & Dean, 2000). However, these methods for predicting VO_2 max have been criticized for their margins of error (Cink & Thomas, 1981; Noonan & Dean, 2000).

Minor modifications were made to the original Astrand-Ryhming method for the bike test used by NKI-RS. Equipment consisted of a recumbent stationary bicycle, heart rate monitor, and

stopwatch. Participants were seated on the bike, the seat height was adjusted, and a resting heart rate was obtained via pulse oximetry. The level of resistance (99.35, 110.62, 121.89 or 133.16 Watts) was determined by the age and gender of each participant. Heart rate was reassessed after participants pedal the stationary bicycle at 70 RPM for six minutes. Failure time and heart rate was obtained if participant was unable to pedal at 70 RPM for the full six-minute period. Predicted VO_2 max was calculated by NKI-RS using the steady heart rate measurement after six minutes of exercise (HRss) and the resistance workload in kg.m/min (Watts x 6.12) based on the following formula (Buono, Roby, Micale, & Sallis, 1989):

Females: VO_2 max $_{ml/kg/min}$ = (.00193 x workload + .326) / (.769 x HRss - 56.1) x 100

Males: VO_2 max $_{ml/kg/min}$ = (.00212 x workload + .299) / (.769 x HRss - 48.5) x 100

Valid measurement of VO_2 max was determined by confirming that each participant registered an increased heart rate from rest. VO_2 max estimates without age correction were used to test hypotheses on the age effects of CRF on WM microstructure and cognition. As described above, participants who were unable to complete the bike test were included for comparisons with bike test completers. Table 2 presents descriptive statistics for CRF and other physical activity variables. (Table 2 here)

Physical activity. The International Physical Activity Questionnaire (IPAQ; Craig et al., 2003) is a self-report measure of current physical activity developed in response to global concerns of growing physical inactivity (Kohl et al., 2012). The IPAQ is particularly suitable for NKI-RS because it was designed to monitor population levels of physical activity across a wide range of age, education, socioeconomic status, and activity levels (Craig et al., 2003). It was developed by a multinational workgroup (representing both developed and developing countries), enhancing the generalizability of IPAQ population-based estimates of physical

activity. Participants are asked to estimate time spent engaged in physical activity over the last seven days across several domains of daily life: occupation, transportation, domestic, and recreation. The IPAQ queries participants about current time spent in vigorous (i.e., hard physical effort requiring harder than normal breathing) and moderate (i.e., moderate effort requiring somewhat harder than normal breathing) activities. Participants are required to quantify the frequency (number of days) and intensity (in hours and minutes) of those physical activities during the past week. The long form of the IPAQ (31 items) was administered to NKI-RS participants.

The pooled data from the 14 study centers of the initial IPAQ validation study evidenced strong test-retest reliability (r_s = .81) (Craig et al., 2003). Criterion validity of physical activity estimated by the IPAQ against an accelerometer was modest (median r_s = .30), but comparable to other established self-report measures (Craig et al., 2003). Using the short form of the IPAQ, which has demonstrated high concurrent validity with the longer version (Craig et al., 2003), Fogelholm et al. (2006) reported a positive dose-response relationship between physical activity reported on the IPAQ and cardiorespiratory fitness. Weekly frequency of vigorous physical activity assessed by the IPAQ demonstrated the strongest dose-response relationship with cardiorespiratory and muscular fitness (Fogelholm et al., 2006).

A tendency for some respondents to overestimate physical activity on the IPAQ has been documented (W. Brown et al., 2004; Rzewnicki, Auweele, & Bourdeaudhuij, 2003). In a study of adult men (N = 913), 10% of participants reported high physical activity on the IPAQ despite poor physical fitness (Fogelholm et al., 2006). Post-hoc analyses revealed that these over-reporters exhibited significantly greater rates of obesity, cigarette smoking, and were less educated (Fogelholm et al., 2006). These studies underscore the importance of accounting for

potential confounders of accurate self-reports of physical activity (e.g., motivation, education) and supplementing the IPAQ with objective measures (e.g., bike test).

Executive function (EF). The Delis-Kaplan Executive Function System (D-KEFS; (Delis, Kaplan, & Kramer, 2001) and Penn Computerized Neurocognitive Battery (CNB (R. Gur, 2001; R. C. Gur, Erwin, & Gur, 1992; Ruben C. Gur et al., 2010) were used to measure EF. Subtests from the D-KEFS and CNB, as described below, were selected based on a recent factor analysis using NKI-RS data (A B Waters, Sawyer, & Gansler, 2017). Descriptive statistics for EF measures are presented in Table 5. (Table 5 here)

Delis-Kaplan Executive Function System (D-KEFS). The D-KEFS consists of nine subtests intended to assess aspects of frontal systems and EF (Strauss, Sherman, & Spreen, 2006). D-KEFS Trail Making Test, Design Fluency Test, Color-Word Interference Test, and Tower Test were extracted for data analysis. These testing paradigms have been repeatedly used to document the negative association between EF performance and aging in healthy adults (Alvarez & Emory, 2006). The clinical utility of the D-KEFS in cognitive aging investigations may stem from its emphasis on mental flexibility or set-shifting. Advancing age is associated with poorer performance on set-shifting tasks, even after controlling for demographic factors (e.g., age, gender, IQ) and component skills tapped by traditional EF tasks (e.g., visual scanning, motor function, processing speed) (Wecker, Kramer, Hallam, & Delis, 2005; Wecker, Kramer, Wisniewski, Delis, & Kaplan, 2000). The D-KEFS was administered by trained research assistants under the supervision of licensed neuropsychologists on the same visit as the MRI protocol. Raw scores were used instead of age-corrected scaled scores because age was a predictor variable of interest. Timed D-KEFS tasks (TM, CWI) were inverted so that positive scores indicated better performance for all EF measures.

Color Word Interference Test. The Color Word Interference Test of the D-KEFS, which is based on a classic measure of cognitive control originally developed by Stroop (1935), assesses selective attention and cognitive flexibility. According to Strauss et al. (2006), the color word interference tests measure "the ease with which a person can maintain a goal in mind and suppress a habitual response in favor of a less familiar one" (p. 744). In classical neuropsychological terms, it taps working memory, processing speed, semantic activation, and response selection (Strauss et al., 2006). The Color Word Interference Test involves four conditions. Condition 3 (inhibition) was used in this study, which requires participants to inhibit an overlearned response (i.e., naming color of the words while ignoring their semantic content). Scoring is based on time to complete and number of errors for each part. Internal consistency reliability for the Color Word Interference Test in the Delis et al. (2001) normative sample was adequate (coefficients between .70 to .79). Test-retest was marginal (Delis et al., 2001). Convergent validity has been evidenced through significant correlations for the inhibition/switching (r = -.31) trial with the number of categories completed on the Wisconsin Card Sorting Test (Heaton et al., 1993), another neuropsychological test of set-shifting (Delis et al., 2001). Decreased performance on the Stroop procedure (i.e., increased interference) has been observed in early Alzheimer's disease (Bondi et al., 2002). Wecker et al. (2000) found that age accounted for a significant proportion of the variance (5%) in D-KEFS Color Word Interference performance after accounting for baseline word and color reading.

Tower Test. The D-KEFS Tower Test is a measure of planning and problem solving that is similar to other tower paradigms (e.g., Tower of Hanoi), which are commonly used by neuropsychologists as measures of EF (Rabin, Barr, & Burton, 2005). Specifically, tower tests are hypothesized to asses both spatial planning (Morris, Miotto, Feigenbaum, Bullock, & Polkey,

1997) and the capacity to resolve conflicts between goals and sub-goals (Goel & Grafman, 1995). Materials consist of a model set that features three rods accompanied by five disks of varying sizes designed to slide onto any of the rods. Participants are asked to move the five disks across the three pegs to construct a target tower using the fewest number of moves possible. The tower paradigm requires two rules: (1) only one disk can be moved at a time and, (2) no disk may be placed on top of a smaller disk. The minimum number of moves required to solve each puzzle increases as participants progress through the nine D-KEFS Tower Test items, which necessitates greater problem-solving and planning ability. Items were timed for discontinuation criteria. Towers successfully completed within the time limit were awarded one point, with additional points given depending on how close a subject solved the Tower using the minimum number of moves (range = 0 to 4 possible points). The scores for each of the nine items were totaled to produce a total achievement score (range = 0 to 30 possible points). In the normative sample, the total achievement score recorded test-retest reliability of 0.44 for all ages, with the lowest value (0.38) in ages 50-89 (Delis et al., 2001). The total achievement score had marginal internal consistency reliability across all age groups (Strauss et al., 2006). Yochim, Baldo, Kane, and Delis (2009) found that patients with frontal lobe lesions demonstrated worse overall performance than controls on the D-KEFS Tower Test, which is consistent with findings from other tower paradigms (Goel & Grafman, 1995; Morris et al., 1997). The D-KEFS Tower Test has demonstrated an association with transportation function, an instrumental activities of daily living (Jefferson et al., 2015).

Trail Making Test. The D-KEFS Trail Making Test is a modified version of the traditional trail making test paradigm (Army Individual Test Battery, 1944; Reitan, 1955), which is one of the most widely used neuropsychological measures (Rabin et al., 2005). It is used as a

key measure of EFs and is theorized to be sensitive to set-shifting, attention, processing speed, and visuomotor scanning (Arbuthnott & Frank, 2000; Sánchez-Cubillo et al., 2009). Participants are asked to connect, by drawing lines, a scattered array of targets (numbers, letters, dotted lines). The D-KEFS Trail Making Test includes five conditions: visual scanning, number sequencing, letter sequencing, number-letter switching, and motor speed. When an error was committed by a participant, the tester instructed them to return to the last correct placement before progressing. The performance measure for this study was completion time for Condition 4, which required participants to visually scan and connect letters in alphanumeric order. The number-lettering switching condition measures EF through its recruitment of primarily working memory and secondarily task-switching ability (Sánchez-Cubillo et al., 2009). Overall test-retest reliability for Condition 4 was .38 (switching), with most coefficients within the moderate range for each age group (Delis et al., 2001). The trail making test paradigm has demonstrated strong inter-rater reliability (.90) (Fals-Stewart, 1992). Frontal lobe lesion patients have been found to perform significantly slower on all D-KEFS Trail Making Test conditions relative to healthy controls, even when controlling for processing speed and motor function (Yochim et al., 2009). Slower performance on the D-KEFS Trail Making Test has also been linked to cognitive aging (Wecker et al., 2000). Letter-number switching condition significantly predicts IADLs, specifically laundry and transportation functions (Jefferson et al., 2015).

Design Fluency Test. The D-KEFS Design Fluency Test is intended to assess planning, cognitive flexibility, and non-verbal fluent productivity (Strauss et al., 2006; Suchy, Kraybill, & Gidley Larson, 2010). Participants are presented rows of boxes that contain an array of dots. They are instructed to draw as many designs as possible within 60 seconds based on the following conditions: connecting filled dots (Condition 1), connecting unfilled dots only

(Condition 2), and alternating connections between filled and unfiled dots (Condition 3). Successful task performance relies on observing the rules and restrictions of the task and inhibiting previously drawn responses. Condition 3, which measures response inhibition and set-shifting, served as the primary Design Fluency performance variable. Raw scores are based on the sum of correct designs completed within the 60 second time limit. Test-retest reliability reported in the normative sample for Design Fluency was low (Delis et al., 2001). Inter-rater reliability for the Design Fluency paradigm has been reported to range from good to excellent (Carter, Shore, Harnadek, & Kubu, 1998; Jones-Gotman, 1991). Impairment in design fluency has been found in patients with AD (Bigler et al., 1988; Harter, Hart, & Harter, 1999; Mickanin, Grossman, Onishi, Auriacombe, & Clark, 1994).

Penn Computerized Neurocognitive Battery (CNB). Executive tasks were also selected from the CNB (R. Gur, 2001; R. C. Gur et al., 1992; Ruben C. Gur et al., 2010). The CNB was designed to isolate brain systems recruited for narrowly defined behavioral tasks based from cognitive neuroscience. It takes approximately one hour to complete via a standardized web-based platform (https://penncnp.med.upenn.edu/index.pl) that presents tasks from each domain in a fixed order. Trained research assistants provide task instructions and observes participants during testing. Participants are oriented to the CNB through a Mouse Practice task to promote familiarity with using a computer; each task begins with a practice trial to ensure understanding of the instructions. The CNB computes performance measures for both accuracy (total scores for correct responses) and speed (median response time) scores for each task, which differently relate to regional brain activation (R. C. Gur et al., 1988) and allow for speed-accuracy analyses.

Penn Conditional Exclusion Test (PCET). The PCET (Kurtz, Ragland, Moberg, & Gur, 2004) assesses abstraction, mental flexibility, and problem-solving. Participants are presented

four figures and are required to select the object that does not belong with the other three. Correct object exclusion is based on three rule categories (line thickness, shape, and size), which change after the participant achieves ten consecutively correct responses within each rule category. Participants are not informed of the rule change but are provided feedback after each response ("correct" or "incorrect"). Therefore, the PCET assesses participants' ability to utilize feedback and adjust to changing task demands. PCET performance can be assessed through the number of correct/incorrect responses, perseverative errors, and median response times. Construct validity has been supported via convergence with related tests (e.g., abstraction, set-shifting, and rule-learning) and discrimination with unrelated tasks (e.g., word memory, verbal reasoning, visuospatial functioning, emotion recognition) (Kurtz, Ragland, et al., 2004; Kurtz, Wexler, & Bell, 2004). PCET performance was found to be significantly more impaired than abstraction or inhibition with aging in a sample of healthy older and younger adults (Silver, Goodman, Gur, Gur, & Bilker, 2011). The dynamic nature of the PCET, which requires participants to investigate different strategies in response to shifting rules over a series of trials, obfuscates estimates of the task's internal reliability (Kurtz, Ragland, et al., 2004).

Penn Letter N-back Test (n-back). The n-back test included in the CNB is a variation of the n-back working memory paradigm first introduced by Kirchner (1958). It is an immediate-memory span task that necessitates continuous maintenance and updating of the most recent *n* items in working memory (Conway et al., 2005). Participants attend to a list of letters presented one at a time on a computer screen during three n-back conditions: 0-back, 1-back, and 2-back. For the 0-back condition, participants press the space bar when the letter 'X' appears on-screen. During the 1-back and 2-back conditions, participants press the space bar when the letter on screen matches the previous letter (i.e., 1 letter back) or two letters ago (i.e., 2 letters back),

respectively. Inter-stimulus interval for all trials is 2.5 seconds and each letter is presented for half a second. Participants practice each condition before testing begins. A methodological review concluded that the n-back paradigm evidenced strong internal consistency reliability (within Cronbach's alpha range of 0.70 to 0.90), test-retest reliability (0.70 to 0.80) in adult samples (Conway et al., 2005). Strong construct validity for the n-back has been established via convergence with tests of attentional control and discriminance with tasks of automatic processing (Conway et al., 2005).

Neuroimaging. Raw neuroimaging data was acquired by NKI-RS and processed at Suffolk University as part of this investigation.

MRI acquisition. The NKI-RS MRI protocol implemented Multiband echo planar imaging, which rapidly accelerates whole brain acquisition through simultaneous multi-slice imaging. The Center for Magnetic Resonance Research at the University of Minnesota for the Human Connectomes Project provided consultation on the design, execution, and troubleshooting for the NKI-RS MRI protocol. DTI and MPRAGE were acquired during the same session using a 3.0 T Siemens Trio scanner. DTI images were obtained using the following measurement parameters: voxel size = 2.0 × 2.0 × 2.0 mm, 64 slices, 137 directions, b-value = 1500 s/mm^2, echo time = 85 ms, repetition time = 2400 ms, field of view = 212 mm, flip angle = 90°, 12 non-diffusion volumes. MPRAGE images were collected using the following measurement parameters: voxel size = 1.0 x 1.0 x 1.0 mm, 176 slices, repetition time = 1900 ms, echo time = 2.52 ms, field of view = 250 mm, flip angle = 9°, dist. factor = 50%. Complete details about the MRI measurement parameters can be located on the NKI-RS website for DTI (http://fcon_1000.projects.nitrc.org/indi/pro/eNKI_RS_TRT/DIff_137.pdf) and MPRAGE (http://fcon_1000.projects.nitrc.org/indi/enhanced/NKI_MPRAGE.pdf) and protocols.

MRI Processing. MPRAGE data included in the NKI-RS dataset were obtained in their unprocessed form (DICOM data) and converted to ".mgz" file format. Cortical reconstruction and volumetric segmentation of MPRAGE images were auto-reconstructed in Freesurfer (Version 5.3). FreeSurfer is a publically available software package for analyzing and visualizing structural and functional neuroimaging data (http://surfer.nmr.mgh.harvard.edu/). FreeSurfer image processing includes: motion correction (Reuter, Rosas, & Fischl, 2010), removal of non-brain tissue (F. Ségonne et al., 2004), automated Talairach transformation, intensity normalization, segmentation of white and gray matter structures (Fischl et al., 2004, 2002), tessellation of white/gray matter boundaries, topical surface correction (Fischl, Liu, & Dale, 2001; Florent Ségonne, Pacheco, & Fischl, 2007), and surface deformation (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). FreeSurfer auto-reconstruction produces a segmented brain volume with labeled subcortical structures. Each participant was mapped into standard morphological space and cortical thickness was generated for region of interest analyses based on the Desikan-Killiany Atlas (Desikan et al., 2006).

DTI Processing. DTI obtained from the NKI-RS dataset have already been converted to NIfTI format and include the diffusion-weighting *b*-values (gradient pulse length and strength) and encoding directions. Diffusion-weighted MRI images and echo planar imaging are more susceptible to the effects of eddy currents (Jehenson & Syrota, 1989; Jezzard, Barnett, & Pierpaoli, 1998). Images were corrected for eddy currents using the FDT Diffusion Toolbox in FSL (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Behrens et al., 2003) as part of TRACULA (A Yendiki et al., 2011) in FreeSurfer 5.3. This corrected for motion between scans and residual eddy current distortions. TRACULA (TRActs Constrained by UnderLying Anatomy) is an ideal tool for large neuroimaging datasets because it automatically reconstructs

major WM tracts from diffusion-weighted MRI. Briefly, the *trac-all* script registered reconstructed T1 images to diffusion DICOM data and generated automated probabilistic reconstruction of a set of major WM tracts using automatic segmentation statistics generated during reconstruction for each subject. Description of all processing steps in the *trac-all* script can be found in the TRACULA documentation (https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula). The output included the 1st eigenvector, the 2nd eigenvector, the 3rd eigenvector, the 1st eigenvalue, the 2nd eigenvalue, the 3rd eigenvalue, and FA. Motion values were generated and compared between subjects as nuisance regressors (Anastasia Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014).

I selected nine major WM TOI reconstructed by TRACULA: anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), corpus collosum forceps minor (Fmin), corpus collosum forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UF). Maximum FA values, sampled from the centers of each tract, served as the primary DTI measure of WM integrity because it minimizes confounding effects due to partial voluming (S. M. Smith et al., 2006). Bilateral WM FA tract values tend to demonstrate moderate to strong inter-correlations (Westlye et al., 2010). To address multicollinearity, FA values from the bilateral TOI (ATR, CAB, CCG, CST, ILF, SLF, UF) were averaged across hemispheres. Frontal (UNC, CCG, CAB, SLF, ATR, Fmin) and non-frontal (CST, Fmaj, ILF) were identified based on trajectories listed in the TRACULA tract statistics page (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TraculaStatistics). Figure 9 andFigure 10 illustrate the TOI and descriptive statistics for the WM regions are presented in Table 4. (Table 4 and Figure 9 andFigure 10 here)

Imaging quality assurance. A quality assurance protocol was conducted to ensure the integrity of the processed DTI and MPRAGE images for use in subsequent analyses. Complete details of the manual (visual inspection) and statistically-based quality assurance are reported elsewhere (A. Waters, Mace, Sawyer, & Gansler, 2017). In short, trained graduate students visually inspected a subsample (n = 220) of MPRAGE and all DTI images for significant image artifacts, head motion, or missing slices using Freeview in the Freesurfer 5.3. This visual inspection occurred after processing steps had been completed. Trained research assistants manually corrected (Savalia, Agres, & Wig, 2015) MPRAGE images with skull stripping errors using the Freeview voxel editing tool using FreeSurfer guidelines for correcting surfaces (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/PialEdits_freeview) and editing the brainmask.mgz.

Supplementary measures.

Additional demographic and clinical variables were explored in supplemental analyses and as covariates in the link between CRF, WM, and EF. The demographic information presented in **Error! Reference source not found.** was collected by NKI-RS through a standardized questionnaire. Table 4 presents descriptive statistics for cardiovascular and other relevant health variables. Vitals were recorded by study staff and lab work was processed by the Office of Mental Health (OMH) Clinical Laboratories at NKI-RS. Participants' cardiovascular conditions were assessed by study staff using a standardized medical history interview. Proxies for physical motivation, including walking MET and sedentary hours per week on the IPAQ, grip strength (dominant hand initial trial) (Roylan, 2003), and Activation Control on the Adult Temperament Questionnaire (Evans & Rothbart, 2007), were also included to control for the possibility of inadequate effort from participants on the bike test. (Table 4 here)

Statistical analysis

Statistical analysis was conducted using R 3.4.0 (R Core Team, 2017) in RStudio 1.0.143 (RStudio Team, 2016) (See Appendix for R packages). R code for all study analyses will be made available for reproducibility with open-access NKI-RS data.

Pre-analysis. Descriptive statistics were used to characterize the sample by reporting participant demographic (age, gender, race/ethnicity, education, language, handedness, socioeconomic status), clinical characteristics (cardiovascular and health variables) and values for study measures (CRF, physical activity, FA, EF). Validity checks were performed to ensure the integrity of study measures. Study measures were visualized in the *ggplot2* package to examine normality and identify outliers. Mean FA values for TOI were compared to previous reports for healthy adults in middle and late age (Burzynska et al., 2014; Hayes et al., 2015; Westlye et al., 2010). VO_2 max values were compared to reference data to ensure representativeness of CRF in NKI-RS (Loe, Rognmo, Saltin, & Wisløff, 2013). Correlation matrices were used to establish convergent validity within the cognitive tests and assess inter-relationships among FA in WM tracts. I examined the convergence between VO_2 max and physical activity (IPAQ), as well as their associations with other cardiovascular health variables.

Exploratory correlational analyses were conducted to identify the relationship between CRF, WM microstructure, and EF for their suitability in subsequent hypothesis testing. Independent-sample t-tests, one-way analysis of variance, chi-square tests of independence, and Pearson correlations were used to explore associations between the study measures and participant demographic factors. Between-groups analyses focused on two participant categories: (a) younger (20 to 59) versus older (60 to 85) age, and (b) bike test completers versus those who

unable to complete the bike test. Characteristics identified as systematically related with CRF, FA, or cognitive functioning were retained as covariates for subsequent analyses.

Hypothesis testing.

Mixed-effects modeling. Mixed-effects modeling in the *lme4* package was used to test Hypotheses 1-4. Mixed-effects models are a flexible tool for modeling a wide variety of correlated data that use both fixed (i.e., how a population differs) and random (i.e., variability among subjects) effects. Mixed-effects models are ideal for high dimensional neuroimaging data because they can handle multiple measurements per subject (i.e., FA for each WM tract). Advantages over traditional linear regression include: (1) enhanced statistical power due to repeated observations (2) robustness to missing data, and (3) management of heteroscedasticity and non-spherical error variance for either participants or study items (Baayen, Davidson, & Bates, 2008). FA values from each participant can be imputed with no prior aggregation; thus, both by-item and by-participant variation are accounted for in a single model (Winter, 2013). An a-priori power analysis using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009) for regression indicated adequate sample size, assuming a small-medium effect ($f2 = 0.10$) and up to 15 predictors (age, VO_2 max, WM TOI, and covariates), for 0.99 power.

The linearity of CRF and FA with age was confirmed prior to mixed-effects modeling. All continuous variables were z-standardized ($M = 0$, $SD = 1$) for compatibility with the *lme4* package and to enhance interpretability of slope. The NKI-RS dataset was reshaped from wide to long format. VO_2 max (continuous), WM tract (categorical factor, 9 TOI levels), and age (continuous) were entered as a three-way interaction term predicting FA (continuous criterion). Intercepts for participants were added as a random effect. The significance of interaction effects within the mixed-effects model were summarized using the *anova* function. The main effect of

CRF on global FA (average FA of WM tracts) was used to test Hypothesis 1 (global WM microstructure). The CRF x WM tract interaction was used to test Hypothesis 2 (local WM microstructure), which allowed for the examination of CRF main effects separately for each tract. For Hypothesis 3 (age dependence), linear trends were dichotomized to examine the differential effects of CRF on FA global (CRF x age) and local (CRF x WM tract x age FA) between younger and older participants. Hypotheses 1–3 were retested after sequential addition of demographic, cardiovascular risk, and physical motivation covariates. To test Hypothesis 4 (self-report of physical activity), mixed-effects analyses were repeated with IPAQ MET scores (continuous) for vigorous and moderate MET. As a-priori analyses, slopes and 95% confidence intervals (CI) for each WM TOI were estimated using the *lstrends* function in the *lsmeans* package (Lenth, 2016) and compared using the *pairs* function.

