CARDIORESPIRATORY FITNESS AND MEMORY IN OLDER ADULTS

INVESTIGATING THE RELATIONSHIP BETWEEN CARDIORESPIRATORY FITNESS AND MEMORY IN OLDER ADULTS

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ABSTRACT

Aging is associated with cognitive decline in various domains, including memory. The age-related increase in systemic inflammation has been identified as a potential mechanism contributing to these memory impairments. Specifically, elevated inflammation may impair neurotrophic factor production and function, which is important for maintaining brain health. Physical activity has been identified as a potential strategy for preventing or delaying memory decline, given its ability to reduce inflammation and stimulate neurotrophic factor expression. The present study investigated the relationship between cardiorespiratory fitness, a proxy for habitual physical activity, and memory in older adults. Inflammation and neurotrophic factors were examined as potential mechanisms mediating this relationship. Sixty-five community dwelling older adults (M_{age} = 70.6 ± 4.0) completed the Rockport 1-mile walk test to predict their cardiorespiratory fitness, as well as the Mnemonic Similarity Task to assess memory. Serum samples were collected to examine inflammatory markers, including interleukin-6 (IL-6), interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), as well as neurotrophic factors, including brain derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1). No relationship was found between cardiorespiratory fitness and memory ($p > .05$). However, older adults with greater cardiorespiratory fitness had lower levels of IL-6 ($p < .01$) and TNF-α ($p < .01$) and trended towards higher levels of BDNF ($p = .078$). Furthermore, IL-6 was negatively correlated with IGF-1 ($p < .01$), suggesting higher inflammation may impair IGF-1 production. Contrary to our hypotheses, sequential mediation analyses revealed no indirect effect of inflammatory markers and neurotrophic factors on the relationship between cardiorespiratory fitness and memory. Our results suggest that cardiorespiratory fitness may promote favourable changes in inflammatory markers and

neurotrophic factors, which—given previous literature—could help to support brain health with advancing age. More research is needed to further examine the relationship between cardiorespiratory fitness and memory.

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LIST OF ABBREVIATIONS

BDNF	Brain derived neurotrophic factor
CBV	Cerebral blood volume
CRP	C-reactive protein
DG	Dentate gyrus
ELISA	Enzyme-linked immunosorbent assay
fMRI	functional magnetic resonance imaging
HIIT	High-intensity interval training
IGF-1	Insulin-like growth factor 1
IL-1β	Interleukin-1-beta
IL-6	Interleukin-6
LPS	Lipopolysaccharide
MCAR	Missing completely at random
MICT	Moderate-intensity continuous training
MoCA	Montreal Cognitive Assessment
MST	Mnemonic Similarity Task
TNF-α	Tumour-necrosis factor-alpha
VO_2 peak	Peak oxygen uptake

DECLARATION OF ACADEMIC ACHIEVEMENT

Alexis Bullock's role:

- Amended ethics application
- Designed study protocol and selected measures
- Recruited participants
- Scheduled visits and set up lab equipment and materials
- Trained and supervised undergraduate students who assisted with data collection
- Led data collection, analysis, and interpretation
- Prepared manuscript

Role of co-authors:

- JH obtained study funding
- JH assisted AB with ethics amendment
- JH assisted AB with study design and selection of measures
- JH assisted AB with data analysis and interpretation

INTRODUCTION

Aging is associated with declines in various domains of cognitive function, including memory, which can negatively impact quality of life and one's ability to live independently (Desai, Grossberg, & Chibnall, 2010). The low-grade systemic inflammation that occurs with advancing age, a phenomenon termed inflammaging, has been identified as a potential mechanism contributing to cognitive decline (Di Benedetto, Müller, Wenger, Düzel, & Pawelec, 2017; Ownby, 2010). Indeed, heightened levels of inflammation impair the production and function of neurotrophic factors, which are intimately involved in promoting cognitive function (Cotman, Berchtold, & Christie, 2007). Physical activity, which is any bodily movement produced by skeletal muscle that results in energy expenditure, is a promising modifiable lifestyle factor capable of preventing or delaying this age-related cognitive decline (Caspersen, Powell, & Christenson, 1985; Etnier, Drollette, & Slutsky, 2018). Physical activity reduces inflammation and enhances neurotrophic factor levels, both of which are important for maintaining brain health (Cotman et al., 2007). The beneficial effects of physical activity on cognition are thought to be mediated by gains in cardiorespiratory fitness, which represents the ability of the circulatory and respiratory systems to supply oxygen during physical activity (Caspersen et al., 1985; Colcombe & Kramer, 2003; Kramer et al., 1999; McAuley, Kramer, & Colcombe, 2004). Given the impact of age-related cognitive decline on quality of life, the present study examined the relationship between cardiorespiratory fitness and memory in a sample of community-dwelling healthy older adults and explored inflammation and neurotrophic factors as potential mechanisms underlying this relationship.

