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White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults☆

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ABSTRACT

White matter structure declines with advancing age and has been associated with a decline in memory and executive processes in older adulthood. Yet, recent research suggests that higher physical activity and fitness levels may be associated with less white matter degeneration in late life, although the tract-specificity of this relationship is not well understood. In addition, these prior studies infrequently associate measures of white matter microstructure to cognitive outcomes, so the behavioral importance of higher levels of white matter microstructural organization with greater fitness levels remains a matter of speculation. Here we tested whether cardiorespiratory fitness (VO_{2max}) levels were associated with white matter microstructure and whether this relationship constituted an indirect pathway between cardiorespiratory fitness and spatial working memory in two large, cognitively and neurologically healthy older adult samples. Diffusion tensor imaging was used to determine white matter microstructure in two separate groups: Experiment 1, $N = 113$ (mean age = 66.61) and Experiment 2, $N = 154$ (mean age = 65.66). Using a voxel-based regression approach, we found that higher VO_{2max} was associated with higher fractional anisotropy (FA), a measure of white matter microstructure, in a diverse network of white matter tracts, including the anterior corona radiata, anterior internal capsule, fornix, cingulum, and corpus callosum ($P_{FDR\text{-}corrected} < .05$). This effect was consistent across both samples even after controlling for age, gender, and education. Further, a statistical mediation analysis revealed that white matter microstructure within these regions, among others, constituted a significant indirect path between VO_{2max} and spatial working memory performance. These results suggest that greater aerobic fitness levels are associated with higher levels of white matter microstructural organization, which may, in turn, preserve spatial memory performance in older adulthood.

Introduction

The aging brain experiences both macro- and microstructural changes, including gray matter atrophy and degeneration of white matter tracts. Older adults are particularly susceptible to precipitous declines in white matter, with anterior tracts showing the most pronounced degradation (Burzynska et al., 2010; Pfefferbaum and Sullivan, 2003; Salat et al., 2005; Westlye et al., 2009). Age-related

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declines in white matter microstructure may lead to disruptions in neural communication, which, in turn, could lead to consequent declines in cognitive function. This notion is supported by studies combining behavioral measures of cognitive performance and diffusion tensor imaging (DTI), which demonstrate that age-related decline in cerebral white matter may be related to cognitive deficits associated with aging. In particular, white matter degeneration in older adults is associated with impaired performance on memory, executive function, and processing speed tasks (Bennett and Madden, 2014; Charlton et al., 2006; Gold et al., 2010; Grieve et al., 2007; Kennedy and Raz, 2009; Madden et al., 2009; Vernooij et al., 2009; Voineskos et al., 2012).

Fortunately, moderate intensity physical activity (PA) may prevent or reverse age-related changes in neural structure and function. For example, randomized controlled trials (RCTs) have demonstrated that 6–12 months of aerobic exercise improves cognitive performance and alters gray matter structural morphology and function in older adulthood (Colcombe and Kramer, 2003; Colcombe et al., 2006; Erickson et al., 2011; Niemann et al., 2014; Ruscheweyh et al., 2011; Voelcker-Rehage et al., 2011; Voss et al., 2010b). Despite the wealth of data on associations between PA, fitness, and exercise on gray matter volume in older adults (Erickson et al., 2014) considerably less is known about these relationships with white matter microstructure. A handful of recent cross-sectional and prospective longitudinal studies provide preliminary evidence that self-reported regular PA may preserve white matter in older adulthood (Gons et al., 2013; Gow et al., 2012; Tian et al., 2014a). In addition, positive relationships between objectively measured PA using accelerometry and fractional anisotropy (FA), a measure of white matter microstructure, have been shown (Burzynska et al., 2014; Tian et al., 2015). Recent work has also examined associations between white matter microstructure and cardiorespiratory fitness (CRF) in older adulthood. CRF, often measured by VO_{2max}, a quantitative estimate of oxygen capacity and utilization during an exercise test, can be improved (increased) by aerobic exercise. Higher CRF levels have been associated with greater white matter microstructural integrity in several tracts including the cingulum, corpus callosum, superior corona radiata, and inferior longitudinal fasciculus (Hayes et al., 2015; Johnson et al., 2012; Marks et al., 2010; Tseng et al., 2013); however see Burzynska et al., 2014). Yet, despite this evidence for associations between PA, fitness, and white matter microstructure, many of these studies have been encumbered by methodological limitations that restrict the scope of interpretation. Most prior studies have had relatively small sample sizes ($n < 30$ healthy older adults) (Johnson et al., 2012; Marks et al., 2010; Tian et al., 2014b; Tseng et al., 2013), or have employed subjective measures of PA that are prone to social desirability bias and may not reflect actual PA patterns (Gons et al., 2013; Gow et al., 2012; Tian et al., 2014a). In addition, there is little agreement across studies on the particular white matter paths that correlate with PA or fitness. This may partially be due to the analytical approaches used in previous work, which in some cases has been limited to particular fiber bundles at the expense of other brain areas (Marks et al., 2010; Tian et al., 2014a). Thus, while previous research suggests a positive linear relationship between fitness and white matter microstructural integrity, regional specificity remains unclear, with small sample sizes and methodological limitations restricting interpretation.