Structural equation modeling. Structural equation modeling was conducted using the *lavaan* package to test Hypothesis 5 (CRF and WM on cognition). Both the direct effects and WM-mediated indirect effects of CRF on EF were assessed (see Figure 8). Structural equation modeling allowed for the examination of a general factor for WM integrity using TOI related to CRF in the mixed effects modeling. D-KEFS and CNB subtests were selected based on factor analysis in NKI-RS to form an underlying common factor of EF (A B Waters et al., 2017). CRF and age were included as single-indicator continuous measures. Prior to structural equation modeling, separate exploratory factor analyses were performed on the EF and WM variables. Maximum likelihood extraction with oblique rotation was used to confirm that the data were factorable. Maximum likelihood extraction is calculated based on the shared variance between variables and oblique rotation is chosen as it allows for factors to be correlated (Costello &

Osborne, 2005). Factor analytic acceptability was determined by Bartlett's test of sphericity ($p < 0.05$), KMO measure of sampling adequacy (> 0.60), and loadings ≥ 0.40.

For the first phase of structural equation modeling, a measurement model was constructed to assess (1) the degree to which indicators loaded on their constructs and (2) the degree to which latent variables were related yet distinct constructs. For the second phase, a progression of structural models evaluated the association between indicators and corresponding latent variables. Chi-square goodness of fit adjusted for degrees of freedom (Cmin and Cmin/Df), comparative-fit index (CFI), and root-mean-square error of approximation (RMSEA) were used to assess model fit. Decisions regarding model were determined using commonly accepted cutoff criteria (Hooper, Coughlan, & Mullen, 2008; Hu & Bentler, 1999): Cmin/df value close to 2 (smaller values indicating better model fit), a CFI value at or above 0.95 (higher values indicating better model fit), and a RMSEA value between 0.002 and 0.08 (smaller values indicating better model fit). Model fit conclusions were drawn based on consideration of all indices as no single measure is considered a "gold standard" (T. A. Brown, 2015; Martens, 2005). Estimated correlation coefficients were used to indicate the bidirectional strength of association between latent variables. Standardized beta values were used to indicate strength of influence (directional pathway) of a latent variable on another latent variable or indicator. The degree of WM mediation in the CRF–EF relationship was assessed using established criteria (Baron & Kenny, 1986; James & Brett, 1984; Judd & Kenny, 1981). Multi-group analysis with the Chi-square difference test was used to test invariance between the dichotomized younger (20 to 59) and older (60 to 85) subsamples (Hu & Bentler, 1999; Milfont & Fischer, 2010; Sivo, Fan, Witta, & Willse, 2006).

Results

Demographics and clinical characteristics

Descriptive statistics of demographics for the total sample (N = 499) are presented in **Error! Reference source not found.**. The average age was 48.59 $_{\text{years}}$ (*SD* = 17.22, range 20 – 85) with 25% and 75% of the sample age 33 and 62 below, respectively. Sixty-six percent (*n* = 331, 66.33%) of the sample identified their sex as female. Nearly three quarters of participants were white (*n* = 372, 74.54%) and most of the sample identified with Non-Hispanic (*n* = 444, 88.98%). Average education was 15.68 $_{\text{years}}$ (*SD* = 2.28, range = 9 – 24); 28.06% of participants had 18 or more years of education. Based on Hollingshead Index (Hollingshead, 1975) scores (*M* = 47.46, *SD* = 11.78), the average socioeconomic status of participants was upper middle class (Cassedy et al., 2013). All were proficient in English, though 6.46% (*n* = 32) of participants listed it as their second language. Less than nine percent of participants were left-handed (*n* = 43, 8.76%).

Descriptive statistics for the cardiovascular and other health variables are presented in Table 4. Most participants (*n* = 472, 95.16%) identified as a "generally healthy person" during the medical evaluation. While 43.89% (*n* = 219) did not have a cardiovascular condition, 35.67% (*n* = 178) had one risk factor, 14.23% (*n* = 71) had two risk factors, and 6.21% (*n* = 31) had three or more risk factors (max = 6). The most common cardiovascular risk factors were: hyperlipidemia (*n* = 150, 30.06%), hypertension (*n* = 93, 18.64%), and tobacco use within the last year (*n* = 70, 14.03%), and diabetes mellitus type-II (*n* = 26, 5.21%). Cases of myocardial infraction, coronary artery disease, and heart valve disease were less than 3%. Participants were evenly distributed across CDC (Centers for Disease Control and Prevention, 2017) body mass index categories of normal (*n* = 162, 32.46%), overweight (*n* = 174, 34.87%), and obese (*n* =

157, 31.46%) weight. Resting heart rates fell within American Heart Association (2015) expectations for adults (M = 66.88 bpm, SD = 9.30, range = 40 – 102).

Table 2 provides descriptive statistics for CRF and physical activity variables. Overall, participants were physically active based on self-report—86.77% (n = 433) and 7 (n = 258) reported moderate and vigorous exercise the week prior to data collection, respectively. Based on IPAQ categories (IPAQ Group, 2005), 54.53% (n = 271) of participants had low, 24.35% (n = 121) had medium, and 21.13% (n = 105) had high levels of vigorous intensity physical activity. Participants reported sitting an average of 4.18 hours (SD = 2.35) per day. Participants reportedly walk an average of 1.94 hours (SD = 2.70) per day across working, transportation, domestic, and leisure domains of activity.

Validity of study measures

VO_2 max validity. The distributions of VO_2 max in this sample exhibited a slight positive skew toward lower CRF (skew = 0.98, kurtosis = 0.34). Average VO_2 max (M = 45.44 ml/kg/min, SD = 17.06) was comparable to VO_2 max estimates reported by similar WM studies (Johnson et al., 2012; Tseng et al., 2013) and reference data for VO_2 max in healthy adults (Loe et al., 2013). Participants who are laborers had significantly higher VO_2 max (M = 52.31 ml/kg/min, SD = 22.31) than those with a background in clerical work (M = 39.78 ml/kg/min, SD = 13.57), $t(87) = 3.28$, $p = 0.001$, $d = 0.73$. VO_2 max was significantly associated with grip strength ($r = 0.25$, $p < 0.001$). Significant and positive associations with VO_2 max were also found for lab results linked to increased CRF, including creatine ($r = 0.23$, $p < 0.001$), hemoglobin ($r = 0.22$, $p < 0.001$), and T. Bilirubin ($r = 0.17$, $p < 0.001$). VO_2 max was significantly and negatively associated with resting heart rate ($r = -0.28$, $p < 0.001$) and levels of low-density lipoprotein ($r = -0.12$, $p = 0.04$). VO_2 max was not significantly associated with body mass index ($r = -0.05$, $p =$

0.30) or the cardiac conditions listed in Table 4 (*p*s > 0.05). Evidence for construct validity, consistency with normative values, and normal distribution confirm the integrity of VO_2 max data and support its use in hypothesis testing.

IPAQ validity. As depicted in Figure 11, IPAQ MET scores for vigorous (skew = 4.10, kurtosis = 21.66) and moderate (skew = 3.83, kurtosis = 20.37) activity were highly positively skewed and kurtotic. The logarithm of vigorous (skew = 0.06, kurtosis = -1.84) and moderate (skew = -1.53, kurtosis = 1.29) MET scores improved summary statistics of normality for use in subsequent analyses. A constant (+1) was added to the transformed IPAQ variables to avoid dropping 47.09% (n = 235) of the sample that reported no vigorous or moderate physical activity. VO_2 max was significantly correlated with vigorous (r_p = 0.23, $p < 0.001$), but not moderate (r_p = 0.05, p = 0.33) MET. Only vigorous MET was significantly associated with grip strength (r_p = 0.14, $p < 0.001$) and hemoglobin (r_p = 0.12, $p < 0.02$). IPAQ MET scores were not significantly associated with occupation or any of the remaining cardiovascular health variables in Table 4 (*ps* > 0.05). In fact, greater moderate MET was significantly associated with higher levels of low-density lipoprotein (r_p = 0.12, p = 0.02). The weak evidence for convergent validity, coupled with lack of normality, limit the usefulness of the IPAQ in hypothesis testing. (Figure 11 here)

FA validity. Descriptive statistics for FA by WM TOI are reported in Table 3. FA values were relatively normally distributed (skew $_{range}$ = -0.90 – 0.15, kurtosis $_{range}$ = -0.55 – 1.56). As presented in Figure 12, FA values were positively and moderately correlated between WM TOI (r range = 0.23 – 0.67); the average inter-TOI correlation was 0.48 (*SD* = 0.12). As presented in Figure 13, scatterplots for each WM TOI suggest that FA has a negative linear relationship with age. (Figure 12 and Figure 13)

EF validity. Descriptive statistics for the EF measures are reported in Table 3. Scores on the EF measures, selected from the D-KEFS and CNB, were normally distributed (skew $_{range}$ = -0.53 – 0.03, kurtosis $_{range}$ = -1.14 – 0.59) except for the TMT (skew = 2.03, kurtosis = 4.91) and CWI (skew = 1.25, kurtosis = 2.81). As presented in Figure 14, EF measures exhibited mild to moderate positive inter-correlations (r range = 0.21 – 0.49, ps < 0.001). The average association between EF measures was 0.33 (SD = 0.08). As expected, EF scores significantly declined with increasing age (r range = -0.19 – -0.31). Education (r range = 0.10 – 0.17) was significantly and mildly associated with EF performance except on the CWI (r = 0.08, p = 0.08). WASI Full Scale IQ had a significant mild to moderate relationship with the EF measures (r range = 0.19 – 0.38, ps < 0.001). (Figure 14 here)

Mixed effects modeling

VO_2 max. Prior to hypothesis testing, preliminary and diagnostics analyses were conducted to ensure that the data met assumptions of mixed effects modeling. Scatter plots indicated a linear relationship between CRF and WM integrity (Figure 15). The VO_2 max–FA relationship was stronger in older (r range = 0.02 – 0.23) than younger ($| r | \leq 0.07$) participants. The residual plot suggested evidenced homogeneity of variance across the fitted range (Figure 16). The Q-Q plot of standardized residuals was adequately normally distributed (Figure 17). A Cook's distance plot presented in Figure 18 highlighted two participants with disproportionate influence, which were excluded from further modeling. (Figures Figure 15Figure 16Figure 17Figure 18 here)

ANOVA results from the mixed-effects model of age x WM TOI x VO_2 max predicting FA (no covariates) are reported in Table 6. Age significantly predicted global FA (p < 0.001). Every 1 SD increase in age (17.22 $_{years}$) was associated with a 0.13 SD (95% CI = -0.21 – -0.06)

decrease in global FA. As presented in Figure 19, FA within several WM TOI exhibited a significant negative association with age: Fmin (β = -0.32, 95% CI = -0.41 – -0.22), ATR (β = -0.28, 95% CI = -0.38 – -0.18), UNC (β = -0.21, 95% CI = -0.31 – -0.11), ILF (β = -0.13, 95% CI = -0.23 – -0.04), and Fmaj (β = -0.13, 95% CI = -0.23 – -0.03). (Figure 19 here)

H1: Global WM microstructure. As presented in Table 6, VO_2 max did not significantly predict global FA (average FA of WM tracts) in the overall model ANOVA (β = 0.04, 95% CI = -0.03 – 0.12). However, the age x VO_2 max interaction suggested that higher CRF was significantly associated with stronger global WM integrity in older but not younger age. For older participants (age > 59), every 1 *SD* increase in VO_2 max (17.06 $_{ml/kg/min}$) was significantly associated with 0.11 *SD* (95% CI = 0.02 – 0.21) increase in global FA. The relationship between VO_2 max and global FA was not significant among younger participants (β = 0.04, 95% CI = -0.3 – 0.12).

H2: Local WM microstructure. Similarly, VO_2 max did not significantly predict the integrity of local WM microstructure (p = 0.17) in the overall model ANOVA (Table 6). As presented in Figure 20, post-hoc analysis (*lstrends*) to further explore H2 indicated that every 1 *SD* increase in VO_2 max was significantly associated with 0.10 *SD* of FA in the CCG (95% CI = 0.003 – 0.21). The remaining WM TOI were not significantly associated with VO_2 max (β_{range} = -0.01 – 0.09, ps < 0.05). (Figure 20 here)

H3: Age dependence. As indicated in Table 6, the age x WM TOI x VO_2 max interaction was significant in the overall mixed-effects model (p = 0.02). As presented in Table 7, VO_2 max significantly predicted FA in five WM TOI among older participants and one WM TOI in younger participants. For older participants, every 1 *SD* increase in VO_2 max was significantly associated with 0.19, 0.19, 0.18, 0.18, and 0.16 *SD* greater FA in the CCG (95% CI = 0.07 –

0.32), CST (95% CI = 0.06– 0.32), SLF (95% CI = 0.05 – 0.31), ILF (95% CI = 0.03 – 0.29), and Fmaj (95% CI = 0.03 – 0.29), respectively. Consistent with H2 above (i.e., in the full sample) the CRF–local WM relationship was only significant in the CCG (β = 0.10, 95% CI = 0.003 – 0.21) in younger adults. The remaining levels of the age x WM TOI x VO_2 max interaction were non-significant (*ps* > 0.05). Figure 21 maps the significant WM TOI in older adults on a three-dimensional rendering of WM by TRACULA. (Table 7 and Figure 21 here)

Covariates. The results for H1 to H3 were re-examined after sequentially adjusting for demographics (sex, race, and SES), cardiac health variables (diabetes mellitus type-II, hyperlipidemia, systolic blood pressure, and body mass index), and proxies for physical motivation and effort (IPAQ of walking MET, sedentary hours per week, initial grip strength with dominant hand, and Activation Control on the Adult Motivation Questionnaire). The full covariate mixed-effects model is presented in Table 8. Only body mass index significantly predicted FA; every 1 *SD* increase in body mass index (5.75 kg/m^2) was associated with a -0.16 *SD* decrease in FA (β = -0.16, 95% CI = -0.26 – 0.06). The findings for H1 to H3 remained constant after including covariates. After adjusting for demographics, cardiac health, and physical effort, the slope for VO_2 max and global FA was 0.16 (95% CI = 0.02 – 0.29). Similarly, the slope for VO_2 max and local FA among older participants was 0.27, 0.25, 0.24, 0.21, and 0.19 for the CCG (95% CI = 0.10 – 0.45), ILF (95% CI = 0.08 – 0.42), CST (95% CI = 0.06 – 0.41), SLF (95% CI = 0.04 – 0.38), and Fmaj (95% CI = 0.02 – 0.36), respectively. (Table 8 here)

Post-hoc comparisons. The *pairs* function was used to conduct post-hoc comparisons between younger and older participants while controlling for body mass index (the only significant covariate). For H1, the difference in slope for the VO_2 max and global FA relationship between younger and older participants was significant (β = 0.08, 95% CI = 0.01 –

0.16, $t(384) = 2.11$, $p = 0.04$. As depicted in Figure 22, the differences in slope (VO_2 max–local FA relationship) between younger and older participants were non-significant for all WM TOI tested for H3 ($\beta_{range} = -0.05 – 0.15$, $p_{range} = 0.38 – 1.00$). (Figure 22 here)

H4: Self-report of physical activity. Despite the validity concerns raised during the integrity checks above, mixed-effects modeling was repeated with the IPAQ due to the a-priori planned comparison between self-reported physical activity and VO_2 max in relation to WM integrity. Visualization ruled out any non-linear relationships between vigorous MET on the IPAQ and WM integrity. The physical activity–FA relationship was relatively weak in older and younger ($| r | \leq 0.08$) participants. The model for IPAQ scores met assumptions of homoscedasticity and normal distribution of standardized residuals. Four participants were excluded from modeling for H4 due to high leverage based on Cook's distance. IPAQ MET scores for vigorous activity did not significantly predict the integrity of global or local WM microstructure (*ps* > 0.05). None of the levels from the age x WM TOI x IPAQ vigorous MET interaction significantly predicted FA at younger or older age (*ps* > 0.05). The relationship between self-report of physical activity and FA did not reach statistical significance when the mixed-effects model was re-run with IPAQ moderate MET (*ps* > 0.05). Only the vigorous MET ANOVA results are reported in

Table *9*. (

Table *9* here)

Structural equation modeling

H5*:* CRF and WM on cognition.

Factor analysis. Preliminary factor analyses (maximum likelihood extraction with promax rotation) confirmed that EF and WM data were factorable and formed unitary constructs. D-KEFS and CNB items (Trails, Design Fluency, Stroop, Tower, N-back, PCET) selected from Waters et al. (2017) loaded on a single EF factor (KMO = 0.81; Bartlett's test, $p < 0.001$, standardized loadings = 0.46 – 0.76, variance explained = 34%). Significant TOI from the mixed effects modeling (SLF, CCG, ILF, CST, Fmaj) were retained and loaded on a single factor for WM integrity (KMO = 0.85; Bartlett's test, $p < 0.001$, standardized loadings = 0.65 – 0.84, variance explained = 56%). Exploratory factor analysis was conducted on pulse, body mass index, systolic blood pressure, and high-density lipoprotein data for comparison with VO_2 max in measuring cardiovascular health. Despite adequate loadings on a single factor (KMO = 0.66; Bartlett's test, $p < 0.001$, standardized loadings = 0.37 – 0.79), the cardiovascular latent variable was not pursued further due to low variance explained (29%) among the cardiovascular indicators.

Measurement model. A measurement model was created to quantify the relationship between the EF and WM latent variables. First, all of the EF and WM variables were entered as indicators of a unitary construct of neurocognition. Model fit (Cmin/df = 9.51, CFI = 0.99, RMSEA = 0.16) and factor loadings (range = 0.08 – 0.84) were poor for the unitary construct (Figure 23). Adequate model fit was achieved for a two factor model assigning EF and FA indicators to their respective latent variable (Cmin/df = 1.72, CFI = 0.98, RMSEA = 0.045). All indicators significantly loaded on their latent variable for EF (range = 0.39 – 0.74) and WM (range = 0.66 – 0.84). The relationship between EF and WM was (r = 0.18, p = 0.006); setting the bidirectional path between the latent variables did not influence model fit. The final measurement model is presented in Figure 24. (Figure 23 and Figure 24 here)

Structural model. Age and VO_2 max were added to the model as observed variables. As presented in Figure 25, directional paths were specified from WM, Age, and VO_2 max to assess the effect of each on EF. Model fit remained adequate (Cmin/df = 1.88, CFI = 0.96, RMSEA = 0.05). The direct path from age to EF was significant (β = -0.26, $p < 0.001$); an age increase of 16.22 years was associated with a 0.26 *SD* decrease in EF ability. In contrast, the direct path from VO_2 max to EF was not significant (β = -0.03, p = 0.43). Given the lack of association between the proposed causal variable and the outcome, mediation of the CRF-EF relationship by WM integrity could not be established in the full sample (Baron & Kenny, 1986; James & Brett, 1984; Judd & Kenny, 1981). Multigroup analysis was performed to determine whether evidence for an association between VO_2 max and EF could be found in the younger or older subsamples. Model fit for the multigroup analysis with VO_2 max remained adequate (Cmin/df = 1.25, CFI = 0.97, RMSEA = 0.04) and all indicator loadings were significant for both subsamples (range =

0.37 – 0.84, *ps* < 0.05). The direct path from VO_2 max to EF was non statistically significant in both younger (β = -0.03, p = 0.66) older (β = 0.01, p = 0.92) participants. (Figure 25 here)

Post-hoc modeling. Post-hoc modeling was performed in an attempt to improve the association of the latent variables with EF. Data-driven WM TOI from the mixed effects model were replaced by WM hypothesized as more related to both CRF and EF because they connect frontal regions. TOI that connect frontal regions (UNC, CCG, CAB, SLF, ATR, Fmin) loaded on a single factor for WM integrity (KMO = 0.84; Bartlett's test, p < 0.001, standardized loadings = 0.46 – 0.86, variance explained = 50%). Assigning these frontal TOI to a WM latent variable and setting it as bidirectionally related to EF resulted in good model fit Cmin/df = 1.58, CFI = 0.98, RMSEA = 0.04, loadings > 0.40). The latent variable of WM TOI that connect frontal regions did not exhibit a stronger association with EF (r = 0.15, p = 0.01) than the data-driven TOI from the mixed effects modeling. Model fit decreased after adding age and VO_2 max and specifying direct paths to EF (Cmin/df = 2.27, CFI = 0.93, RMSEA = 0.06). Again, the direct path of VO_2 max to EF exhibited no relationship (r = 0.00, p = 0.96).

Supplemental analyses

Bike test failure. Predicted VO_2 max data were unavailable for 20.24% (n = 101) of NKI-RS participants who attempted but were unable to finish the bike test. Exploratory analyses were conducted to understand participant qualities that may have interfered with this submaximal exercise test. Participants who failed the bike test were significantly older (M diff. = 10.17 $_{years}$, t(497) = 5.45, p < 0.001, d = 0.55) and evidenced signs of poorer physical health than those who completed the bike test. Participants who failed the bike test also had significantly weaker grip strength (M diff. = 7.40 $_{kg}$, t(411) = 5.97, p < 0.001, d = 0.75) and self-reported less physical activity (M diff. = 1545.92 $_{total\ MET}$, t(495) = 2.30, p = 0.02, d = 0.40). Bike test failure was

significantly associated with significantly higher pulse (*M* diff. = 3.17 $_{bpm}$, $t(141) = 2.84$, $p = 0.005$, $d = 0.32$) and rates of diabetes mellitus type-II (9.58% diff., $X^2(1) = 13.00$, $p < 0.001$, Cramer's $V = 0.17$) and hypertension (16.68% diff., $X^2(1) = 12.34$, $p < 0.001$, $V = 0.16$). Participants who failed the bike test were significantly more likely to endorse medical illness (22.42% diff., $X^2(1) = 19.49$, $p < 0.001$, $V = 0.20$) and take medications (19.88% diff., $X^2(1) = 11.98$, $p < 0.001$, $V = 0.16$). Physical restrictions, including shorter height (*M* diff. = 5.39 $_{cm}$, $t(157) = 5.18$, $p < 0.001$, $d = 0.58$) and higher rates of arthritis (11.22% diff., $X2(1) = 5.49$, $p = 0.02$, $V = 0.11$), were significantly associated with failing the bike test. Ability to complete the bike test was not significantly associated with body mass index, cholesterol, pain (back, neck), depressive symptoms, integrity of WM TOI, or performance on EF measures ($p > 0.05$).

Younger versus older participants. Given that the CRF-WM relationship was age dependent, supplemental exploratory analyses were conducted to further understand group differences between older and younger participants. Ninety-two percent (91.89%) of older participants were White compared to 70.13% for younger participants (21.76% diff., $X^2(1) = 20.62$, $p < 0.001$, $V = 0.21$). Older participants had nearly one more year of education (*M* diff. = 0.84 $_{year}$, $t(496) = 3.47$, $p < 0.001$, $d = 0.37$) and higher socioeconomic status than younger participants (*M* diff. = 8.79 $_{Hollingshead}$, $t(496) = 7.31$, $p < 0.001$, $d = 0.78$). The age groups did not significantly differ on by sex, English as second language, and handedness ($p > 0.05$).

Older participants had significantly larger waist sizes (*M* diff. = 5.77 $_{cm}$, $t(495) = 3.61$, $p < 0.001$, $d = 0.39$) and higher systolic blood pressure (*M* diff. = 9.34 $_{mmHg}$, $t(494) = 6.31$, $p < 0.001$, $d = 0.68$). Compared to younger participants, older adults had weaker grip strength (*M* diff. = 5.87 $_{kg}$, $t(411) = 4.99$, $p < 0.001$, $d = 0.59$) and self-reported less physical activity (*M* diff. = 1643.02 $_{total\ MET}$, $t(495) = 2.54$, $p = 0.01$, $d = 0.27$). Yet, older participants endorsed lesser

sedentary time per week than younger adults (*M* diff. = 4.17 $_{hr\ sitting}$, $t(493) = 2.37$, $p = 0.02$, $d = 0.25$). The age groups did not significantly differ on body mass index, cholesterol, and pulse (*ps* > 0.05). Most pertinent to this study, older (34.46%, $n = 51$) participants were significantly more likely to fail the bike test than younger (14.24%, $n = 50$) participants (20.22% diff, $X^2(1) = 25.01$, $p < 0.001$, $V = 0.23$). Older adults that failed the bike test had significantly higher body mass index sizes (*M* diff. = 2.28 $_{kg/m^2}$, $t(144) = 2.68$, $p = 0.008$, $d = 0.43$) and lower grip strength (*M* diff. = 6.92 $_{kg}$, $t(119) = 4.76$, $p < 0.001$, $d = 0.91$) than older adults that completed the bike test.

Discussion

The association between VO_2 max and FA found in this study substantiates the neuroprotective benefits of CRF on both local and global WM integrity. The CRF–WM relationship was stronger and more widely distributed in older adults, which supports the age-dependent hypothesis of the influence of CRF on brain structure (Hayes et al., 2015; Hötting & Röder, 2013). Among older participants, CRF was significantly related to stronger whole-brain (*z*-score slope = 0.11) and local WM integrity within five TOI (*z*-score range = 0.14 – 0.20). The CRF–WM relationship was only significant in the cingulum cingulate gyrus (CCG; *z*-score = 0.11) among younger participants and CRF was not associated with global WM. The magnitude of these relationships aligned with previous MRI research (Hayes et al., 2015; Sexton et al., 2016) and remained constant after adjusting for demographics, cardiac health variables, and approximations for physical motivation and effort. Overall, the results align with accumulating evidence that positive lifestyle factors, such as physical activity, promote brain health with advancing age (Fratiglioni et al., 2004; Gorelick et al., 2017; Livingston et al., 2017; Reuter-Lorenz & Park, 2014; Xu et al., 2015). More granularly, this lifespan study advances our understanding of the anatomical specificity of the relationship between CRF and WM.

CRF was significantly associated with stronger WM integrity across the cerebrum. For older participants, every 1 *SD* increase in VO_2 max (17.06 ml/kg/min) was significantly associated with a 0.11 *SD* increase in global WM integrity (0.008 FA). This relationship, while weak, is an optimistic finding within the context of an expected decline in global WM by 0.13 *SD* (0.010 FA) per 17 years of age. This study is only the second to examine the relationship between CRF and global WM using DTI (Sexton et al., 2016) and the first to include a younger subsample. In a large sample of older adults (N = 691), Gow et al. (2012) found that higher self-reported physical activity at age 70 was significantly associated with global FA at 3-year follow-up. This effect (0.10, $p = 0.014$) was nearly identical to the relationship between CRF and global WM found for older adults in the present study (*z*-score slope = 0.11). However, self-report of physical activity was not predictive of WM integrity using NKI-RS data, as interpreted in further detail below. This study complements evidence for the positive association between CRF and WM volume (Benedict et al., 2013; Gow et al., 2012) and supports the notion that CRF makes unique contributions to the microstructural integrity of both local and global WM. The neuroprotective effects of CRF on global WM may reflect broadly-distributed neural enrichment factors, as discussed under the "Potential Mechanisms" subheading below.

CRF-related improvements in WM microstructure were greater during the lifespan phase of expected neurocognitive decline (older age) than a period of relative stability (younger age). The age-dependent hypothesis posits that environmental factors, such as physical and cognitive activity, minimally influence neural architecture during middle age when integrity is typically at their lifetime peak. Conversely, environmental factors exert maximal influence during brain structural and functional changes in childhood (neurodevelopmental) and older age (neurodegeneration) (Chaddock-Heyman et al., 2014; Hayes et al., 2015; Hötting & Röder,

2013). Particularly in the sixth decade and beyond, aging is a major risk factor for MCI and dementia (Flier & Scheltens, 2005), loss of brain volume (Bennett & Madden, 2014; A. M. Fjell et al., 2010; Gunning-Dixon et al., 2009; N. Raz et al., 2010; N Raz et al., 2005b), degradation in microstructure (Bennett & Madden, 2014; Gunning-Dixon et al., 2009; Head et al., 2004; O'Sullivan et al., 2001; Sullivan & Pfefferbaum, 2006; Westlye et al., 2010; Yang et al., 2016), and cardiovascular disease (S. N. Lockhart & DeCarli, 2014). As the balance between risk and protective factors tips toward the former with advancing age, the neuroprotective benefits of a healthy lifestyle become increasingly critical for preventing cognitive decline.

Tract-specific WM Correlates of CRF

Only one WM TOI was significantly associated with CRF when combining younger and older participants. VO_2 max was significantly associated with the cingulum cingulate gyrus (CCG) in the full sample (*z*-score slope = 0.10), albeit comparably weaker than the relationship with CRF found in older age. Reconstructions of the cingulum widely vary among DTI studies (Bubb, Metzler-Baddeley, & Aggleton, 2018); the CCG in this study is the dorsal component of the cingulum bundle that runs along the length of the cingulate gyrus above the splenium (Budisavljevic et al., 2016). In a lifespan analysis of WM integrity, Westyle et al. (2010) found that FA within the dorsal cingulum was highly stable and one of the last TOI to deteriorate. Additionally, evidence from neurodevelopmental studies suggest that the dorsal cingulum exhibits a prolonged microstructural maturation process relative to other WM TOI (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Tamnes et al., 2010; Westlye et al., 2010). The cingulum, with connections to the hippocampus and cingulate cortex, demonstrated "selective preservation" amongst widespread WM degradation in a recent DTI and fMRI study of healthy older adults (Yang et al., 2016). Indeed, the CCG exhibited one of the lowest age associations in

the mixed-effects model (*z*-score slope = -0.09). Perhaps the dorsal cingulum may be more sensitive to CRF, as an indicator of general health across the adult lifespan, than age-related degradation in WM integrity.

Subdividing the mixed model by age group revealed additional regional differences in the relationship between CRF and WM integrity. This study highlights the importance of considering age as an interaction term, as opposed to a covariate, when investigating brain-behavior relationships (Z. Liu et al., 2012; Madden et al., 2012, 2009; Tian et al., 2014). Among older adults, higher VO_2 max was significantly associated with greater integrity of three WM association bundles (*z*-score range = 0.20 – 0.16): the CCG, superior longitudinal fasciculus (SLF), and the inferior longitudinal fasciculus (ILF). The CCG is the most consistently reported WM correlate of CRF in the DTI literature on physical activity (B. Marks et al., 2011; B. L. Marks et al., 2007; Tian et al., 2014; Walther et al., 2010). The CCG projects posteriorly from the cingulate gyrus and terminates in the entorhinal cortex—a critical substrate for memory (Bubb et al., 2018; Schultz, Sommer, & Peters, 2015; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). Previous research has also localized the effects of CRF within the SLF and ILF (Z. Liu et al., 2012; Tseng et al., 2013; Walther et al., 2010). The SLF connects the frontal with the occipital lobe and has connections to posterior regions of the temporal and parietal lobes (Kamali, Flanders, Brody, Hunter, & Hasan, 2014; Schmahmann, Smith, Eichler, & Filley, 2008) and the ILF connects the occipital lobe to anterior temporal regions (Herbet, Zemmoura, & Duffau, 2018). CRF was also significantly associated with WM integrity in the cortico-spinal tract (CST; *z*-score = 0.22), a bundle of projection fibers that connect the brain stem with the motor cortex, somatosensory cortex, and premotor areas (Welniarz, Dusart, & Roze, 2017), and aligned with previous DTI studies of physical activity (Z. Liu et al., 2012; Tseng et al., 2013).

This pattern of findings suggest that CRF may selectively preserve a collection of anterior and posterior WM connections related to visuospatial function, motor control, and coordination (Z. Liu et al., 2012). The midcingulate comprises several motor areas (Brent A. Vogt, Vogt, Farber, & Bush, 2005) and has been linked to motor function (Beckmann, Johansen-Berg, & Rushworth, 2009), pain processing (B. A. Vogt, Sikes, & Vogt, 2009), as well as overlapping processes of attention and motor control (Paus, 2001). The CCG also receives input from the rostral cingulate motor area (Walther et al., 2010), which controls internally selected movements by cognitive control (Buhmann et al., 2005). MRI studies on functional subdivisions of the SLF indicate that the superior parietal lobule (SLF1) regulates higher order motor behavior (e.g., tracking body part locations using internal reference points) while the inferior parietal lobule (SLF2) subserves visuospatial and oculomotor functioning (see Makris et al. 2015 for a review). The ILF is primarily responsible for visually mediated decision-making and behavior (Herbet et al., 2018). Cortical control of the fore- and hindlimbs, including voluntary movements that require skill and flexibility (Martin, 2005), are innervated by the CST (Kamiyama et al., 2015). Exercise-induced demands on brain systems that underpin visuomotor function may promote myelin-related processes that protect local WM integrity from neurodegeneration (Feter et al., 2018).

Predominantly, CRF-related improvements in FA were not localized in TOI most vulnerable to aging. WM TOI that connect frontal regions (Fmin, ATR, UNC, ILF), which I hypothesized would correlate most strongly with CRF, showed significantly decreased FA with advancing age but were not associated with VO2 max. This pattern of microstructural decline confirms that aging primarily disrupts WM connections with frontal regions (Davis et al., 2009; Head et al., 2004; Salat et al., 2005; Sullivan et al., 2010). While anterior WM has been reported

to be more sensitive to age than posterior WM (Burzynska et al., 2010; Hayes et al., 2015; Zahr et al., 2009), the Fmaj, a posterior commissural fiber bundle, was the only TOI that correlated with both CRF and age. Integrity of the splenium, the posterior end of the corpus callosum and midpoint of the Fmaj, is correlated with motor function (Zahr et al., 2009) and exercise and declines with aging (Yang et al., 2016). One interpretation of this set of associations is that CRF fortifies the Fmaj by recruiting a complex system of interhemispheric WM to integrate multiple motor functions with speed and dexterity required during exercise. Further extrapolating the findings, enhanced WM integrity from CRF may delay age-related or neurodegenerative disruption in neural networks that support cognitive functioning (Davis et al., 2009; Head et al., 2004; Kennedy & Raz, 2009; O'Sullivan et al., 2001; Salat et al., 2010).

Potential Mechanisms of CRF on Brain Microstructure

Improved vasculature and cerebral perfusion in CRF is thought to strengthen WM structure via enhanced oxygen and nutrient delivery (Sexton et al., 2016). Aerobic exercise protects against cerebrovascular damage by improving arterial wall integrity, reducing arterial stiffness, and decreasing blood pressure (McDonnell et al., 2013). MRI angiography studies show that CRF is associated with an increased number of small blood vessels among older adults (Bullitt et al., 2009) and greater capillary density in animal models (Y. H. Ding et al., 2006; Swain et al., 2003). Aging is associated with significantly decreased supply (cerebral metabolic rate of oxygen) and increased demand (cerebral blood flow) of oxygen in the brain, which results in diminished venous blood oxygenation (Lu et al., 2011). Cerebral hypoperfusion has been identified as a population-based marker of accelerated cognitive decline and greater risk for dementia (Wolters Frank J. et al., 2017). Increased cerebral blood flow with CRF may be a critical process for preventing cerebrovascular pathology in the aging brain and occurrence of

dementia (Baker et al., 2010; Cotman & Berchtold, 2002; Radak et al., 2010), particularly given the increased risk for arterial stenosis and ischemia (Lu et al., 2011).

CRF is hypothesized to particularly influence distal vasculatures, also known as "watershed" or "border zone", in parietal and medial temporal regions of the brain (Tian et al., 2016). Distal branches, which are located at the end of circulation and receive dual blood supply from major arteries, are highly susceptible to changes in blood oxygen levels (Lu et al., 2011; Marchal et al., 1992). Figure 26 presents classification of brain infarcts that occur in distal regions, which account for approximately 10% of all brain infarcts, adapted from Mangla, Kolar, Almast, and Akholm (2011). Lu et al. (2011) found significantly lower cerebral blood flow in the prefrontal cortex, insular cortex, and caudate with aging. These regions, which support cognitive functions that tend to decline in aging (executive control and memory), are highly susceptible to changes in blood oxygenation levels (Bladin, Chambers, & Donnan, 1993). This may explain why the beneficial effects of CRF on brain macrostructure have been most frequently localized in the prefrontal cortex and medial temporal lobe (Alosco et al., 2013; S. J. Colcombe et al., 2003, 2006; Erickson et al., 2014, 2009; McAuley et al., 2011; Weinstein et al., 2012). (Figure 26 here)

CRF-related increases in FA, at both global and local microstructure, can be thought of in the context of brain compensatory processes such as neural scaffolding and cognitive reserve (Gelfo et al., 2018; Reuter-Lorenz & Park, 2014). The cognitive reserve hypothesis posits that lifestyle and inherent factors, such as exercise, education level, IQ, and socioeconomic status, can enhance coping (i.e., not exhibit cognitive or behavioral symptoms of dementia) with advancing brain pathology in senescence by preserving brain structure and function (Richards & Deary, 2005; Stern, 2002). Neuroimaging findings suggest that intra-individual differences in

reserve factors, including CRF and education, may make unique contributions to preserved cognitive functioning through separable effects on brain structure in old age (Gordon et al., 2008). Figure 27 presents a comprehensive model of brain compensatory processes, including neural scaffolding and cognitive reserve, adapted from Reuter-Lorenz and Park (2014). The cognitive reserve hypothesis predicts that higher CRF, as a neural enrichment factor, enhances brain structure and function, which in turn predicts preserved cognitive functioning with aging. The Reuter-Lorenz and Park (2014) model also incorporates physical activity as a "compensatory scaffolding" factor that can counteract the deleterious effects of age-related neural and cognitive decline. (Figure 27 here)

The positive relationship between CRF and WM in this study likely reflect a complex interaction of neurobiological factors that influence brain structure across the lifespan. Perhaps the most compelling CRF-related reserve mechanism is associated with increased expression of brain-derived neurotrophic factor (BDNF) (Sexton et al., 2016). BDNF plays a critical role in neurogenesis through synaptic plasticity (Cao et al., 2007), regenerating damaged axons (Mamounas et al., 2000), and age-related neuronal damage from ischemia and hypoxia (Cheng, Gidday, Yan, Shah, & Holtzman, 1997). BDNF may have a specific neuroprotective effect on WM: it has been linked to increased WM volume in a neurologic sample (Weinstock-Guttman et al., 2007) and used a marker for neuroplasticity in cognitive aging (de Lange et al., 2016). A recent meta-analysis concluded that moderate, continuous exercise could enhance myelin sheath regeneration (Feter et al., 2018). Exercise may also be neuroprotective by increasing insulin sensitivity and counteracting age-related decline in adenosine triphosphate production and mitochondrial oxidative capacity (Halter et al., 2014).

Implications for Cognitive Aging and Neurodegeneration

The potential for CRF to enhance WM integrity has several important implications related to cognitive aging. WM disruption, through demyelination, axonal degradation, and gliosis (Assaf, 2008; Beaulieu, 2002; Lebel et al., 2008), may precede cognitive and functional decline (Amieva et al., 2005; Bennett & Madden, 2014; Grober et al., 2008; Jedynak et al., 2012). Generally, DTI studies reveal widespread decreases in WM microstructure (Bennett & Madden, 2014; Gunning-Dixon et al., 2009; Head et al., 2004; O'Sullivan et al., 2001; Sullivan & Pfefferbaum, 2006; Yang et al., 2016); specifically, reduced FA in aging is associated with the loss of axonal and myelin integrity (Bennett et al., 2010; Burzynska et al., 2010). Age-related alterations in WM may correlate with changes in brain macrostructure, such as gray matter atrophy (Andrews-Hanna et al., 2007; Sullivan & Pfefferbaum, 2007). Conversely, CRF-related increases in FA suggest improved signal transmission between gray matter structures and closer integration of functional networks (Kennedy & Raz, 2009; Liston et al., 2006; Perry et al., 2009; Tuch et al., 2005; Zahr et al., 2009). A systematic review of DTI studies suggests that increased FA has a positive influence on a range of brain–behavior relationships in cognitive aging (for a comprehensive review, see Bennett & Madden, 2014).

The positive influence of CRF on WM was found in tracts that degrade in dementia, including cingulum (B. Ding et al., 2008; Fellgiebel et al., 2008; Rose et al., 2000; Y. Zhang et al., 2007) and splenium of the corpus collosum (Bozzali et al., 2002; Naggara et al., 2006; Sydykova et al., 2007; Yamauchi et al., 2000) with Alzheimer's disease, ILF in semantic dementia (Acosta-Cabronero et al., 2011; Agosta et al., 2010), as well as frontotemporal (Borroni et al., 2007) and Parkinson's dementia (Kamagata et al., 2013) in the SLF. Significantly lower FA values have been found in the splenium, cingulate, and SLF among MCI patients (B. Parente et al., 2008; Cho et al., 2008; Stahl et al., 2007; Y. Zhang et al., 2007). WM integrity has been

investigated as a biomarker for MCI and dementia (Bendlin et al., 2010; Lim, Park, Jang, Park, & Kim, 2014; Wu et al., 2015) and FA deserves equal attention as a possible signal for neuroprotection. Tracts that are susceptible to both CRF and neurodegeneration are ideal sites to further investigate the interaction between risk and resiliency factors in the aging brain.

The connection between CRF and WM related to visuomotor control paths highlight additional benefits of previous exercise on physical functioning. Aging is associated with a loss of CST connectivity and atrophy in the motor cortex that contributes to disability and functional dependence (Clark & Taylor, 2011; Rantanen et al., 1999). Cross-sectional and longitudinal studies have linked gait disturbances and falls to the disruption of WM integrity (Baezner et al., 2008; Camicioli, Moore, Sexton, Howieson, & Kaye, 1999; de Laat et al., 2011; Guttmann et al., 2000). WM changes in the CST have been identified in neurological disorders, such as stroke (Puig Josep et al., 2013; Schaechter et al., 2009), Parkinson's disease (S.-J. Lee et al., 2010; Silbert & Kaye, 2010), and multiple sclerosis (Pawlitzki et al., 2017; Reich et al., 2008). Fortunately, growing evidence suggests that physical activity exerts a positive influence on markers of CST health (Hassanlouei, Sundberg, Smith, Kuplic, & Hunter, 2017; Hou et al., 2015; W. Zhang et al., 2019). Ameliorating age-related decline of the neuromuscular system could mitigate loss of coordination, muscle strength, and fatigue resistance (Srikanth et al., 2009; Starr et al., 2003; Wakefield et al., 2010). These faculties are critical for maintaining independence in performing activities of daily living.

Although CRF was linked to enhanced WM structure with aging, the neuroprotective effects of CRF were not directly observed on measures of neurocognitive function. This study focused on EF because it is the most consistent cognitive correlate of CRF (Ahlskog et al., 2011; S. Colcombe & Kramer, 2003; P. J. Smith et al., 2010; Tian et al., 2016), relates to FA in older

adults (Nowrangi et al., 2015), declines with age (Harada et al., 2013; S. Lockhart et al., 2014; Salthouse, 2011), and was thoroughly assessed by the D-KEFS and CNB in the NKI-RS. The significant, albeit weak, association between WM and EF latent variables provided initial validation of the measurement model; however, the direct path from VO_2 max to EF was not significant. Lack of mediation persisted despite multigroup analysis (young versus old). In this study, the variance explained by the EF latent variable was poor (34%) and the D-KEFS has been criticized for inadequate reliability (Strauss et al., 2006), both of which may have suppressed a relationship with VO_2 max. The EF latent variable fell within range of the variance explained by a single factor EF (20–48%) reported in healthy samples (Colom, Rebollo, Abad, & Shih, 2006; de Frias, Dixon, & Strauss, 2006; R.A. Mace, Waters, Sawyer, Turrisi, & Gansler, 2019) and below estimates (e.g., 78%) in clinical samples (Gansler, Huey, Pan, Wasserman, & Grafman, 2017), suggesting that EF paradigms may be more meaningful in the latter (Abigail B. Waters, Swenson, & Gansler, 2018). The results are congruent with meta-analyses on aerobic exercise interventions (Brasure et al., 2018; Young et al., 2015) and cross-sectional studies (Etnier, Nowell, Landers, & Sibley, 2006) that failed to substantiate a link between CRF and improved cognition among healthy older adults. Perhaps the greatest benefit of CRF on cognition is reducing age-related or pathological decline and that longitudinal studies with longer follow-ups are better suited to detect its neuroprotective effects (Aichberger et al., 2010; Bherer et al., 2013). Studies that include a measure of cognitive stimulation, such as Wirth et al. (2014), are better positioned to assess the positive impact of lifestyle activity on EF with aging.

Nevertheless, the results confirm that preserved WM integrity is important for neurocognitive functioning. In the structural equation model, WM TOI that correlated with CRF also showed a small, positive association with EF ability. EF tasks from the D-KEFS and CNB

were designed to assess frontal systems, but likely recruit multiple regions across a frontal–parietal network (Collette et al., 2005). Processing speed and working memory are significantly associated with WM integrity both globally (Borghesani et al., 2013; Chopra et al., 2018; Kennedy & Raz, 2009; Penke et al., 2010) and locally within anterior TOI (Sasson et al., 2013), which was likely evident on the timed components of several EF measures used in this study. Decreased integrity of anterior WM is associated with decline in processing speed and EF in cognitive aging (Charlton et al., 2006; Anders M. Fjell et al., 2017; Grieve, Williams, Paul, Clark, & Gordon, 2007; Madden et al., 2009) and neurodegeneration (Nowrangi et al., 2015). The potential for CRF to enhance WM integrity in the dorsal cingulate is noteworthy because this TOI has been linked to EF performance (Bubb et al., 2018), particularly cognitive control in cognitive aging and MCI (Metzler-Baddeley et al., 2012). Localization of CRF in the SLF is notable because WM integrity in this TOI is associated with higher-order EF (Sasson et al., 2013) and cognitive decline in patients with cardiac risk (Li et al., 2015). Researchers and clinicians should continue to explore the impact of CRF on cognition through other paths such as reducing vascular burden, promoting psychological health, and maintaining functional independence with advancing age.

Contributions to Brain Health

Health care professionals often encourage patients to exercise and physical activity has become a treatment recommendation for people with cognitive disorders (American Academy of Neurology, 2017)—but who is most likely to benefit? In contrast with previous research (S. Colcombe & Kramer, 2003; Sen et al., 2012; Sexton et al., 2016), the neuroprotective effects of exercise in this study were not moderated by demographic variables. Aerobic exercise offers a low-cost and easily disseminated prevention and treatment intervention for improving

cardiovascular and cerebrovascular health. Although medical conditions may limit exercise, such as increased frailty with aging, a wide variety of physical activity modalities allow for feasibility at any age. CRF is a modifiable lifestyle factor in which an individual can become actively involved in reducing their own risk for MCI or dementia. While the neuroprotective benefits of exercise were observed mostly in older age, younger readers are equally encouraged to establish active lifestyles. Population based studies suggest that the risks for cognitive decline emerge in midlife (Andel et al., 2008; Baumgart et al., 2015; Geda et al., 2010; Hamer & Chida, 2009; Xu et al., 2015) and that the cerebrovascular benefits of CRF in mid-life accrue over the lifetime (Ahlskog et al., 2011; Barnes & Yaffe, 2011). Questions still remain on the optimal management of cardiovascular risk factors with respect to preventing late-life cognitive decline or the brain injury that precedes it (Baumgart et al., 2015; Carmichael, 2014). Greater specificity on the "therapeutic window" of CRF on brain health is needed to determine when it is most important to prescribe" aerobic exercise.

While *importance* of exercise as a brain healthy behavior is increasing among the general public, *motivation* remains low. Society is increasingly knowledgeable about the role of vascular and lifestyle risk factors in cognitive decline (Schroeder et al., 2012). Yet, persuading the population to exercise remains difficult. Only 7% of patients with cardiovascular risk factors meet treatment goals established by their healthcare providers. Older adults are less likely to meet cardiovascular health guidelines set by the American Heart Association; greater than 60% of Americans older than 60 have ≤ two cardiovascular health metrics at ideal levels (Benjamin et al., 2017). In a large (N = 1,003) cross-sectional survey of adults (ages 20 to 75), 41.5% of respondents believed it is possible to lower one's risk for dementia (B. J. Smith, Ali, & Quach, 2014); however, only 26.9% were *very confident* that they could accomplish this. Indeed, 31.3%

of adult respondents in the Smith et al. (2014) survey identified physical activity as a beneficial option for reducing dementia. A combination of barriers likely explain why less than one quarter of adults in the US meet recommended guidelines for aerobic exercise (US Department of Health and Human Services, n.d.). In addition to its physical demands, exercise may be linked to negative emotions and memories (embarrassment, performance anxiety, shame). Sedentariness is often equated to characterological flaws (e.g., laziness) and is promoted by both biological (i.e., conserving energy) and societal forces (e.g., screen time). Establishing a fitness routine may become more challenging with age due to executive difficulties, social isolation, multimorbidity, and disability (Riegel et al., 2017). In the NKI-RS, half of participants' self-report of recent vigorous physical activity fell within the "low" category (IPAQ Group, 2005).

Psychologists with expertise in behavioral medicine and neuropsychology are well-placed to promote exercise among patients in the context of cognitive aging. Evidence-based strategies such as goal-setting, self-monitoring, planning, and feedback enhance the effectiveness of lifestyle modification interventions (Janssen, De Gucht, Dusseldorp, & Maes, 2013; Tuso, 2015). A holistic approach that incorporates these techniques is often required to address the co-morbidity of problematic health behaviors. Systematic reviews support the effectiveness of motivational interviewing to promote exercise alongside diet (Martins & McNeil, 2009) and cardiovascular risk factors (Knight, McGowan, Dickens, & Bundy, 2006). Innovative behavioral strategies, such as digital monitoring devices (IBHCRP, n.d.), telehealth coaching, and gamification (Cattaneo et al., 2018), have the potential to both reinforce exercise and identify determinants of activity through passive monitoring. Based on direct clinical experience leading the *My Healthy Brain* group at *Massachusetts General Hospital,* patients are highly interested in evidence-based psychosocial programs designed to reduce familial risk of MCI and dementia.