There is also a dearth of knowledge on the role of white matter in the relationship between fitness and cognitive function. Higher levels of aerobic fitness are frequently associated with better cognitive performance and, as recent research suggests, greater white matter microstructural integrity (Hayes et al., 2015; Johnson et al., 2012; Tian et al., 2014b; Tseng et al., 2013). Given the association between white matter and cognition in healthy older adults, fitness-related variation in white matter microstructure may partially mediate the relationship between fitness and cognitive function, although this remains a matter of speculation. Only two studies have examined whether microstructural changes associated with fitness are also linked to elevated cognitive performance (Prakash et al., 2010; Voss et al., 2013b). Following a one-year aerobic exercise intervention ($n = 70$), Voss et al. (2013b) found that greater gains in CRF were associated with greater FA in prefrontal and temporal white matter. However, the increases in white matter FA post-intervention were not associated with memory improvement, although this may be a consequence of lack of statistical power for the cognitive measure employed (backward digit span) (Voss et al., 2013b). Similar patterns emerged in a study of multiple sclerosis (MS) (MS $n = 21$; Healthy controls $n = 15$), but in this study higher FA was associated with both greater fitness levels and faster processing speed (Prakash et al., 2010). Thus, while only a small number of studies have examined the link between fitness and white matter microstructure, even fewer have investigated the cognitive implications of this relationship.

Our primary aim was to further examine the relationship between CRF and white matter microstructure in older adulthood. Using diffusion imaging, we examined the relationship between CRF and tensor-based models of white matter structure in two large samples of healthy older adults (each with $n > 110$). Importantly, the two samples include an objective measure of aerobic fitness (CRF), collected using identical assessment methods, employed similar spatial memory tasks, and had similar demographic characteristics. Such similarities between two large, and independent, samples provided us with a unique opportunity to examine associations between fitness and white matter microstructure on a voxelwise basis to better characterize the tract-specificity of these associations. Based on studies of grey matter, fitness and exercise are most consistently associated with volume of the hippocampus and prefrontal cortex (Erickson et al., 2009, 2011, 2014; Weinstein et al., 2012). Therefore, we predicted that higher CRF would be associated with greater FA, particularly in tracts that facilitate communication between subcortical, hippocampal, and prefrontal regions. A secondary aim was to examine whether fitness and white matter associations would constitute significant indirect pathways to spatial working memory performance, a cognitive domain that is sensitive to aging (Schmiedek et al., 2009), and fitness effects (Erickson et al., 2009). In addition, performance on the spatial working memory paradigm used in the present investigation has been linked in prior studies to fitness and hippocampal volume (Erickson et al., 2009, 2011) and resting connectivity (Voss et al., 2010b), making this measure well-suited for the purposes of the present study. Also, similar spatial working memory paradigms were used in both experiments described here, which allowed us to test associations between white matter and spatial memory performance in two different samples. To this end, quantitative mediation modeling was applied on a voxelwise basis to both samples to investigate whether white matter microstructure statistically mediated the relationship between fitness and spatial working memory performance. We predicted that white matter microstructure would be a significant indirect pathway by which higher CRF would be associated with superior spatial working memory performance. Characterizing such pathways provides insight into the putative mechanisms and neurocognitive implications of fitness-related variation in white matter microstructure in older adults.

Methods

We tested our hypotheses in two separate samples that are described below as Experiment 1 and 2. The data analysis and analytic procedures are described last as they were the same across both experiments.

Experiment 1

Participant characteristics

One hundred and seventy-three participants between the ages of 60 and 81 (mean age 66.6 years; standard deviation = 5.6 years) were recruited to take part in a one-year, single-blind randomized controlled

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