Individualized programs are promising and warrant clinical trials of their ability to promote brain health (Hellmuth, Rabinovici, & Miller, 2019). Initial multidomain interventions resulted in significant reductions in cognitive decline (Ngandu et al., 2015; SPRINT MIND Investigators for the SPRINT Research Group et al., 2019).

Population-based evidence from surveys (Cations, Radisic, Crotty, & Laver, 2018) and web searches for brain supplements (see Figure 28) indicate that knowledge of dementia prevention is poor. Pseudomedicine for dementia is rapidly growing (Hellmuth et al., 2019) and the responsibility of health care professionals to disseminate evidence-based brain health interventions is more important than ever. Coordination among public health organizations is needed to champion population-targeted exercise recommendations (World Health Organization, 2007) and public education on brain health behaviors (National Acadamies of Sciences, 2017). A recent call to action by UsAgainstAlzheimer's (2019) urges the U.S. health care system to arm medical providers with lifestyle and risk-reduction strategies. Hopefully, the role of CRF on brain health underscored herein will highlight the timeliness of exercise and enhance the persuasiveness of psychoeducational materials that promote a more active lifestyle. (Figure 28 here)

Notable Caveats and Limitations

Supplemental analyses suggest the two potential caveats to the CRF–WM relationship observed in the NKI-RS. With respect to CRF measurement, 20.24% (n = 101) of eligible participants attempted but were unable to pedal the stationary bicycle at 70 RPM for the full six minutes. While the reasons were not documented in the NKI-RS data, missing bike test data appeared non-random. Participants that failed the bike test were ten years older on average, had more cardiovascular risk factors, and endorsed a less active lifestyle. Various physical

limitations, including significantly shorter height, higher rates of arthritis, and lower strength, may have further restricted the accessibility of bike testing. Submaximal exercise testing was selected to circumvent these barriers to participation (Noonan & Dean, 2000). The empirical cumulative distribution of VO_2 max scores did not indicate a floor effect and bike test failure was not associated with WM integrity of EF. Nevertheless, CRF analyses were likely constrained by physical ability because successful completion of the bike test intrinsically represented a feat of fitness. High attrition and failure to include participant dropout in analyses are common limitations in aerobic intervention studies (Begley, 2018; Brasure et al., 2018). Consequently, survival bias may confound objective physical fitness measures, including the bike test in the present study. Including the IPAQ, which was completed by all NKI-RS participants, helped address missing data; however, it failed to serve as a valid alternative to VO_2 max. The estimation of CRF may be improved in future lifespan studies by including long-term exercise assessments and scaling the difficulty of fitness testing based on participant characteristics associated with bike test failure as identified above. For example, the six-minute walk test (American Thoracic Society, 2002) and/or digital monitoring devices (Paul et al., 2015) are safe alternatives for assessing CRF in older and less physically active adults. Actigraphy data was collected in the NKI-RS but it was used to track sleep and not steps.

Repeating the mixed-effects model with IPAQ data served to include all NKI-RS participants in the analysis regardless their ability to complete the bike test. One advantage of self-report questionnaires over VO_2 max measurement is that its fitness estimates are derived from non-exercise data, which is low-cost and offers an alternative to tests of exertion. This was the first DTI study of CRF to compare both fitness measurement methods. As hypothesized, a performance-based CRF test was a stronger predictor of WM integrity than self-reported

physical activity. MET scores for both vigorous and moderate physical activity on the IPAQ were not significantly associated with global or local WM integrity. In the Sexton et al. (2016) systematic review, MRI studies are evenly split in their use of performance-based and self-report measurement of physical fitness; both methods have yielded mixed associations with WM integrity. Validity checks of IPAQ data in the NKI-RS revealed high positive skew and kurtosis, as well as evidence of poor construct validity. The modest association between VO_2 max and vigorous MET on the IPAQ (r_p = 0.23) aligned with previously reported correlations between CRF and self-reported physical activity (Craig et al., 2003). Both overestimation (e.g., social desirability, lower education levels) and underestimation (e.g., failure to account for low-intensity activities, misremembering) may contribute to inaccurate accounting of physical activity via self-report (W. Brown et al., 2004; Erickson et al., 2014; Fogelholm et al., 2006). Furthermore, the IPAQ assessed activity within the last week, which may be less sensitive to WM integrity than long-term exercise measurements.

An additional caveat to the CRF–WM relationship in this study is the possibility of sampling bias by age group in NKI-RS participants. To prevent cohort effects, NKI implemented zip code-based recruitment within a US-representative county and monitored enrollment based on demographics. Yet, supplementary analyses suggest that the older subsample was disproportionately White, had higher SES, and endorsed fewer sedentary time per week than the younger participants. Compared to younger participants, older adults recruited by NKI-RS may have been more physically active for their age and possessed greater motivation to participate in laboratory research. Older adults were less likely to complete the bike test than younger participants—those that did had significantly lower body mass index and higher grip strength. Consequently, the observed CRF-WM relationship may be more generalizable to “healthy agers”

than the activity levels maintained by typical community-dwelling older adults. Further research that prioritizes patient sampling across the health–illness spectrum is needed to advance our understanding of CRF as a neuroprotective factor with aging. In addition to performance-based CRF tests, such studies should administer measures of sustained cognitive stimulation to compare the neuroprotective benefits of an active lifestyle, both physical and intellectual.

In addition to these caveats, several study limitations warrant consideration in light of the findings. First, causality in the CRF-WM relationships cannot be inferred because cross-sectional data from NKI-RS were analyzed. While CRF likely enhances cerebrovasculature via the mechanisms discussed herein, it is also plausible that one's ability to exercise is incumbent on WM integrity (Sexton et al., 2016; Tian et al., 2016). The absence of longitudinal data and exclusion of adults with neurodegenerative disease preclude evaluations of CRF, compared to other cardiovascular risk factors, in the secondary prevention of MCI and dementia. Effect size estimates for brain-behavior relationships in clinical neuropsychology are often weaker in community samples compared to clinical populations (Ryan A. Mace, Waters, Sawyer, Turrisi, & Gansler, 2018; Pan, Sawyer, McDonough, Slotpole, & Gansler, 2018). Second, without an aerobic intervention, this observational study is unable to help reconcile the mixed literature on whether changes in CRF can prevent age-related decline in cognition and microstructure. While this study bolsters common recommendations by health care professionals to increase patients' CRF, questions still remain about the optimal timing and dosage of aerobic exercise to enhance brain health. Participants' exercise regimens were not directly assessed and the relationship between IPAQ and VO_2 max was too weak to identify the most beneficial forms of activity. Fourth, the younger and older subsamples were determined based on previously reported lifespan trajectories of FA (Westlye et al., 2010), neurocognitive function (Salthouse, 2011), and

prevalence of cardiovascular risk factors (DeCarli et al., 2005). Larger lifespan samples are needed to derive data-driven breakpoints for age in the relationship between WM and CRF. Fifth, while FA is highly sensitive to the influence of age and neuropathology on WM, it is not specific to the underpinnings of such microstructural changes (Alexander et al., 2007). Signal may be influenced by axonal density and organization, membrane permeability, or myelination (Jones, Knösche, & Turner, 2013). FA, the most commonly reported DTI metric in WM studies of physical activity, should be interpreted judiciously. Future research is encouraged to separate differential effects of CRF on MD, RD, and AD. Finally, I was unable to control for family history and genetic risk, which has been found to interact with both WM integrity (Persson et al., 2006) physical activity in aging (J. C. Smith et al., 2016). It also important that future studies assess non-cardiac brain health factors (e.g., sleep, nutrition, socialization) given their increasing role in behavioral medicine interventions for brain health.

Conclusion

In spite of these caveats and limitations, this study several has defining features that bolster its scientific contribution. First and foremost, this study addressed three of five gaps in MRI research on the CRF-WM relationship identified by Sexton et al. (2016): (1) tract specificity, (2) age-dependency, and (3) whether neuroprotective effects translate to enhanced cognition. Second, this was the largest DTI study of CRF on the aging brain by nearly two-fold and included community-dwelling adults age 20 to 85. This lifespan sample provided a fuller picture of CRF on the aging brain compared to previous research that only included older adults (e.g, Tian et al., 2014) or excluded middle age (e.g., Hayes et al., 2015). Third, NKI-RS allowed for a multimodal analysis of demographic, neuroimaging, physiological, and cognitive data in the link between CRF and WM integrity. Fourth, this is the first study to simultaneously estimate

the hierarchical organization of the CRF–WM relationship at the global and local microstructural levels. Mixed-effects modeling of VO_2 max and DTI data provided a robust method for identifying WM neural correlates of CRF while accounting for demographics, cardiac health, and physical effort variables. Finally, this was the first study to compare objective and subjective measurement of fitness. The results add to growing cross-sectional evidence that CRF is more consistently related to brain structure than self-report of physical activity (Erickson et al., 2014).

Public concerns about developing Alzheimer's disease or related dementia are widespread and increasing (Kessler, Bowen, Baer, Froelich, & Wahl, 2012; MetLife Foundation, 2011; Tang et al., 2017), particularly among those aged 60 and over (B. J. Smith et al., 2014). At the same time, there is growing interest in the role of modifiable risk factors in preventing cognitive decline and promoting healthy aging. The recent availability and popularity of wearable technology (Llamas, Ubrani, & Shirer, 2017) and use of fitness tracking among older adults (AARP Project Catalyst, 2014; Tedesco, Barton, & O'Flynn, 2017) suggests growing interest in meeting personalized health goals and monitoring physical activity. Exercise is a critical self-care behavior with undeniable health benefits that extend beyond the brain. Improved awareness of vascular risk factors and healthier lifestyle choices among adults may underlie recent decreases in new cases of cardiovascular disease and dementia (Langa et al., 2008; Larson et al., 2013; Santos et al., 2017). The current findings offer hope by highlighting the importance of experience-based factors in the promotion of brain health across the lifespan.

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Table 1

Descriptive statistics of demographics and participant characteristics

Variable	Category	*n*	*%*	*M*	*SD*	*Min*	*Max*	*Skew*	*Kurtosis*
Age		499		48.59	17.22	20	85	0.05	-1.09
Education		498		15.68	2.28	9	24	0.18	0.17
SES		498		47.46	11.78	14	75	-0.64	-0.04
Sex	Female	331	66.33%						
	Male	168	33.67%						
Ethnicity	Non-Hispanic	444	88.98%						
	Hispanic	53	10.62%						
	Missing	2	0.40%						
Race	White	372	74.55%						
	Black	83	16.63%						
	Asian	25	5.01%						
	American Indian	3	0.60%						
	Other	13	2.60%						
	Missing	3	0.60%						
Language	English	463	92.79%						

	ESL	32	6.41%
	Missing	4	0.80%
Handedness	Right	448	89.78%
	Non-right	43	8.62%
	Missing	8	1.60%

Note. Socioeconomic status (SES), English as a second language (ESL)

Table 2

Descriptive statistics for CRF and other physical activity variables

Measure	*n*	*M*	*SD*	*Med*	*Min*	*Max*	*Skew*	*Kurtosis*
Complete bike test	398 (79.76%)							
VO_2 max (*ml/kg/min*)	398	45.44	17.06	41.47	19.25	90.00	0.98	0.34
Grip strength (*kg*)	412	27.75	9.85	25.55	8.80	66.80	1.09	1.20
Sedentary (*hrs/wk*)	495	29.26	16.47	28.00	0.00	77.00	0.62	0.20
Working MET	497	1971.60	4854.65	0.00	0.00	47103.00	4.10	22.69
Transport MET	497	858.38	1661.26	247.50	0.00	14900.00	3.97	20.92
Domestic MET	497	2584.21	4012.48	1260.00	0.00	38640.00	4.16	25.62
Leisure MET	497	1871.60	3061.13	798.00	0.00	26296.00	3.80	20.33
Walking MET	497	2038.76	3089.88	891.00	0.00	25196.00	3.09	12.87
Moderate MET	497	2964.13	4451.29	1440.00	0.00	39120.00	3.83	20.37
Vigorous MET	497	2282.90	4813.02	240.00	0.00	41280.00	4.10	21.66
Total MET	497	2059.82	6047.17	0.00	0.00	55472.00	4.84	29.34

Note. Maximal oxygen uptake (VO_2 max), metabolic equivalent of task (MET) based on the International Physical Activity Questionnaire (IPAQ).

Table 3

Descriptive statistics for EF measures

Measure	*n*	*M*	*SD*	*Med*	*Min*	*Max*	*Skew*	*Kurtosis*
TMT	484	81.18	38.5	72	25	240	2.03	4.91
DF	481	8.03	2.67	8	0	15	0.03	-0.10
CWI	473	55.05	14.07	53	29	120	1.25	2.81
Tower	483	16.07	4.11	16	2	27	-0.53	0.59
N-back	480	0.02	0.01	0.02	0	0.03	-0.35	0.47
PCET	490	0.19	0.09	0.19	0	0.38	-0.07	-1.14

Note. Penn Conditional Exclusion Test (PCET) and n-back (2-back trial) from the Penn Computerized Neurocognitive Battery (CNB) and Design Fluency Test, (DF), Color Word Interference Test (CWI), Tower Test, and Trail Making Test (TMT) from the Delis-Kaplan Executive Function System (D-KEFS).

Table 4

Descriptive statistics for FA by WM TOI

TOI	*n*	*M*	*SD*	*Med*	*Min*	*Max*	*Skewness*	*Kurtosis*
ATR	465	0.30	0.03	0.30	0.16	0.42	-0.01	0.12
CAB	465	0.20	0.03	0.20	0.11	0.30	-0.26	1.05
CCG	465	0.32	0.05	0.32	0.14	0.45	-0.09	-0.32
CST	465	0.33	0.03	0.33	0.25	0.42	0.15	-0.55
Fmaj	463	0.44	0.08	0.44	0.14	0.64	-0.51	0.08
Fmin	465	0.36	0.06	0.36	0.13	0.51	-0.90	1.56
ILF	464	0.32	0.05	0.32	0.19	0.47	0.09	0.07
SLF	465	0.33	0.04	0.33	0.22	0.45	-0.09	-0.05
UNC	465	0.28	0.04	0.28	0.14	0.37	-0.30	0.78

Note. White matter (WM) tracts of interest (TOI): anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), corpus collosum forceps minor (Fmin), corpus collosum forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

Table 5

Descriptive statistics for cardiovascular and other health variables

Measure	*n*	*M*	*SD*	*Med*	*Min*	*Max*	*Skew*	*Kurtosis*
BMI (kg/m^2)	497	28.11	5.75	27.28	16.26	50.96	0.82	0.83
Blood pressure ($mmHg$)	496	117.68	14.23	118	78	188	0.61	1.94
Pulse (bpm)	497	66.88	9.3	66	40	102	0.25	-0.05
Creatine (mg/dL)	379	0.87	0.21	0.8	0.5	2.3	1.97	8.04
T. Bilirubin (mg/dL)	379	0.54	0.44	0.5	0.1	6.9	8.77	118.85
Hemoglobin (g/dL)	371	13.56	1.86	13.6	3.19	17.6	-2.35	10.03
LDL (mg/dL)	375	113.39	34.96	110	26	219	0.5	0.02
HDL (mg/dL)	375	62.36	17.58	61	26	130	0.71	0.95
High cholesterol	150 (30.01%)							
HTN	106 (21.24%)							
HoTN	47 (9.42%)							
DM-II	26 (5.21%)							
HVD	13 (2.61%)							
CAD	10 (2.00%)							
MI	7 (0.60%)							

Note. Body mass index (BMI), low density lipoprotein (LDL), high density lipoprotein (HDL), hypertension (HTN), hypotension (HoTN), diabetes mellitus type-II (DM-II), heart valve disease (HVD), coronary artery disease (CAD), myocardial infraction (MI).

Table 6

Summary of the mixed-effects model for VO_2 max predicting WM integrity (FA)

Predictor	*Sum sq*	*Mean sq*	*Num df*	*Den df*	*F-value*	*P-value*
Age	6.40	6.45	1	385	12.97	< 0.001
TOI	0.20	0.02	8	3080	0.05	1.000
VO_2 max	0.60	0.59	1	385	1.20	0.275
Age x TOI	42.10	5.27	8	3080	10.59	< 0.001
Age x VO2 max	1.70	1.68	1	385	3.39	0.066
TOI x VO2 max	5.60	0.70	8	3080	1.40	0.191
Age x TOI x VO2 max	9.00	1.12	8	3080	2.25	0.021

Note. Maximal oxygen uptake (VO_2 max), fractional anisotropy (FA), white matter (WM) tracts of interest (TOI). Sum of squares (Sum sq), mean square (Mean sq), numerator (Num df) and denominator (Den df) degrees of freedom.

Table 7

Full results for the age x WM TOI x VO_2 max interaction predicting FA

Subgroup	*TOI*	*Slope*	*Lower CI*	*Upper CI*
Younger	CCG	0.105	0.004	0.205
	SLF	0.094	-0.007	0.194
	Fmaj	0.070	-0.030	0.171
	CST	0.058	-0.043	0.158
	ILF	0.049	-0.052	0.150
	CAB	0.006	-0.095	0.107
	UNC	0.005	-0.096	0.106
	ATR	-0.001	-0.102	0.100
	Fmin	-0.013	-0.114	0.088
Older	CCG	0.195	0.066	0.323
	CST	0.193	0.064	0.321
	SLF	0.179	0.051	0.307
	ILF	0.163	0.035	0.291
	Fmaj	0.144	0.015	0.272
	ATR	0.077	-0.051	0.206
	UNC	0.064	-0.064	0.192
	Fmin	0.039	-0.089	0.168
	CAB	-0.055	-0.183	0.073

Note. Slopes and 95% confidence intervals (CI) from the age x white matter (WM) tracts of interest (TOI) x VO_2 max interaction. Z-score slopes are VO_2 max over fractional anisotropy.

White matter (WM) tracts of interest (TOI): anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), corpus collosum forceps minor (Fmin), corpus collosum forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

Table 8

Summary of the controlled mixed-effects model predicting WM integrity (FA)

Predictor	*Sum sq*	*Mean sq*	*Num df*	*Den df*	*F-value*	*P-value*
Age	1.90	1.86	1	293	3.59	0.059
TOI	6.50	0.81	8	2454	1.57	0.129
VO_2 max	0.80	0.78	1	293	1.50	0.222
Race	3.80	0.95	4	293	1.84	0.122
SES	0.30	0.31	1	293	0.59	0.442
Sex	0.40	0.39	1	293	0.75	0.386
DM-II	0.10	0.11	1	293	0.21	0.647
BMI	5.00	5.03	1	293	9.71	0.002
Cholesterol	0.10	0.15	1	293	0.28	0.594
Blood pressure	0.40	0.37	1	293	0.72	0.397
Walking MET	0.00	0.00	1	293	0.00	0.945
Sedentary time	0.30	0.33	1	293	0.64	0.425
Activity control	1.20	1.20	1	293	2.31	0.129
Grip strength	0.00	0.03	1	293	0.06	0.802
Age x TOI	44.00	5.50	8	2454	10.62	< 0.001
Age x VO2 max	2.30	2.30	1	293	4.44	0.036
TOI x VO2 max	9.10	1.14	8	2454	2.20	0.025
Age x TOI x VO2 max	7.50	0.93	8	2454	1.80	0.072

Note. Maximal oxygen uptake (VO_2 max), white matter (WM) tracts of interest (TOI), socioeconomic status (SES), diabetes mellitus type-II (DM-II), body mass index (BMI), metabolic equivalent of task (MET) based on the International Physical Activity Questionnaire

(IPAQ). Sum of squares (Sum sq), mean square (Mean sq), numerator (Num df) and denominator (Den df) degrees of freedom.

Table 9

Summary of the mixed-effects model for self-reported physical activity predicting WM integrity

Predictor	*Sum sq*	*Mean sq*	*Num df*	*Den df*	*F-value*	*P-value*
Age	6.082	6.0824	1	459	12.13	< 0.001
TOI	0.089	0.0111	8	3669.1	0.02	1.00
IPAQ	0.009	0.0086	1	459	0.02	0.90
Age x TOI	49.81	6.2263	8	3669.1	12.41	< 0.001
Age x IPAQ	0.086	0.0855	1	458.9	0.17	0.68
TOI x IPAQ	2.882	0.3603	8	3669.1	0.72	0.68
Age x TOI x IPAQ	1.676	0.2095	8	3669	0.42	0.91

Note. Self-reported vigorous metabolic equivalent of task (MET) on the International Physical Activity Questionnaire (IPAQ). The integrity of white matter (WM) tracts of interest (TOI) was measured in fractional anisotropy (FA). Sum of squares (Sum sq), mean square (Mean sq), numerator (Num df) and denominator (Den df) degrees of freedom.

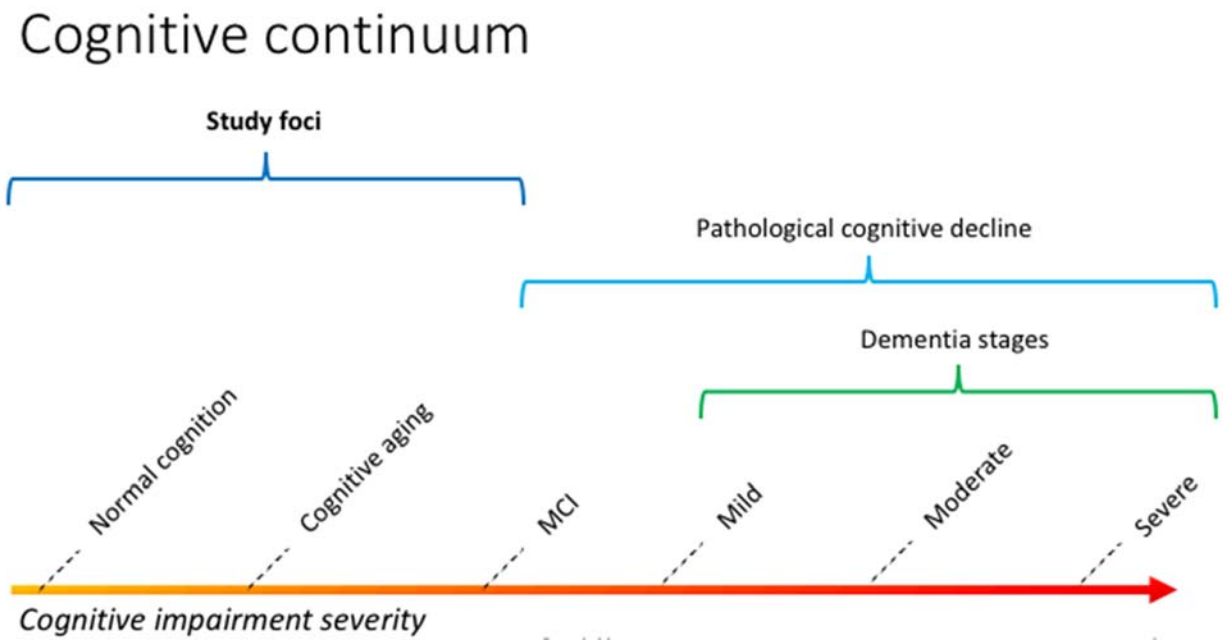


Figure 1. Conceptual model of the cognitive continuum. Mild cognitive impairment (MCI).

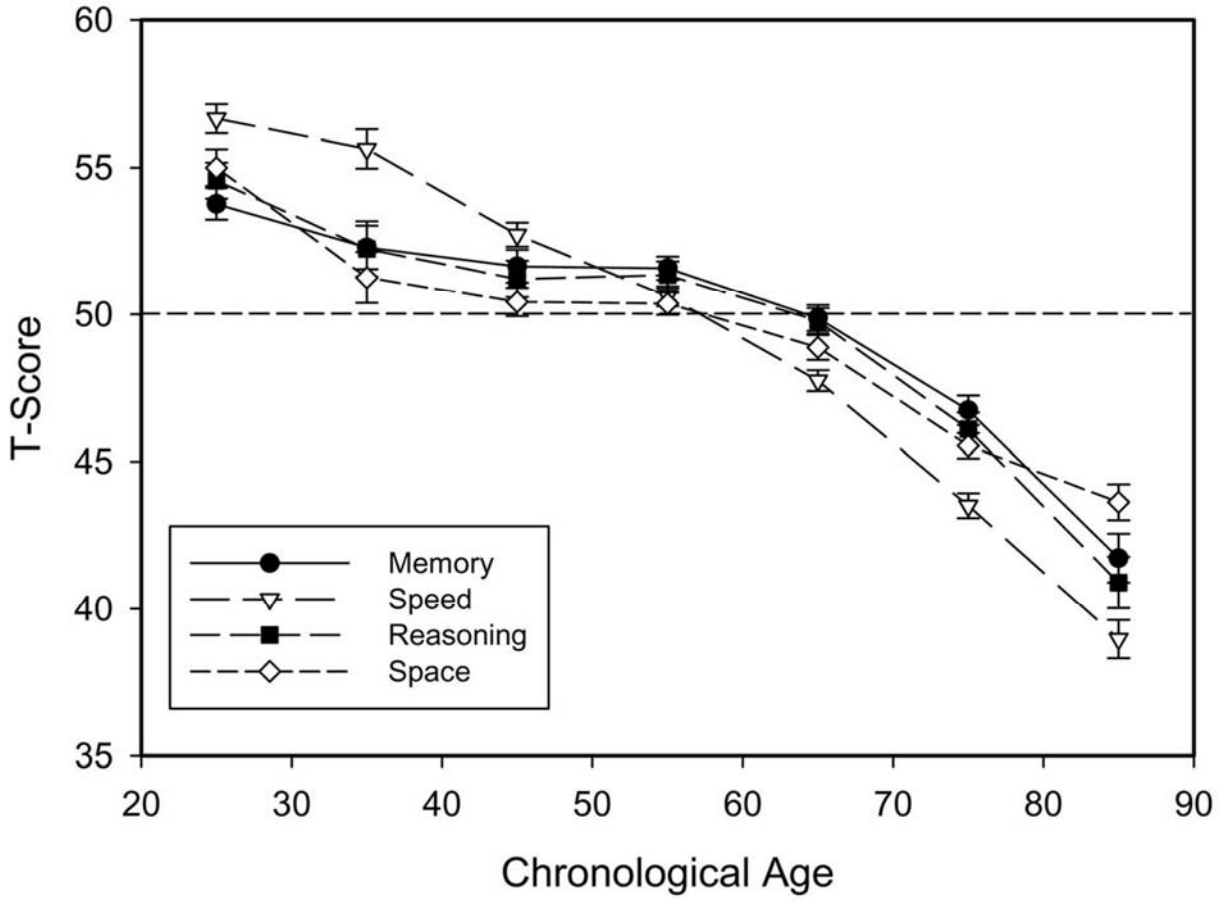


Figure 2. Means and standard error bars for fluid cognitive abilities across the adult lifespan in a cross-sectional sample (N = 1,500, M retest interval = 2.5 years) by Salthouse (2011).

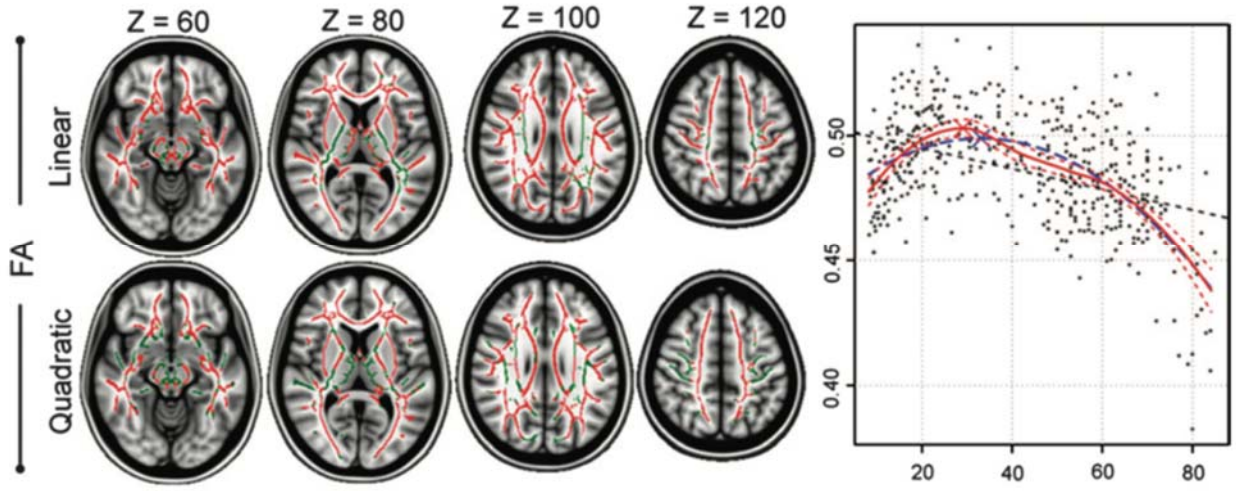


Figure 3. Red areas indicate significant ($p < .05$) effects of age (linear) or age^2 (quadratic) on FA. Mean FA plotted as a function of age with linear (black dotted), quadratic (blue), and nonparametric (red) fit lines. Blue and red crosses mark the estimated maximum for the quadratic and nonparametric fits, respectively. Figure belongs to Westlye et al. (2010).

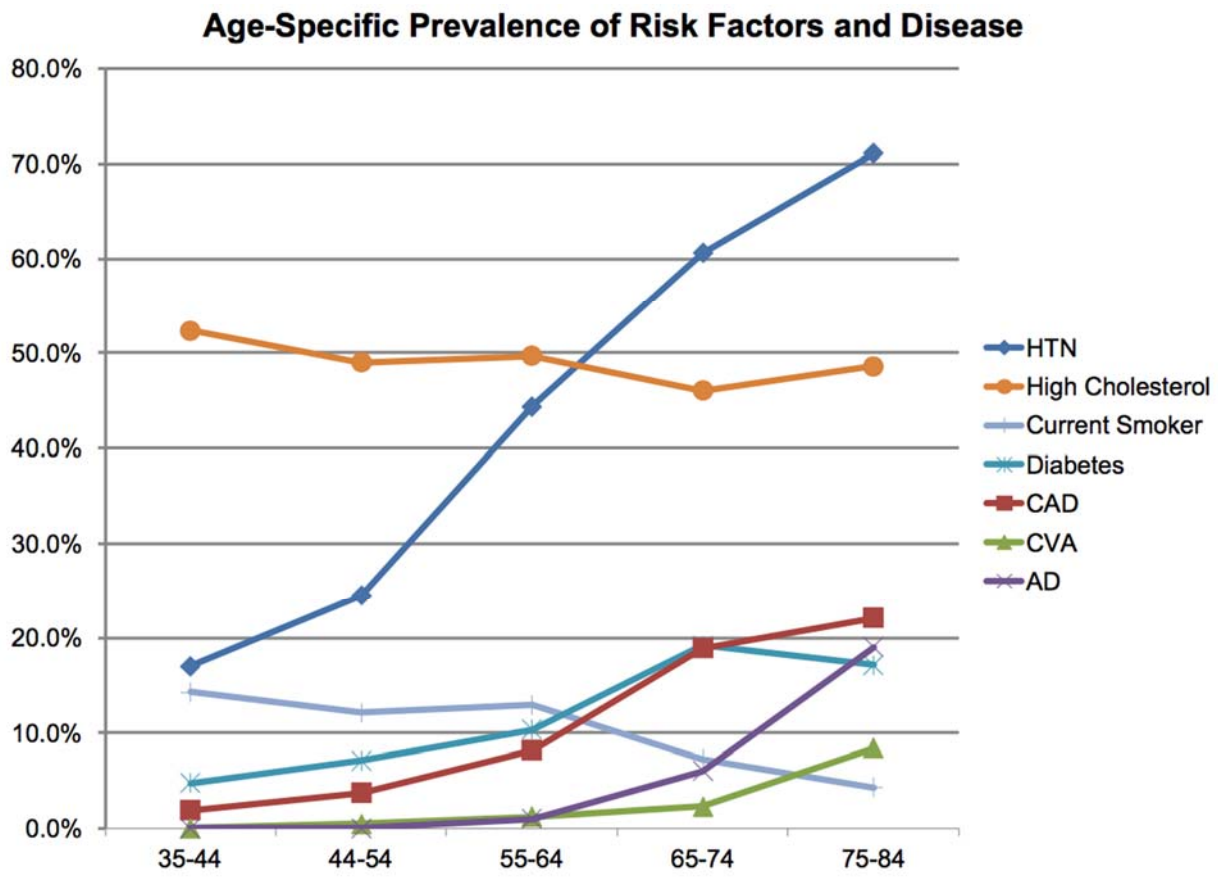


Figure 4. Age-specific prevalence of cardiovascular risk factors and disease among the Framingham Offspring from 2004 to 2009 (S. N. Lockhart & DeCarli, 2014). HTN (hypertension), CAD (coronary artery disease), CVA (cerebrovascular accident), AD (Alzheimer's disease).

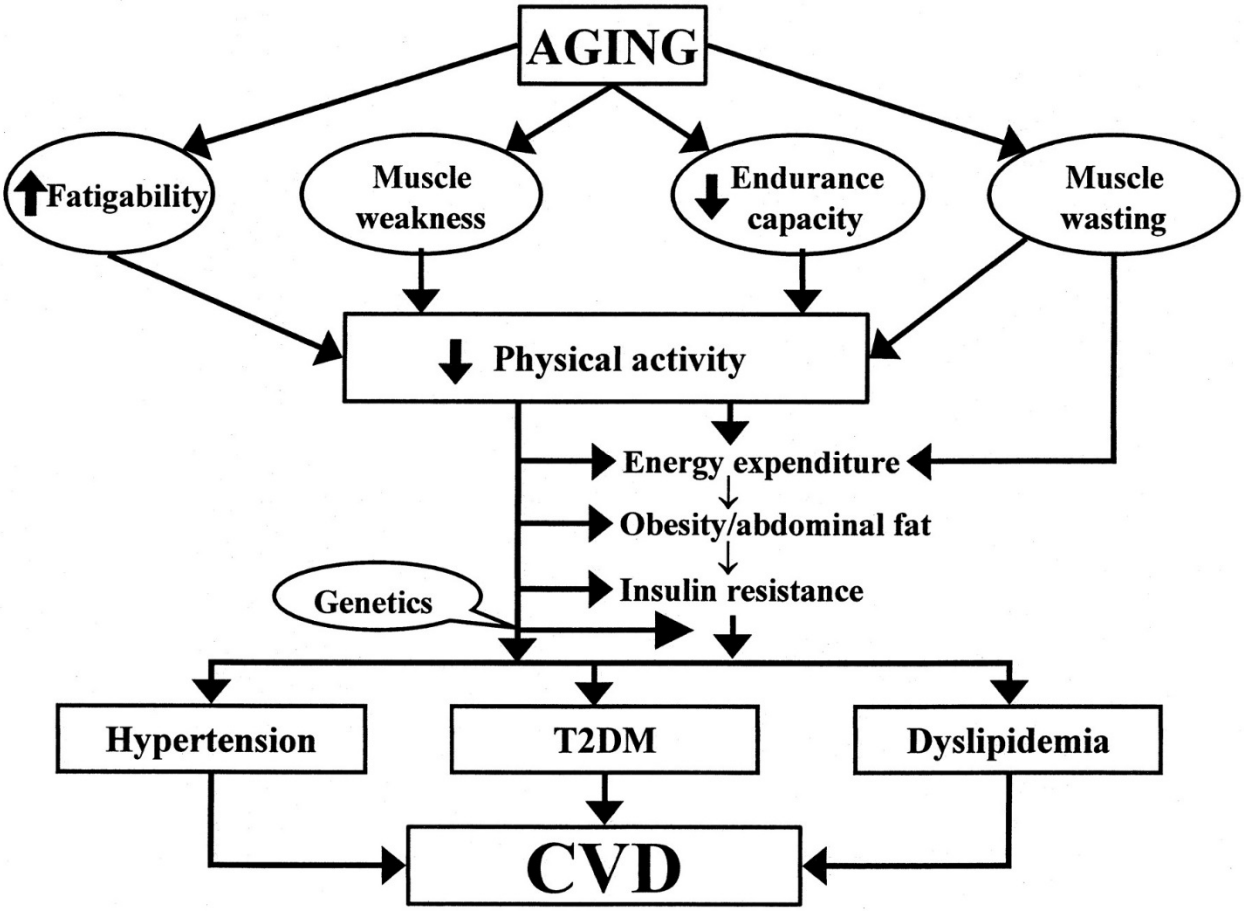


Figure 5. Model of age-related contributors of cardiovascular disease (CVD) from Nair (2005). T2DM (type 2 diabetes mellitus).

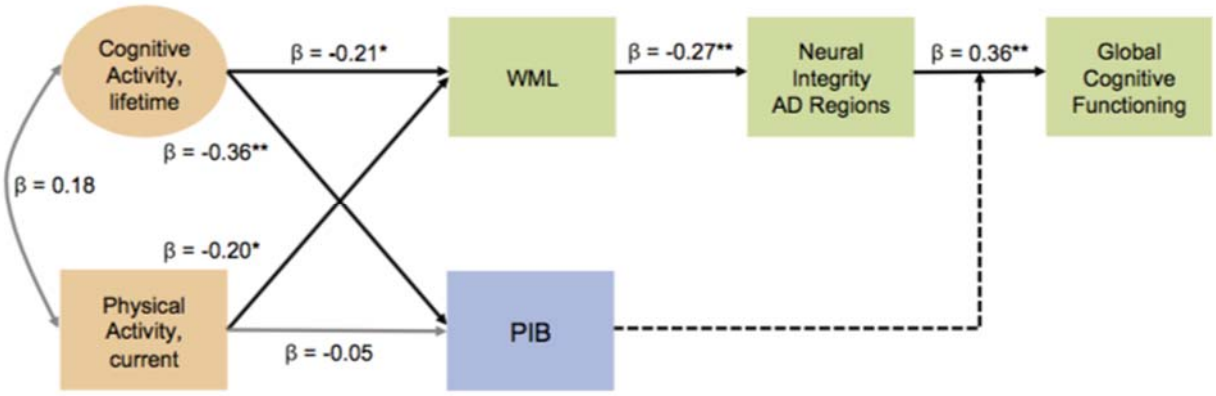


Figure 6. Wirth et al. (2014) path analysis (adjusted for age, gender, and education) of lifestyle factors predicting global cognitive function medicated by white matter lesions (WML) and integrity of regions impacted by Alzheimer's disease. Beta-amyloid burden (Pittsburgh-Compound-B retention; PIB) moderated the impact of neural integrity on cognition.

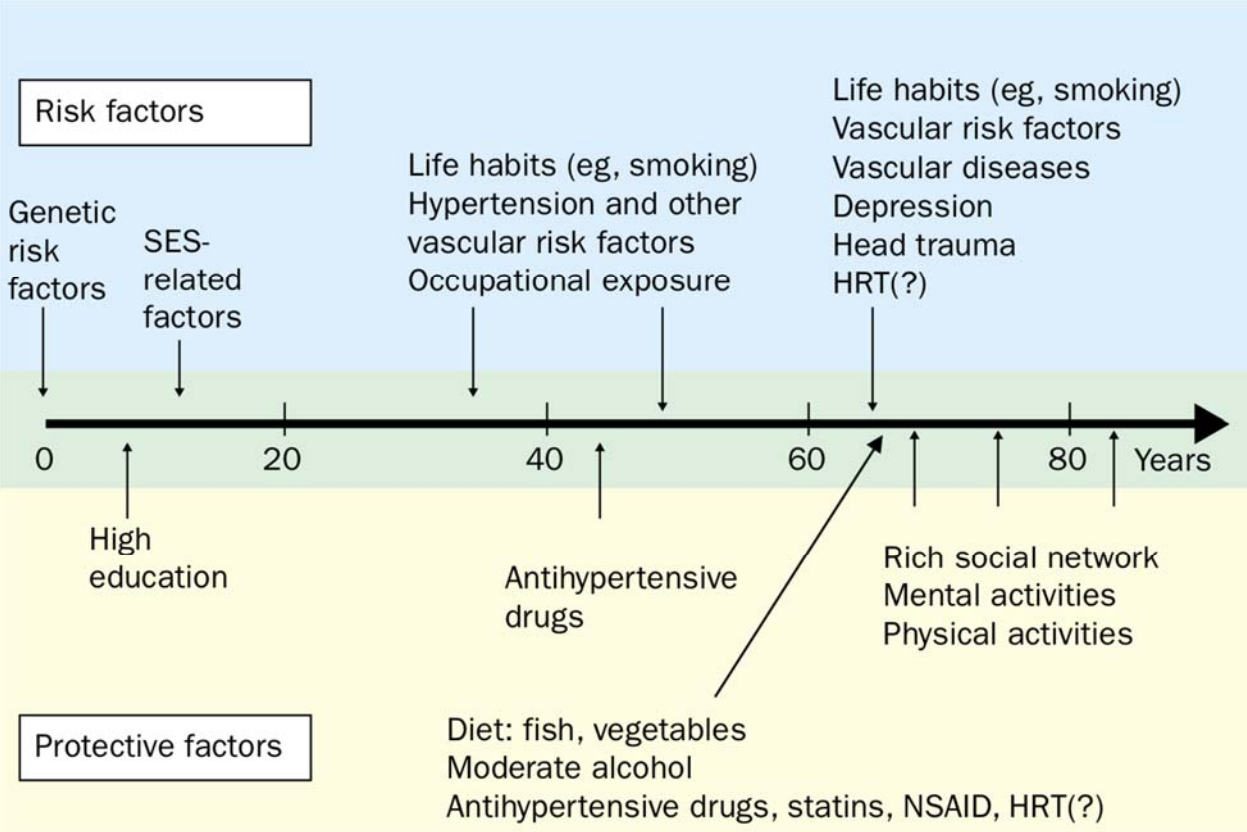


Figure 7. Hypothesized timeline of risk and protective factors for dementia from Fratiglioni et al. (2004). Socioeconomic status (SES), hormone replacement therapy (HRT), nonsteroidal anti-inflammatory drug (NSAID).

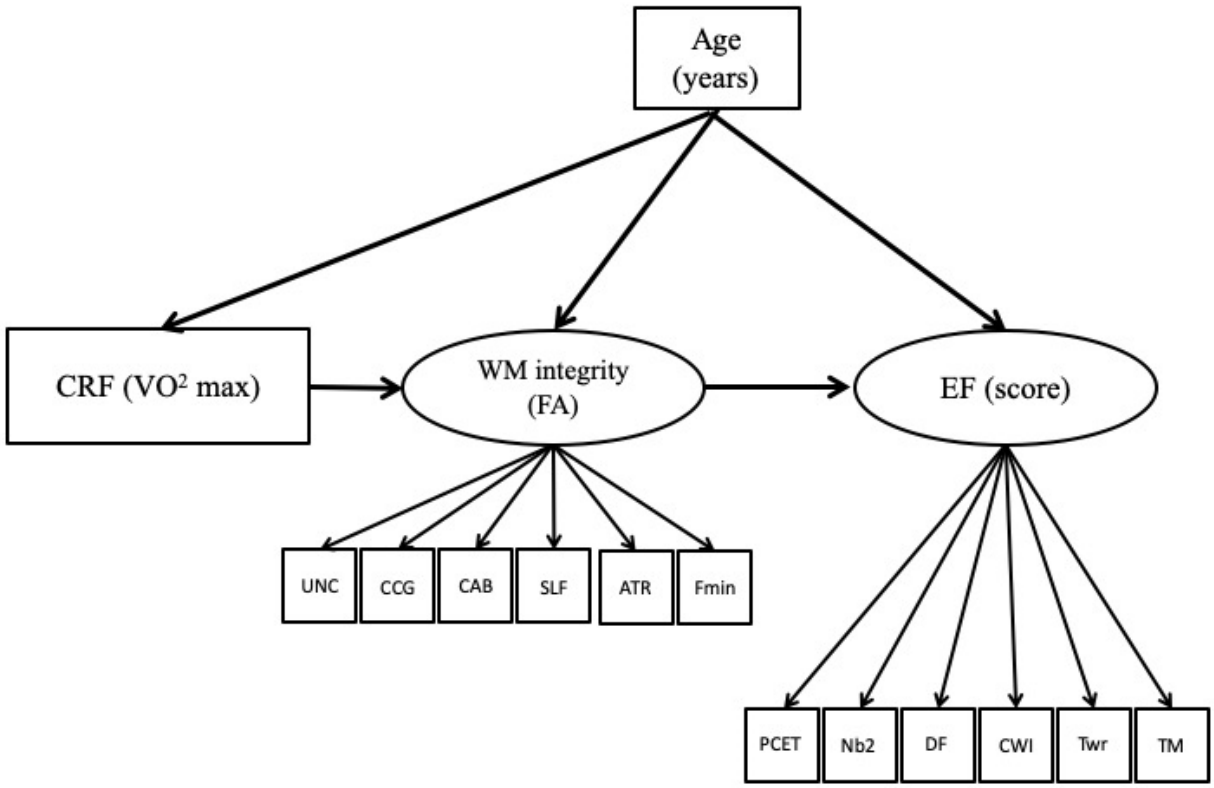


Figure 8. Hypothesized model of cardiorespiratory fitness (CRF) predicting executive function (EF) mediated by white matter microstructure and age. WM TOI that connected frontal regions included the uncinate fasciculus (UNC), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), superior longitudinal fasciculus (SLF), anterior thalamic radiation (ATR), and forceps minor (Fmin). EF measures were the Penn Conditional Exclusion Test (PCET), n-back (2-back trial), Design Fluency Test (DF), Color Word Interference Test (CWI), Tower Test, and Trail Making Test (TMT).

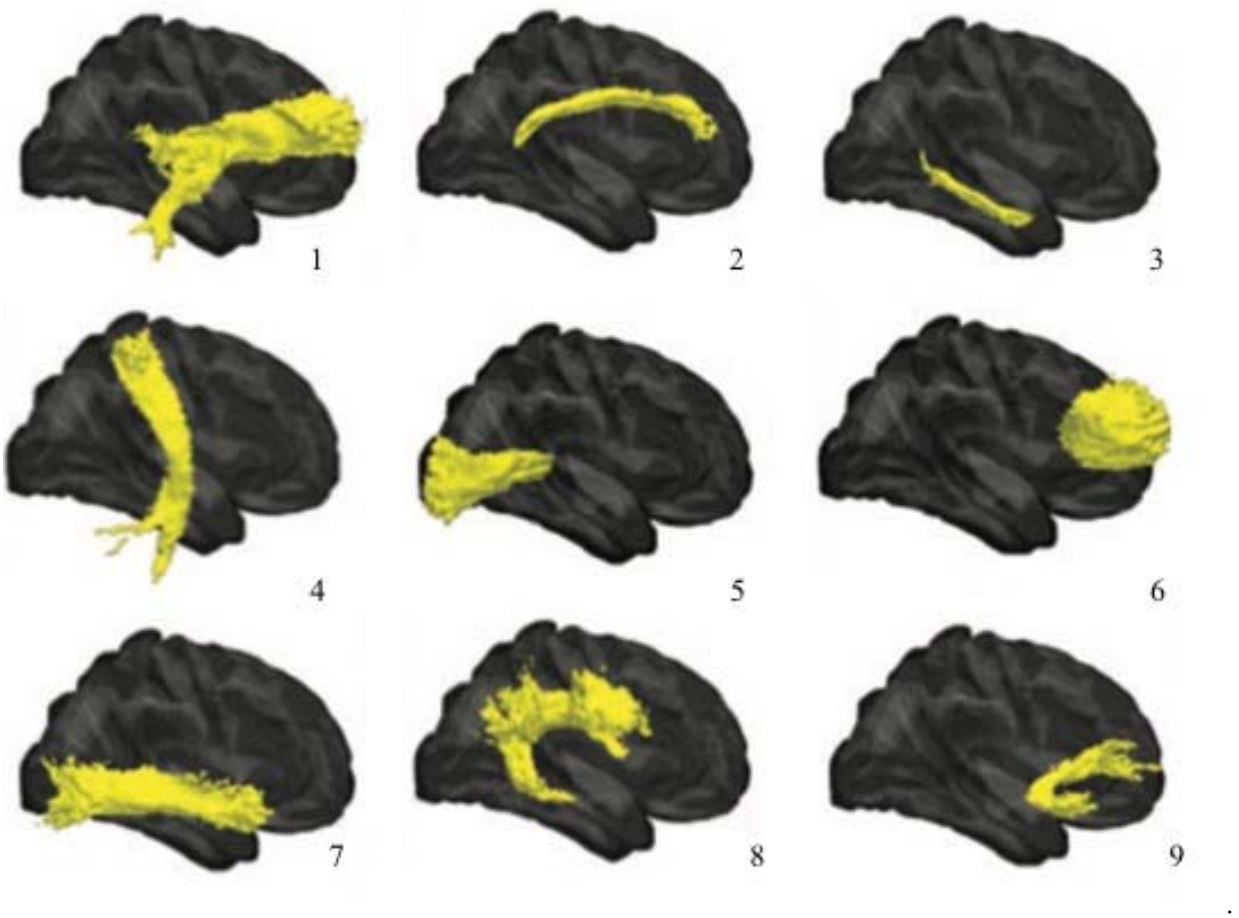


Figure 9. Highlighted regions represent the probabilistically defined WM tracts of interest (TOI): (1) anterior thalamic radiation (ATR), (2) cingulum cingulate gyrus (CCG), (3) cingulum angular bundle (CAB), (4) corticospinal tract (CST), (5) forceps major (Fmaj), (6) forceps minor (Fmin), (7) inferior longitudinal fasciculus (ILF), (8) superior longitudinal fasciculus (SLF), and (9) uncinate fasciculus (UNC). Figure from Westlye et al. (2010).

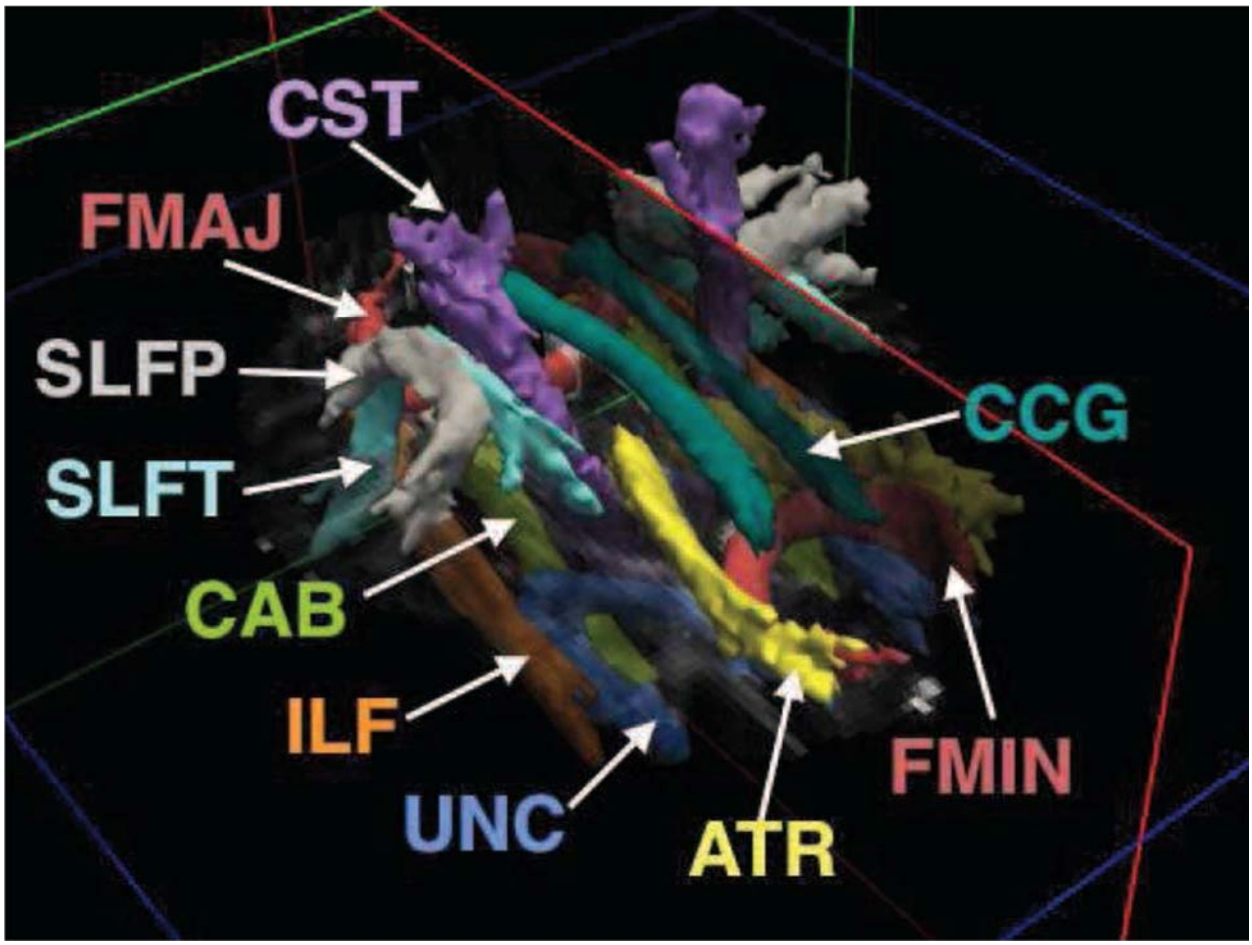


Figure 10. Three-dimensional rendering of WM tracts of interest (TOI) reconstructed by TRACULA: anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), forceps minor (Fmin), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF; parietal, temporal), and uncinate fasciculus (UNC). Figure from Yendiki et al. (2014).

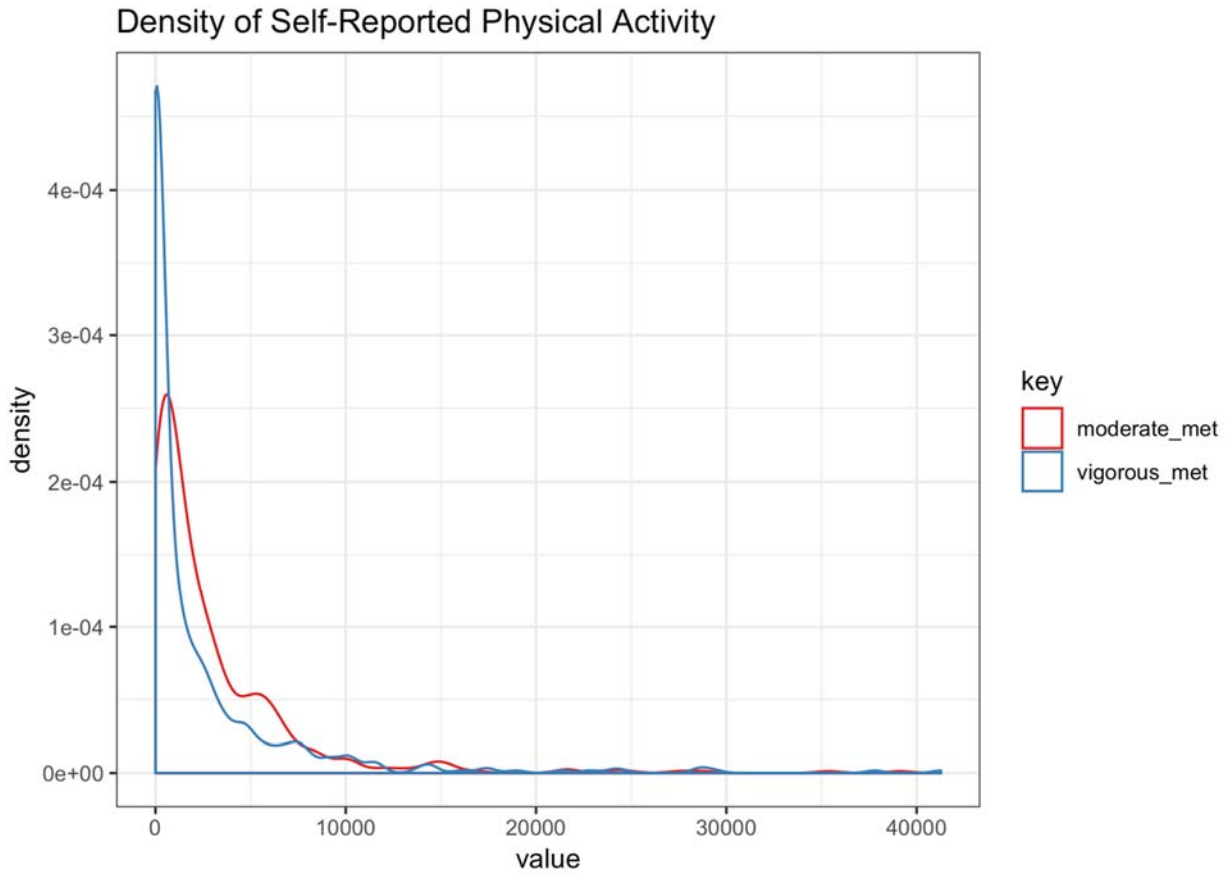


Figure 11. Density plot showing the high positive skew for self-reported moderate and vigorous metabolic equivalent of task (MET) on the International Physical Activity Questionnaire (IPAQ).

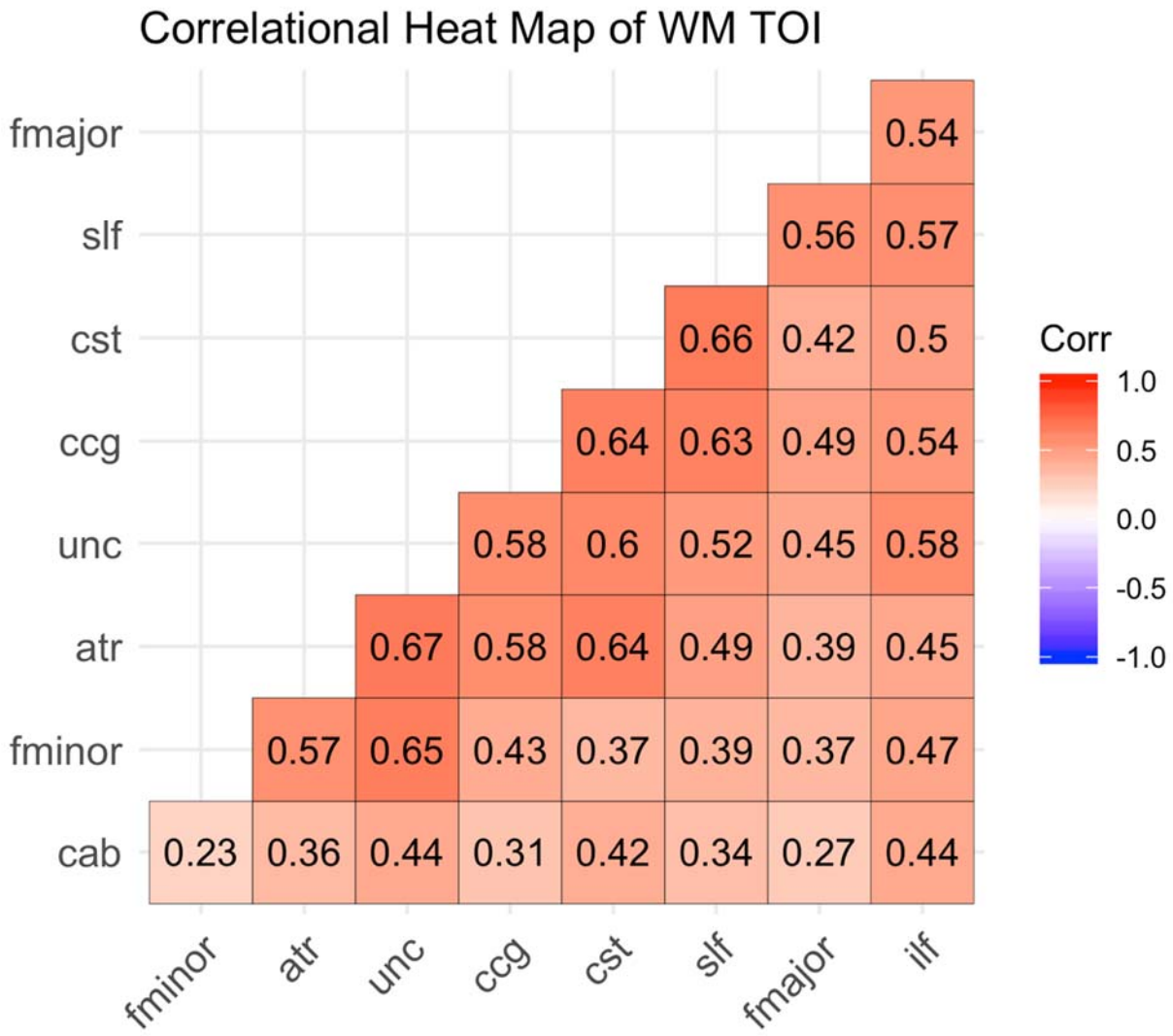


Figure 12. Correlational heat map of fractional anisotropy (FA) values for white matter WM tracts of interest (TOI): thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), forceps minor (Fmin), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

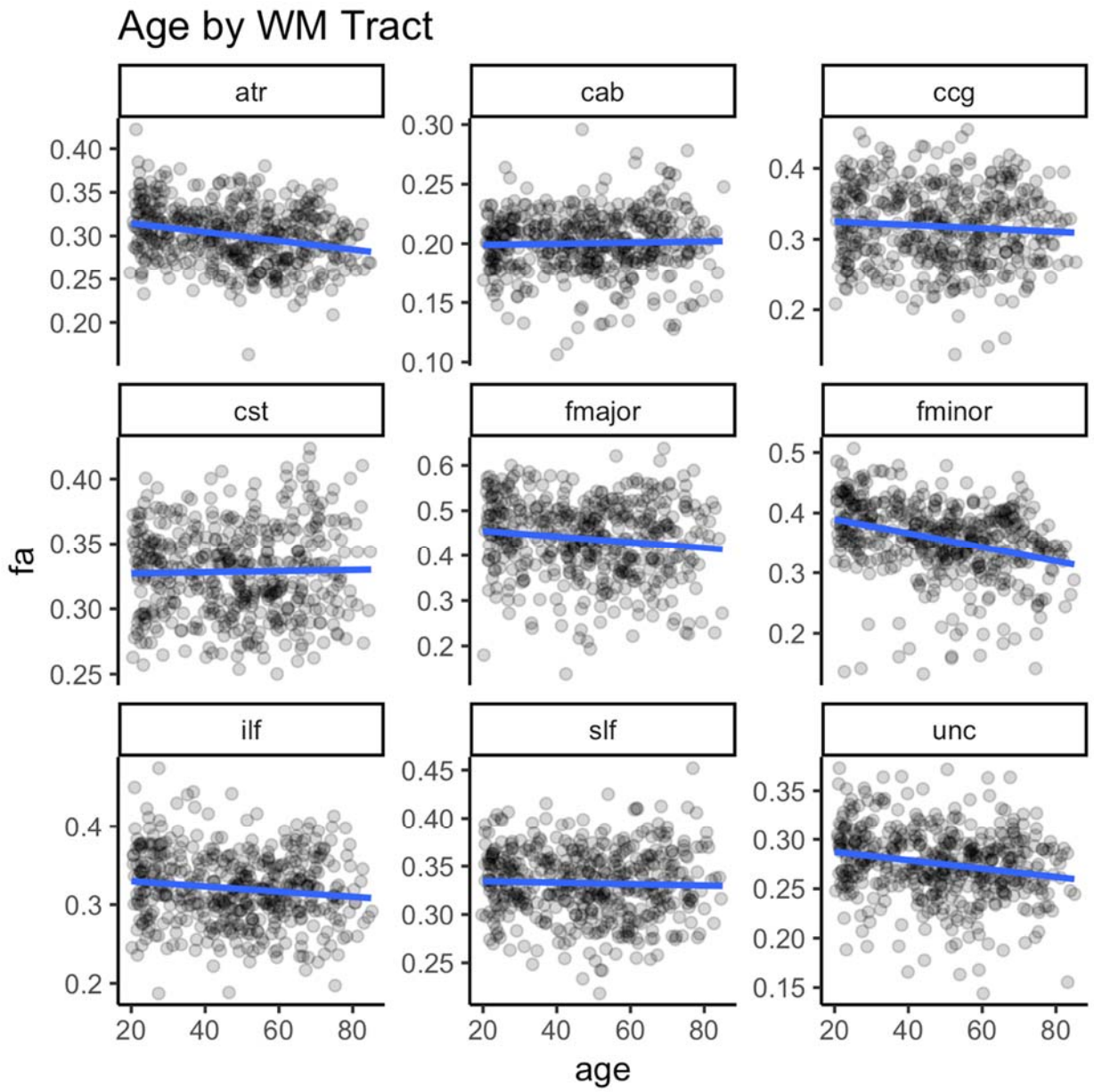


Figure 13. Relationship between fractional anisotropy (FA) and age for each white matter WM tracts of interest (TOI): anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), forceps minor (Fmin), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

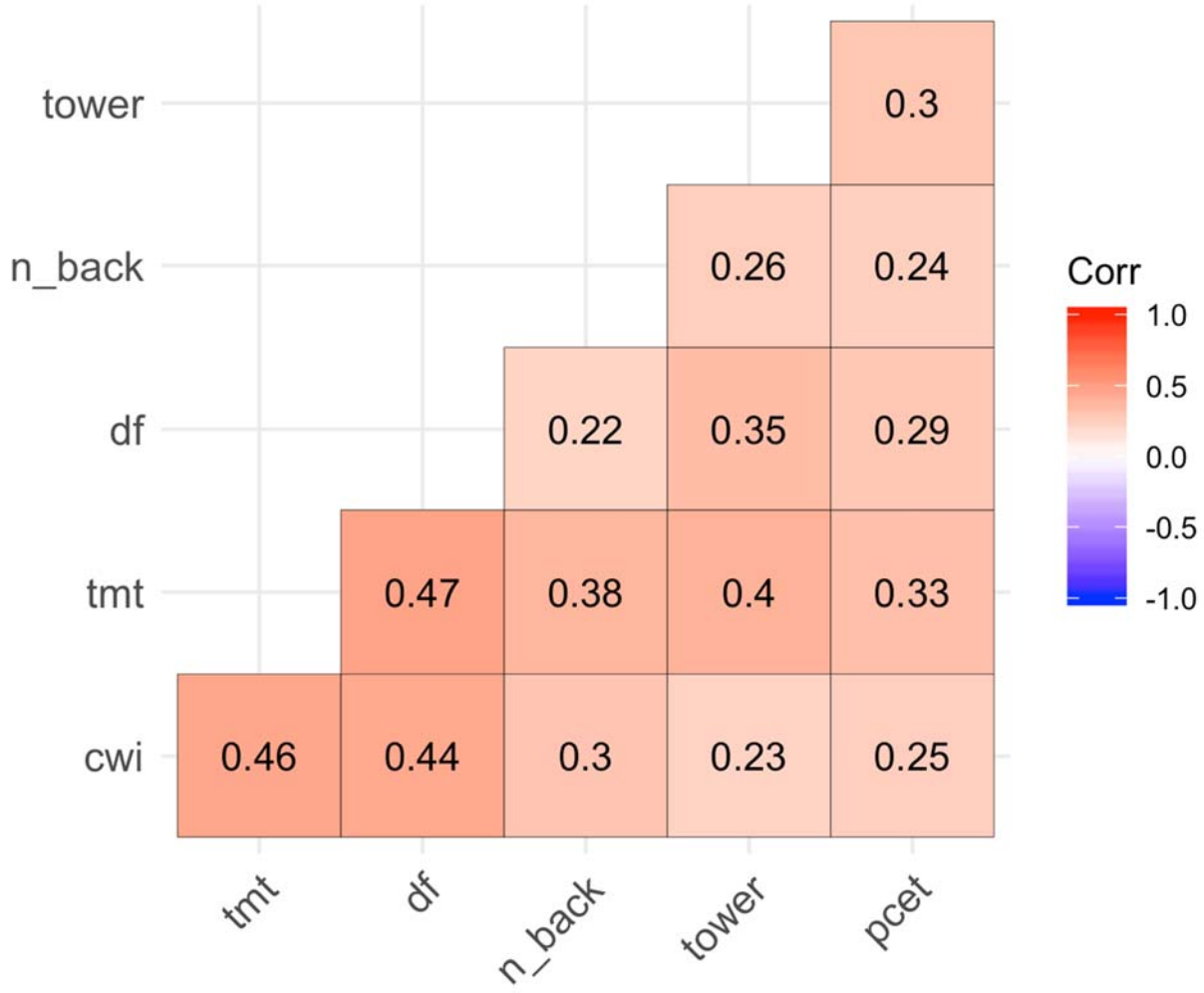


Figure 14. Correlational heat map of the Penn Conditional Exclusion Test (PCET) and n-back (2-back trial) from the Penn Computerized Neurocognitive Battery (CNB) and Design Fluency Test, (DF), Color Word Interference Test (CWI), Tower Test, and Trail Making Test (TMT) from the Delis-Kaplan Executive Function System (D-KEFS).

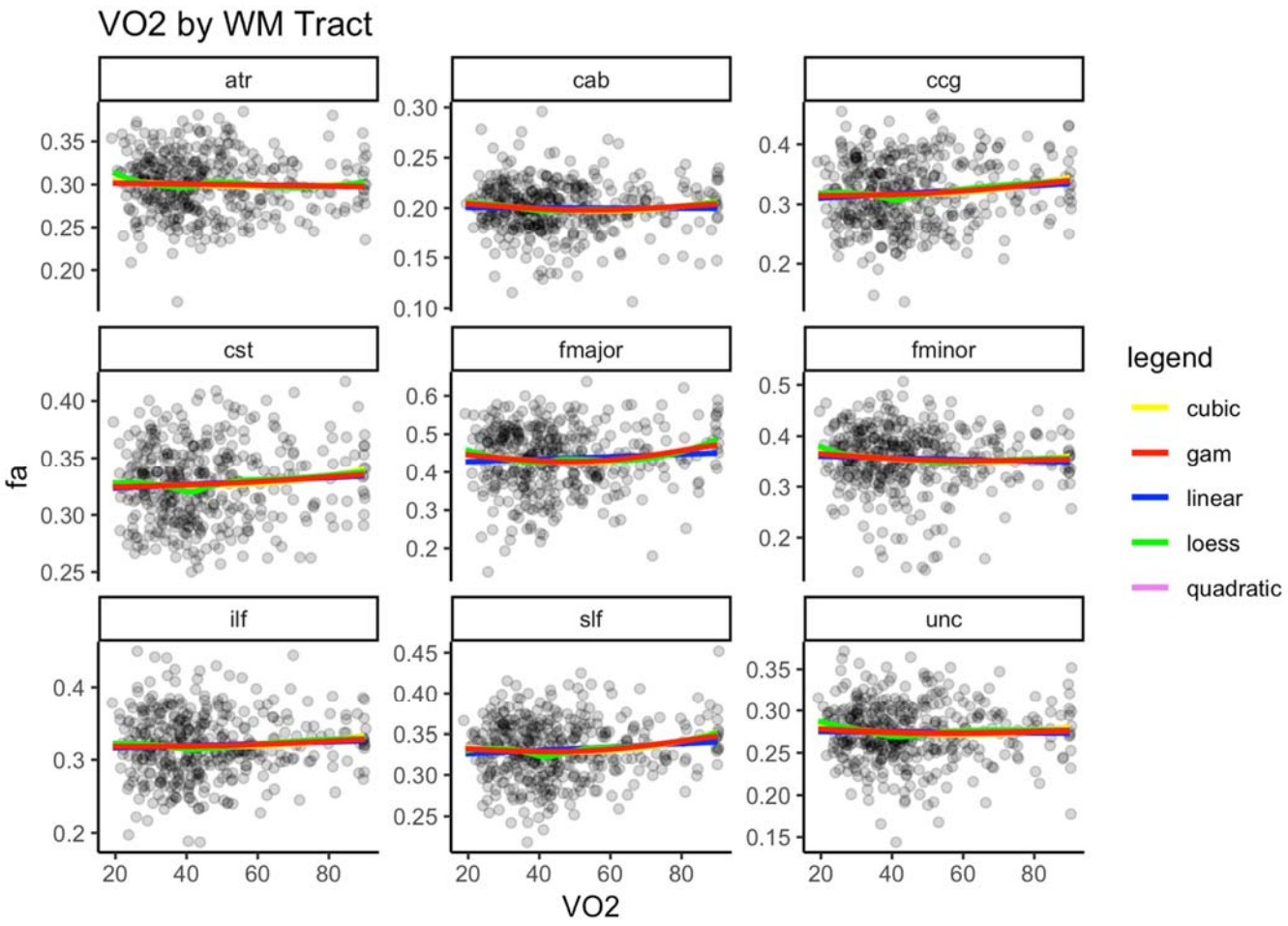


Figure 15. Relationship between fractional anisotropy (FA) and VO_2 max for each white matter WM tracts of interest (TOI): anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), forceps minor (Fmin), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

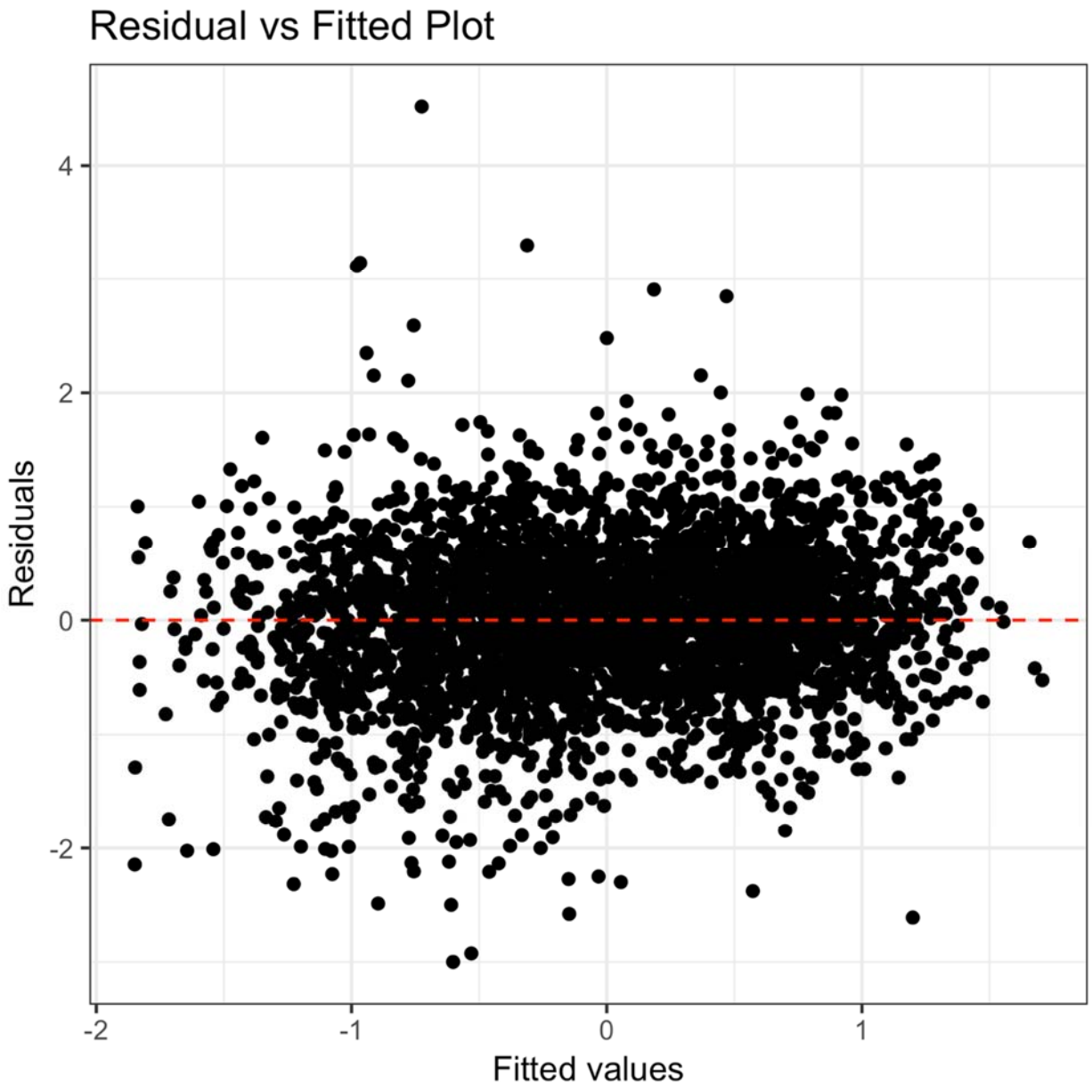


Figure 16. Fitted values against residuals from the mixed-effects model predicting fractional anisotropy (FA) to test homogeneity of variance.

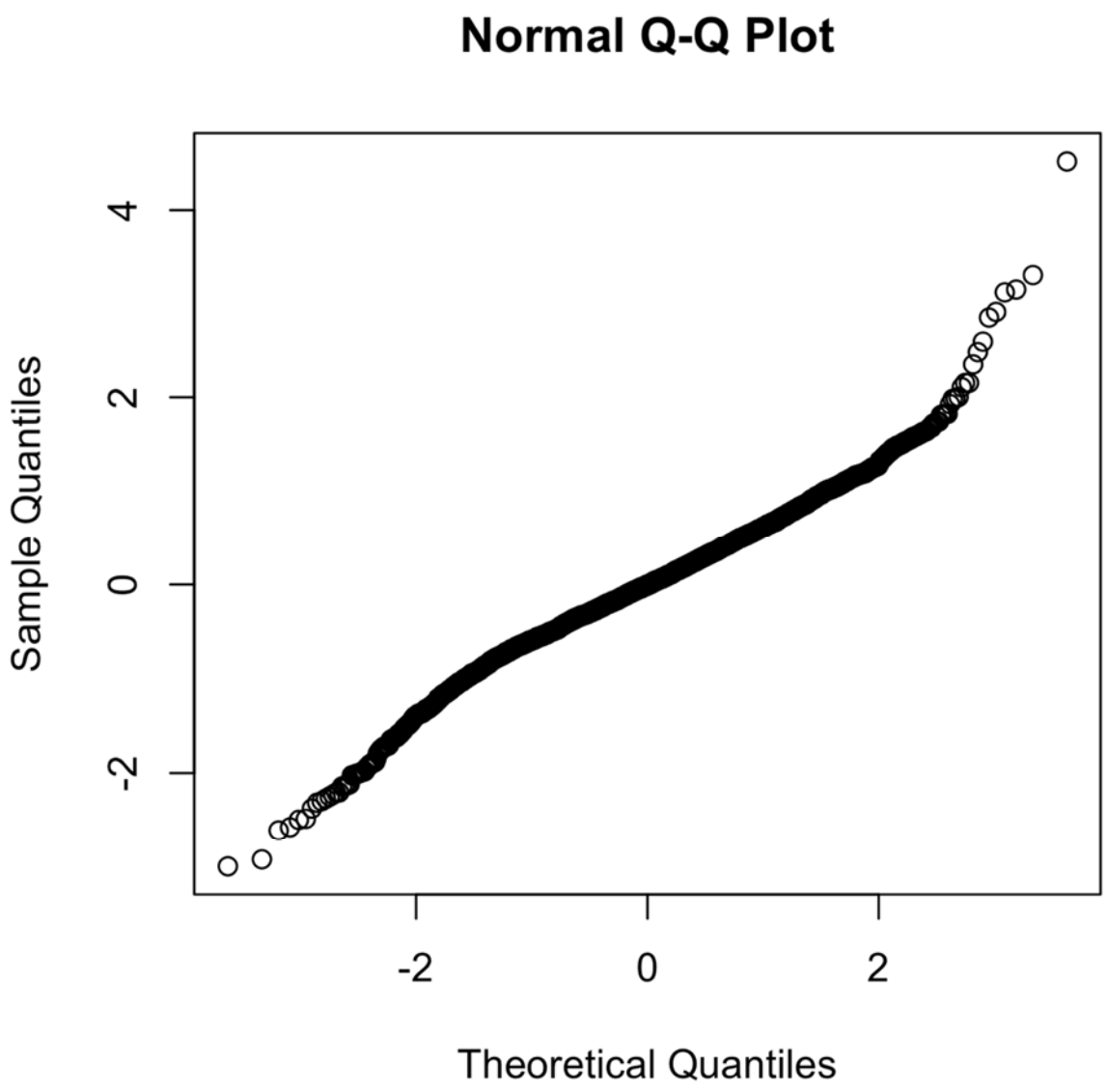


Figure 17. The Q-Q plot of standardized residuals from the mixed-effects model predicting fractional anisotropy (FA).

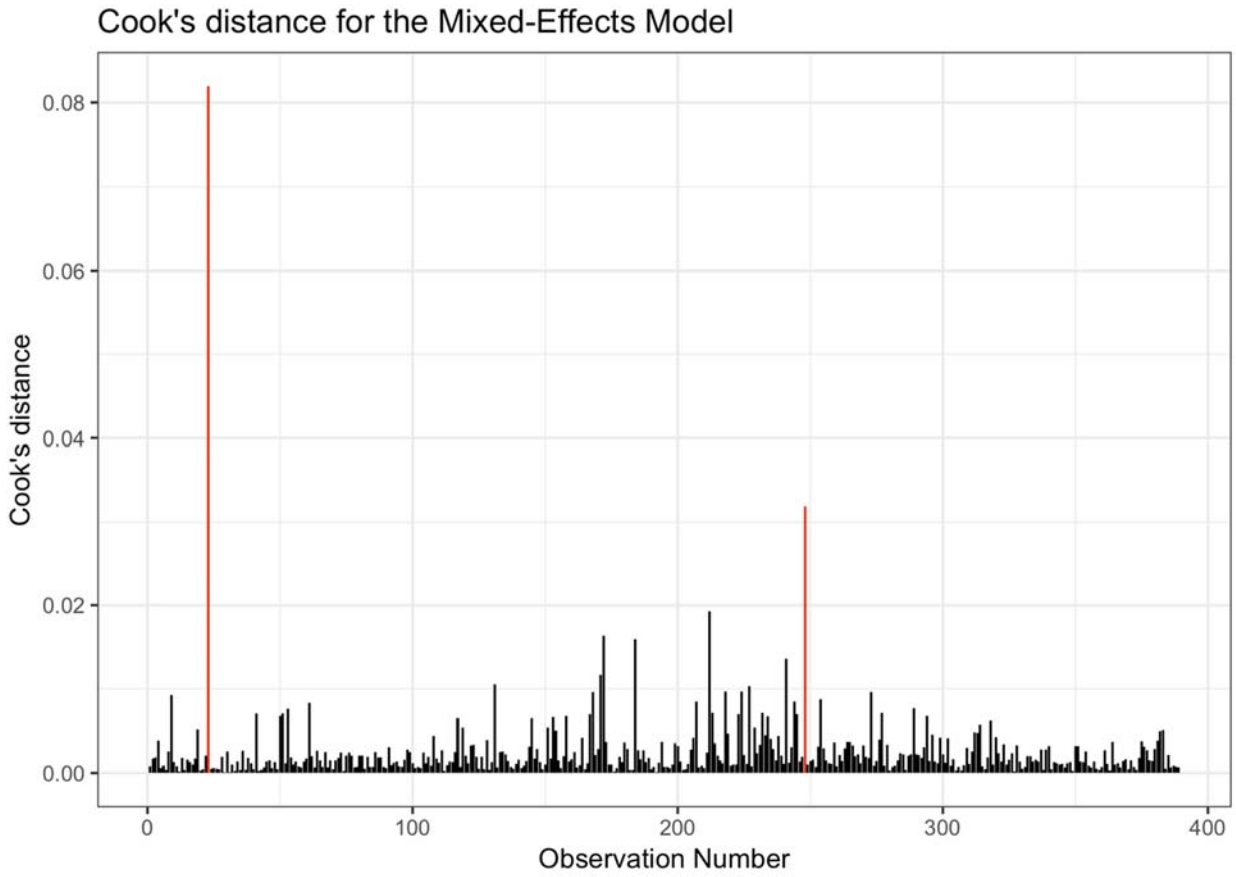


Figure 18. Cook's distance plot from the mixed-effects model predicting fractional anisotropy (FA). Two influential observations are highlighted in red.

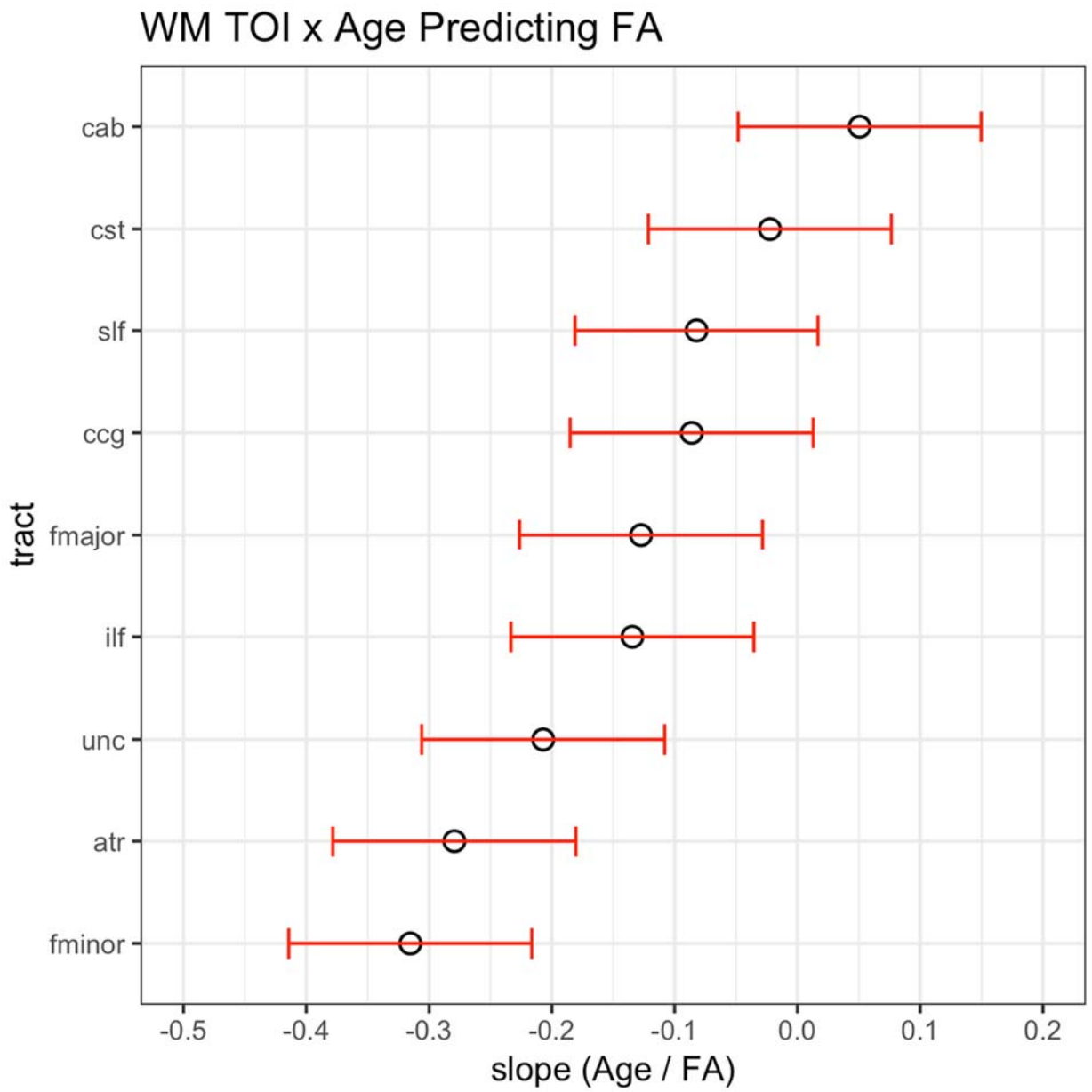


Figure 19. Z-standardized slopes and 95% confidence intervals (horizontal error bars) for the white matter (WM) tracts of interest (TOI) and age (continuous) interaction predicting fractional anisotropy (FA). WM TOI included the anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), forceps minor (Fmin), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

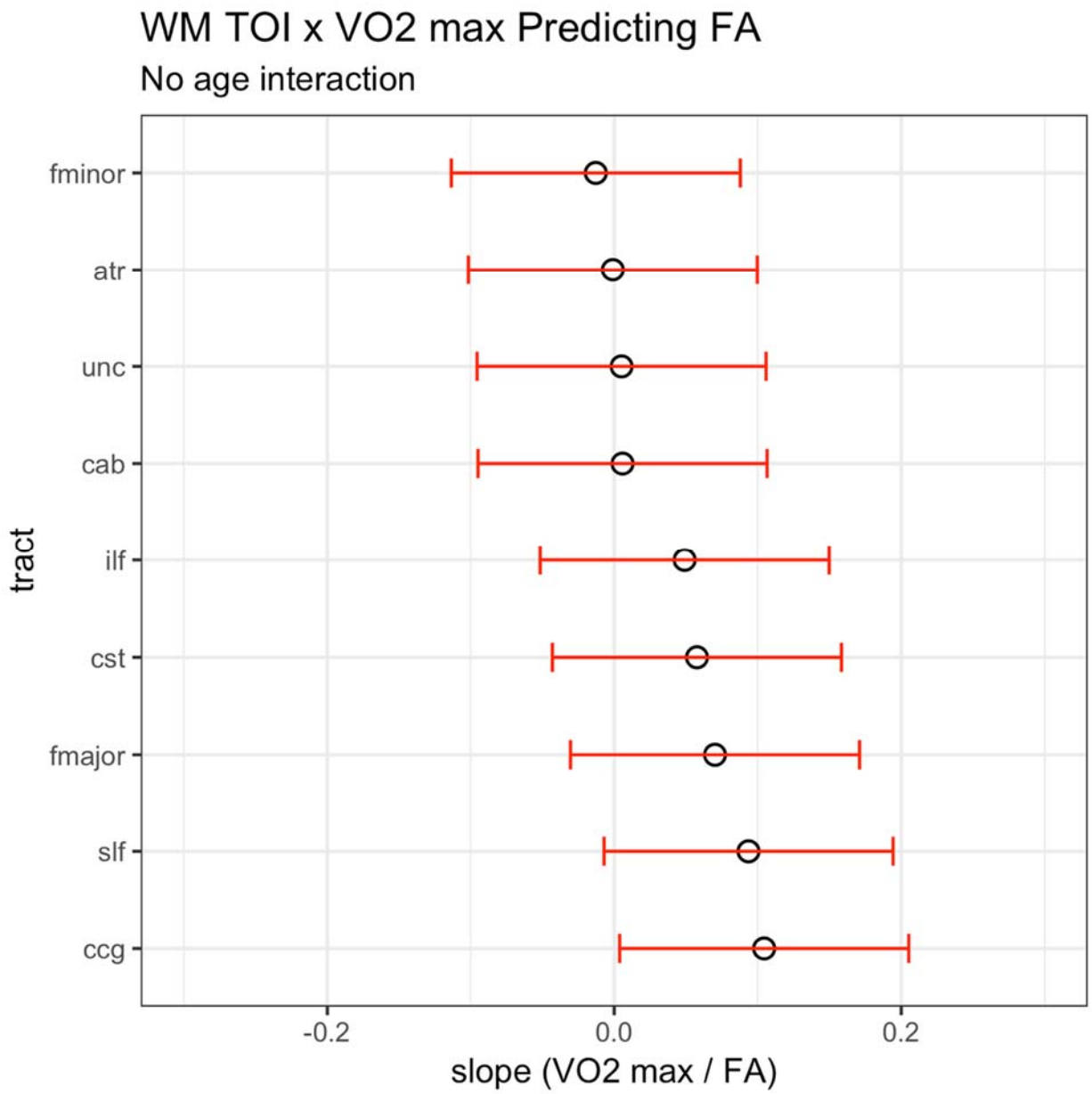


Figure 20. Z-standardized slopes and 95% confidence intervals (horizontal error bars) for the white matter (WM) tracts of interest (TOI) and VO_2 max interaction predicting fractional anisotropy (FA). WM TOI included the anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), forceps minor (Fmin), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

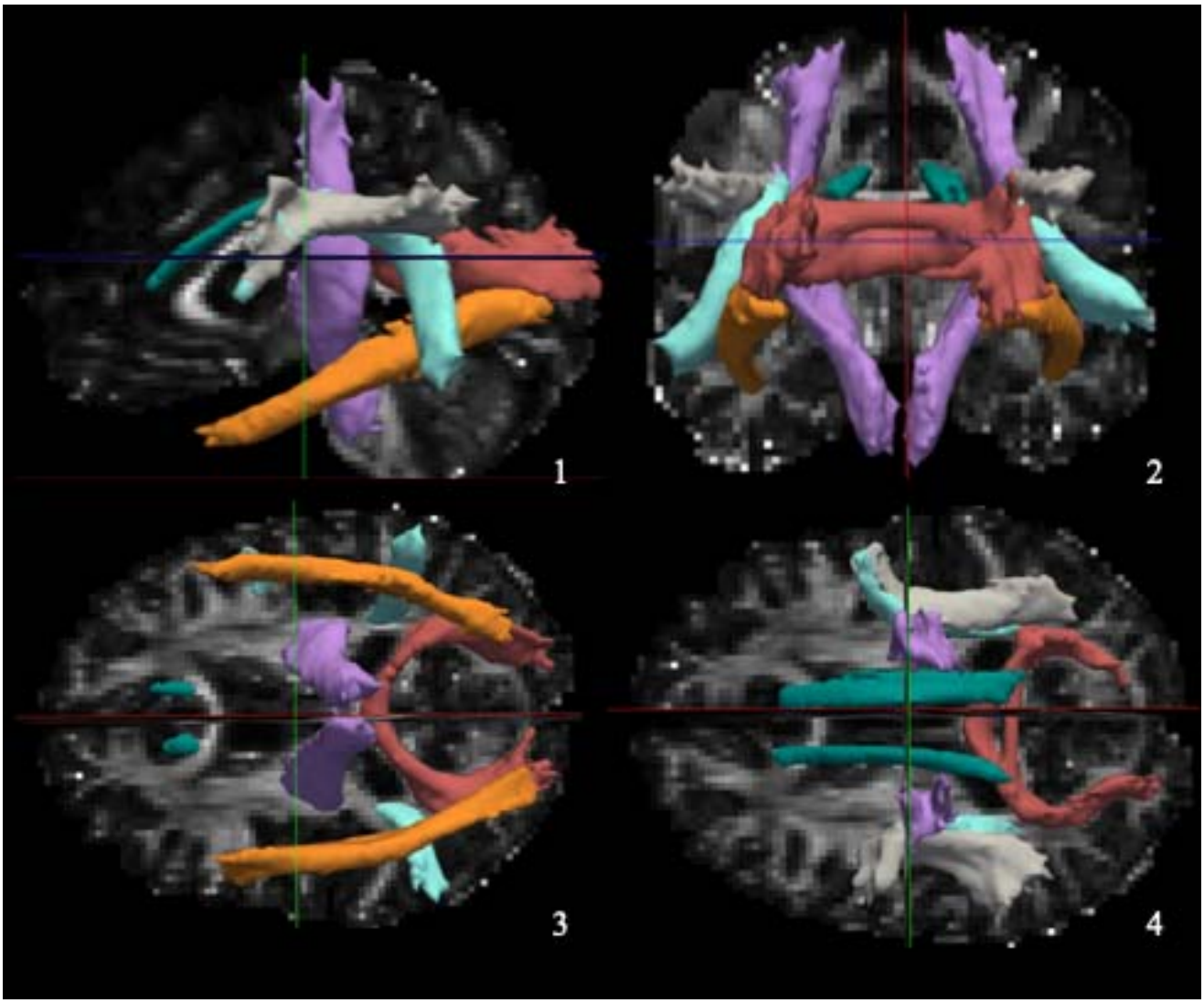


Figure 21. White matter (WM) tracts significantly associated with cardiorespiratory fitness (CRF) in older age (see Table 7). *Lateral (1), posterior (2), inferior (3), and superior (4) orientations.* Forceps major (Fmaj) in red, inferior longitudinal fasciculus (ILF) in orange, superior longitudinal fasciculus (SLF) in grey (parietal) and light blue (temporal), corticospinal tract (CST) in purple, and cingulum cingulate gyrus (CCG) in teal. Three-dimensional rendering of diffusion tensor imaging (DTI) data by TRACULA.

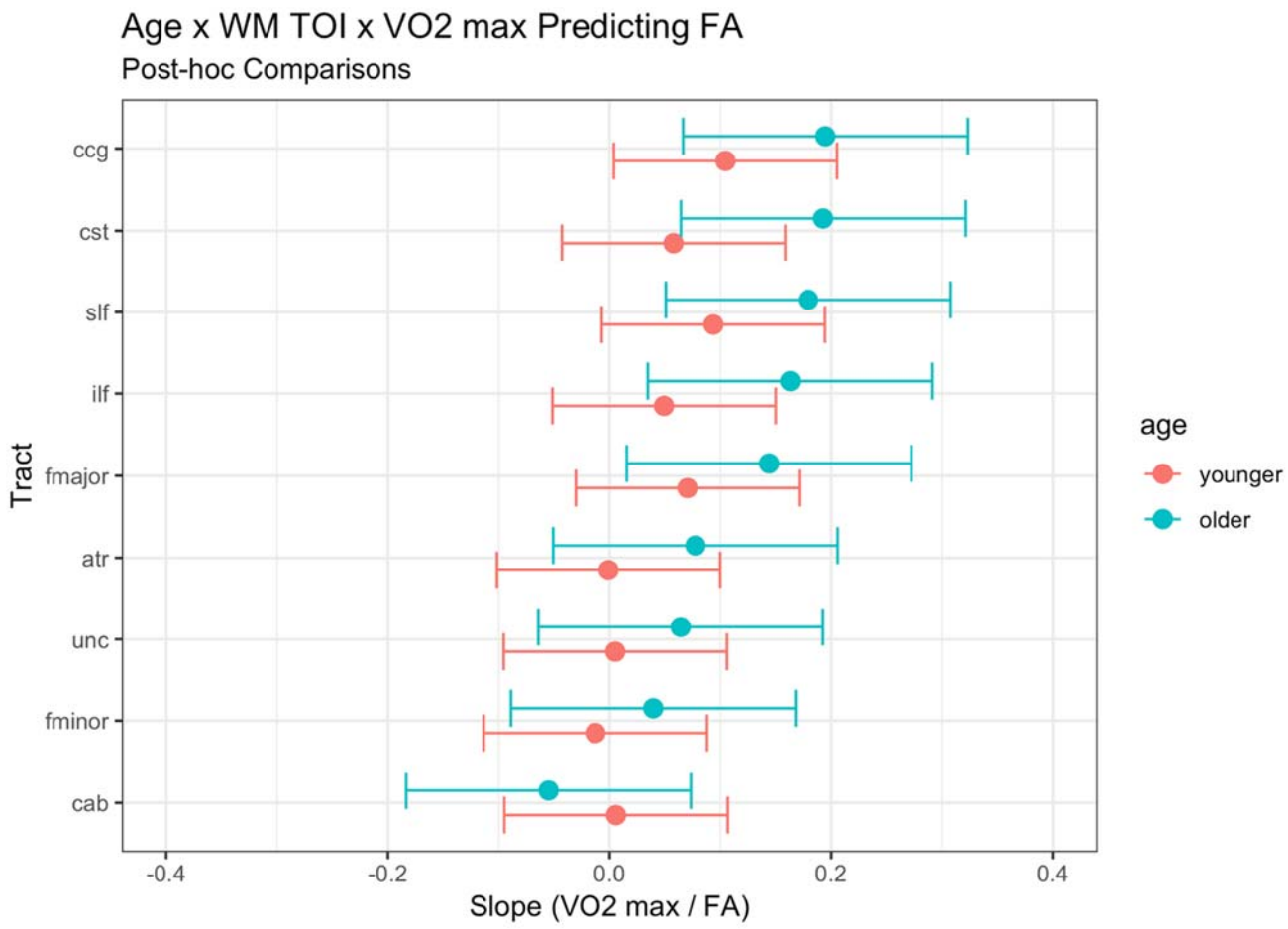


Figure 22. Post-hoc comparison of the age x white matter (WM) tracts of interest (TOI) x VO_2 max interaction (Table 7). Z-standardized slopes and 95% confidence intervals (horizontal error bars) for the white matter (WM) tracts of interest (TOI) and VO_2 max interaction predicting fractional anisotropy (FA). WM TOI included the anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), cingulum angular bundle (CAB), corticospinal tract (CST), forceps minor (Fmin), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

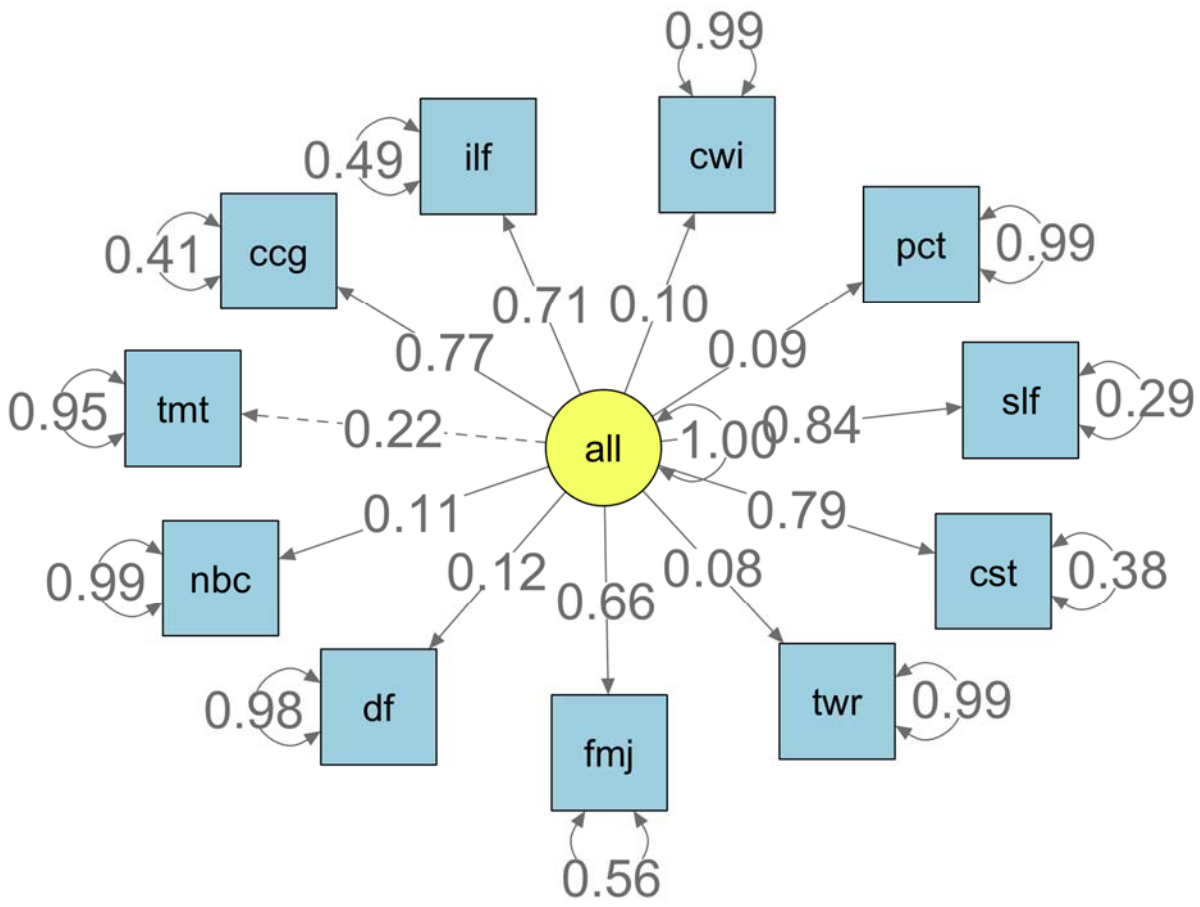


Figure 23. Unitary construct for neurocognition combining executive function (EF) and white matter (WM) variables (Measurement Model Step 1). Model fit (Cmin/df = 9.51, CFI = 0.99, RMSEA = 0.15) and factor loadings (range = 0.08 – 0.84) were poor. WM TOI included the cingulum cingulate gyrus (CCG), corticospinal tract (CST), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF). EF measures were the Penn Conditional Exclusion Test (PCET), n-back (2-back trial), Design Fluency Test (DF), Color Word Interference Test (CWI), Tower Test, and Trail Making Test (TMT).

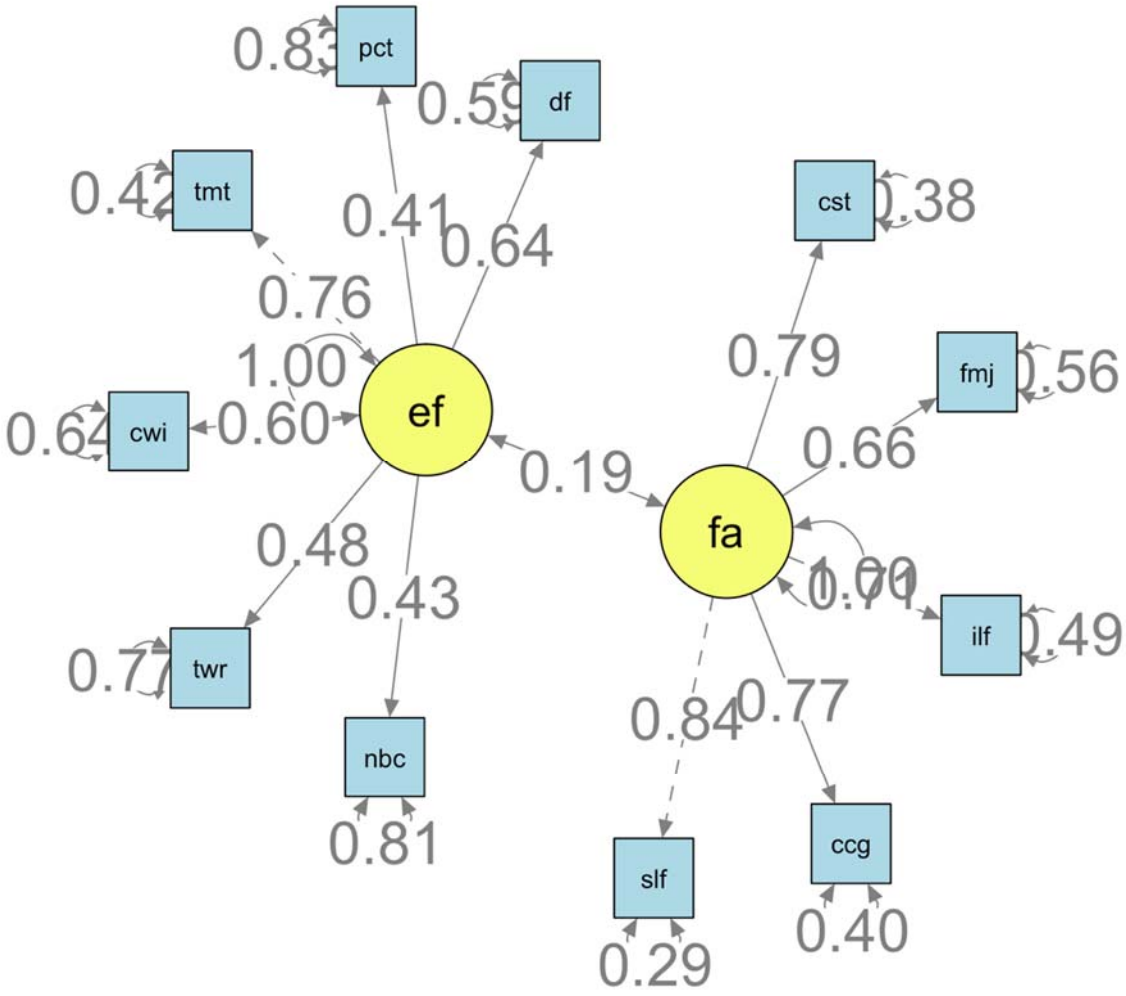


*Figure 24***.** Measurement model for the relationship between executive function (EF) and white matter (WM). Model fit indices were: Cmin/df = 1.72, CFI = 0.98, and RMSEA = 0.045. WM TOI included the cingulum cingulate gyrus (CCG), corticospinal tract (CST), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF). EF measures were the Penn Conditional Exclusion Test (PCET), n-back (2-back trial), Design Fluency Test (DF), Color Word Interference Test (CWI), Tower Test, and Trail Making Test (TMT).

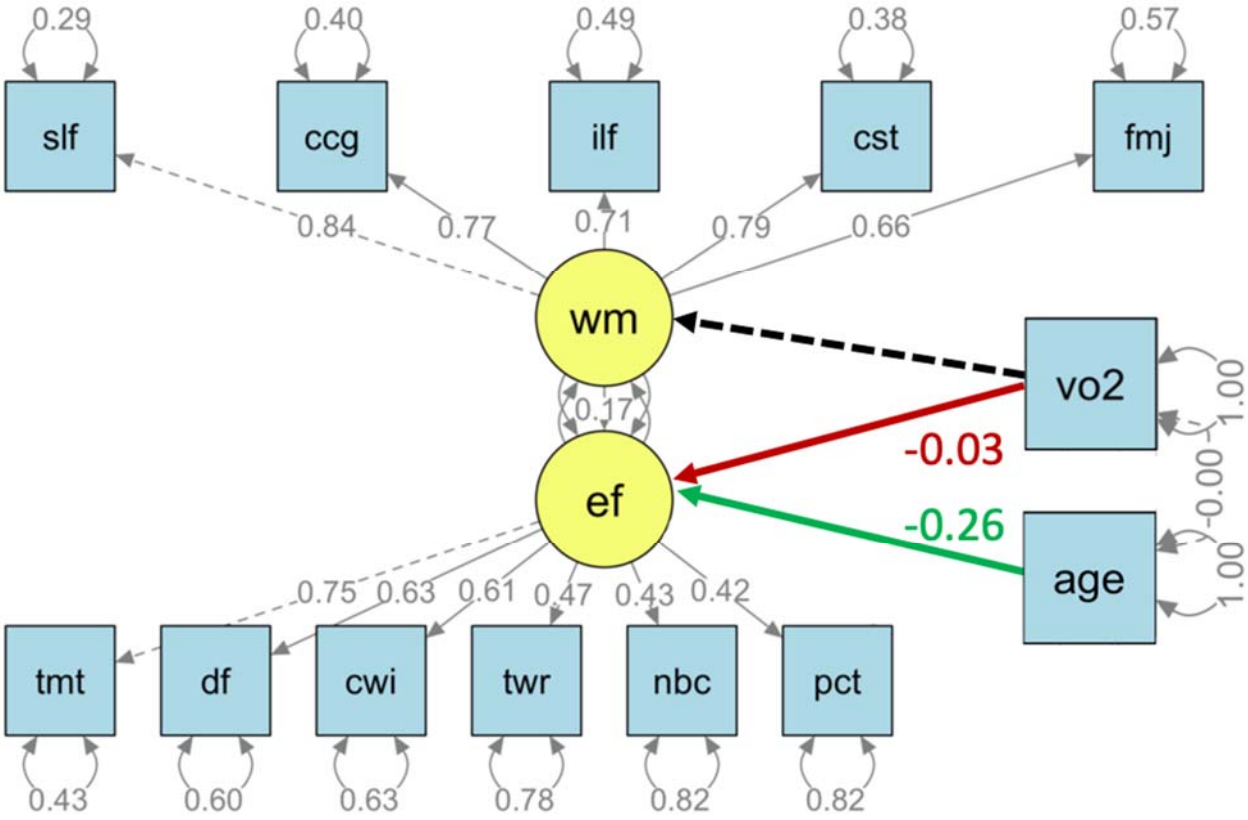
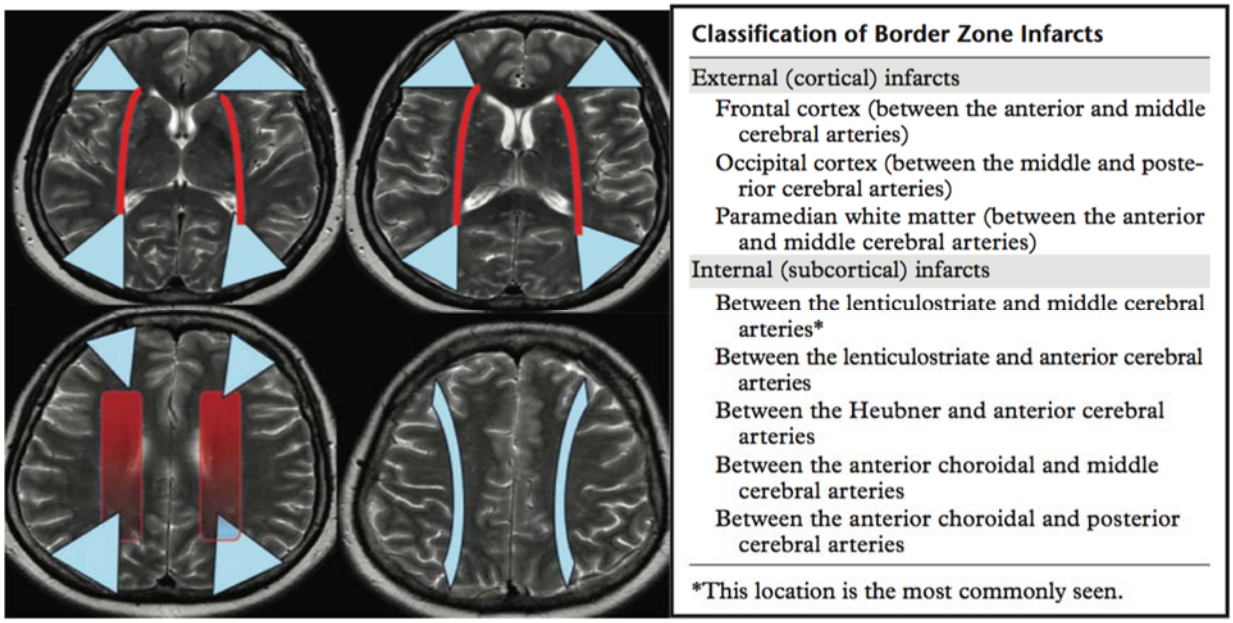


Figure 25. Structural model with directional paths were specified from white matter (WM), age, and VO_2 max on executive function (EF). Model fit was adequate (Cmin/df = 1.88, CFI = 0.96, RMSEA = 0.05). Given the lack of association between the causal variable (VO_2 max) and the outcome (EF), mediation by WM integrity could not be established. WM TOI included the cingulum cingulate gyrus (CCG), corticospinal tract (CST), forceps major (Fmaj), inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF). EF measures were the Penn Conditional Exclusion Test (PCET), n-back (2-back trial), Design Fluency Test (DF), Color Word Interference Test (CWI), Tower Test, and Trail Making Test (TMT).



Classification of Border Zone Infarcts

External (cortical) infarcts
Frontal cortex (between the anterior and middle cerebral arteries)
Occipital cortex (between the middle and posterior cerebral arteries)
Paramedian white matter (between the anterior and middle cerebral arteries)
Internal (subcortical) infarcts
Between the lenticulostriate and middle cerebral arteries*
Between the lenticulostriate and anterior cerebral arteries
Between the Heubner and anterior cerebral arteries
Between the anterior choroidal and middle cerebral arteries
Between the anterior choroidal and posterior cerebral arteries

*This location is the most commonly seen.

Figure 26. T2-weighted magnetic resonance images (MRI) of expected locations for external (blue) and internal (red) watershed infarcts from Mangla et al. (2011).

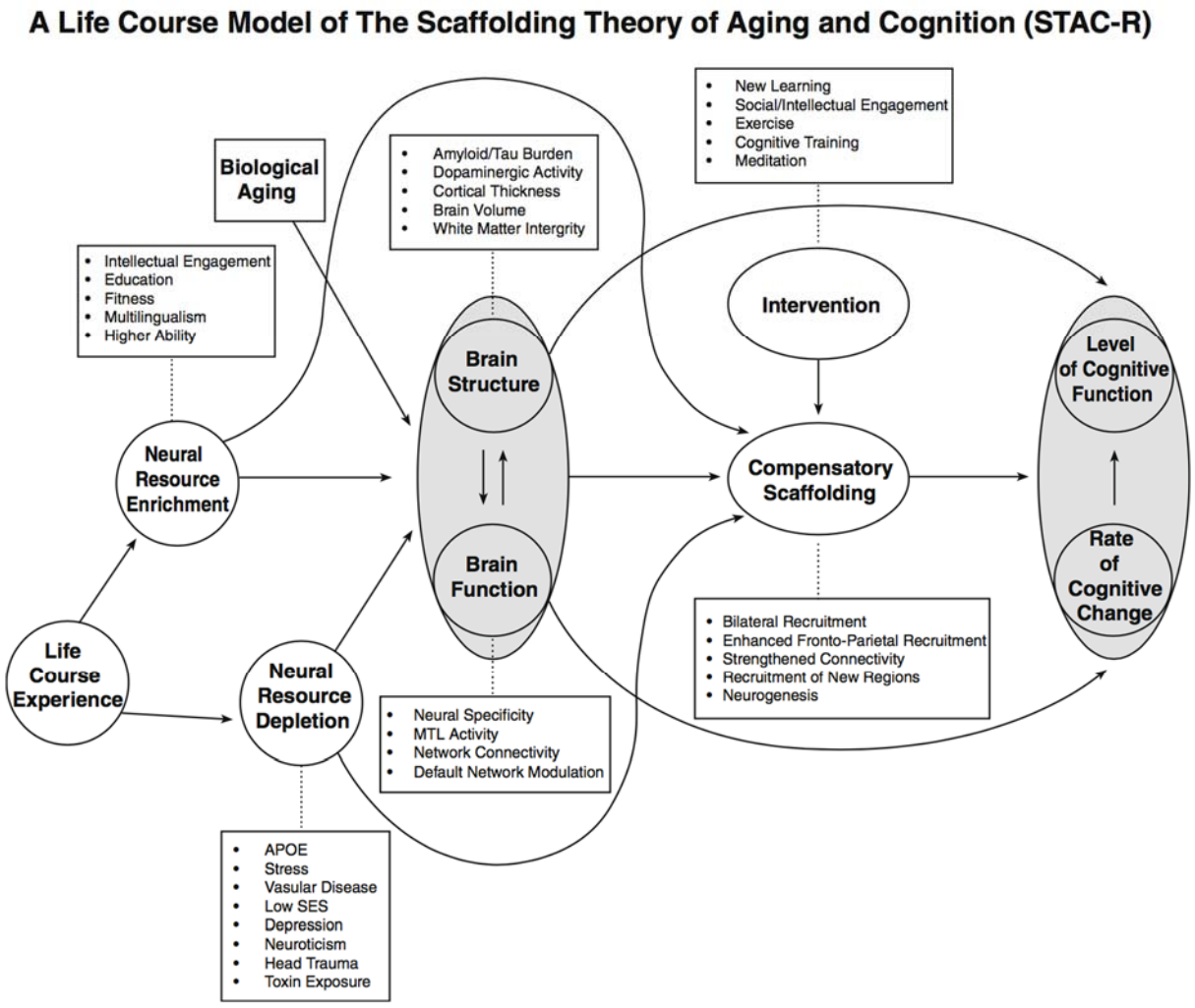


Figure 27. A comprehensive model of brain compensatory processes, including neural scaffolding and cognitive reserve, adapted from Reuter-Lorenz and Park (2014).

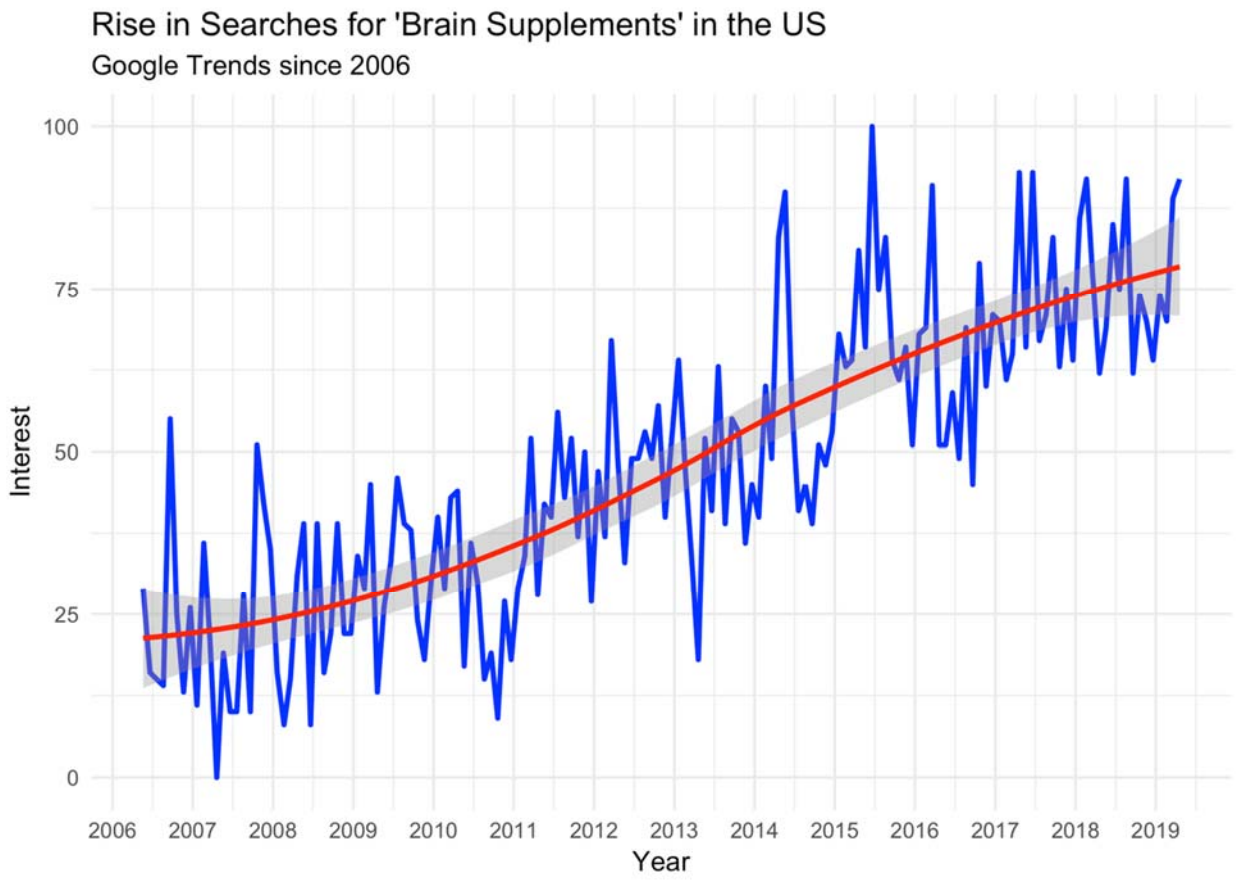


Figure 28. Google Trends data of searches for "Brain Supplements" in the United States since 2006. Interest represents the percentage of peak popularity for the term's search history.

Glossary

AD	Axial diffusivity
APOE-ε4	Apolipoprotein-E epsilon 4
ATR	Anterior thalamic radiation
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CAB	Cingulum angular bundle
CAD	Coronary artery disease
CCG	Cingulum cingulate gyrus
CNB	Computerized Neurocognitive Battery
CRF	Cardiorespiratory fitness
CST	Corticospinal tract
D-KEFS	Delis-Kaplan Executive Function System
DM	Diabetes mellitus type-II
DSM	Diagnostic Statistical Manual
DTI	Diffusion tensor imaging
EF	Executive function
ESL	English as a second language
FA	Fractional anisotropy
FLAIR	Fluid intensity inversion recovery
Fmaj	Forceps major
Fmin	Forceps minor
HDL	High density lipoprotein
HVD	Heart valve disease
HTN	Hypertension
HoTN	Hypotension
ILF	Inferior longitudinal fasciculus
IPAQ	International Physical Activity Questionnaire
LDL	Low density lipoprotein
MCI	Mild cognitive impairment
MD	Mean diffusivity
MET	Metabolic Equivalent of Task
MI	Myocardial infraction
MRI	Magnetic resonance imaging
NKI-RS	Nathan Kline Institute – Rockland Sample
PCET	Penn Conditional Exclusion Test
RD	Radial diffusivity
SES	Socioeconomic status
SLF	Superior longitudinal fasciculus
TBSS	Tract-based spatial statistics
TOI	Tracts of interest
UNC	Uncinate fasciculus
VO_2 max	Volume oxygen maximum
WM	White matter