This introduction provides an overview of 1) aging and memory, 2) inflammaging and brain health, 3) physical activity and memory, and 4) potential mechanisms underlying the relationship between physical activity and memory.

Aging and memory

With age, specific aspects of memory exhibit greater decline than others (Harada, Natelson Love, & Triebel, 2013). There are two main categories of memory: declarative and non-declarative (Tulving, 1972). Declarative memory involves the conscious recollection of facts and events, whereas non-declarative memory is acquired and used unconsciously (Harada et al., 2013; Tulving, 1972). Aging primarily affects episodic memory, a form of declarative memory that involves the recollection of autobiographical or personal events that occur at a specific place and time (Harada et al., 2013). The decline in episodic memory begins in early adulthood and continues until age 60, after which the magnitude of decline accelerates to four times greater than those under the age of 60 (Salthouse, 2009). Since increasing age is the greatest risk factor for developing Alzheimer's disease, a condition that is marked by a substantial reduction in episodic memory (Lindsay et al., 2002), it is imperative to investigate strategies capable of mitigating the rate of decline that occurs with advancing age.

Episodic memory is highly reliant on the hippocampus, a brain region located in the medial temporal lobe (Burgess, Maguire, & O'Keefe, 2002; Squire, 1992; Vargha-Khadem et al., 1997). The hippocampus is composed of three subfields—the dentate gyrus (DG), area CA3, and area CA1—which each support different memory processes (Amaral & Witter, 1989; Olsen, Moses, Riggs, & Ryan, 2012). The DG is involved in pattern separation, a computational process whereby similar memories are encoded as distinct, non-overlapping representations (Kesner & Rolls, 2015; Leutgeb, Leutgeb, Moser, & Moser, 2007; McHugh et al., 2007). Area CA3 is

primarily involved in retrieving complete memory representations from partial or degraded cues, a computational process termed pattern completion (Nakazawa et al., 2002, 2003), while area CA1 is involved in encoding memories (Nakazawa, McHugh, Wilson, & Tonegawa, 2004). Information first enters the hippocampus from the entorhinal cortex, which projects to the DG via the perforant path (Amaral & Witter, 1989; Voss et al., 2019). The entorhinal cortex contains fewer neurons than the DG and this projection from a smaller to larger number of neurons is thought to facilitate pattern separation processes (Myers & Scharfman, 2011; Treves & Rolls, 1992; Voss et al., 2019). From the DG, information is sent to area CA3, and finally area CA1, forming the trisynaptic hippocampal circuit (Amaral & Witter, 1989; Voss et al., 2019).

The behavioural expression of pattern separation is high-interference memory, which is the ability to discriminate between highly similar contexts and experiences (Heisz et al., 2017; Yassa & Stark, 2011), and is a crucial component of the episodic memory system. For example, high-interference memory allows an individual to differentiate their car from another car of the same make and model in a parking lot, or to accurately recall whether they took their medication today or yesterday. Evidence for the role of the DG in high-interference memory has come from rodent studies that lesion hippocampal subfields. Specifically, rats with lesions to the DG, but not area CA1, are impaired in their ability to distinguish between two similar objects (Gilbert, Kesner, & Lee, 2001). In humans, functional magnetic resonance imaging (fMRI) has revealed elevated activity in the DG/CA3 region during performance on high-interference memory tasks (Bakker, Kirwan, Miller, & Stark, 2008; Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Yassa, Lacy, et al., 2011). While it is difficult to distinguish between the DG and CA3 regions due to spatial limitations with fMRI, its possible that the increased activation in both of these

hippocampal subregions may reflect information being projected from the DG to the CA3 (Voss et al., 2019), forming the first component of the trisynaptic hippocampal circuit.

One unique property of the DG is that new neurons are continuously produced here throughout the lifespan, a process termed neurogenesis (Boldrini et al., 2018; Eriksson et al., 1998). These newborn cells are thought to contribute to the process of pattern separation by encoding novel stimuli and reducing interference between highly similar items (Becker, 2017; Finnegan & Becker, 2015). However, the DG, as well as the CA3 and perforant path, exhibit structural and functional deficits with advancing age (Yassa, Mattfeld, Stark, & Stark, 2011). Altogether, the hippocampus experiences a volume loss of 1-2% per year in healthy older adults without dementia (Raz et al., 2005). These structural changes are of clinical importance given that hippocampal volume is associated with memory performance in older adults (Rosen et al., 2003) and that hippocampal atrophy increases the risk of developing cognitive impairment (Jack et al., 2010). Mirroring these structural changes is an age-related decline in hippocampal neurogenesis in rodents (Kuhn, Dickinson-Anson, & Gage, 1996) and humans (Spalding et al., 2013). The impaired integrity of these brain regions in older adults manifests at the behavioural level as reduced high-interference memory performance (Bullock, Mizzi, Kovacevic, & Heisz, 2018; Stark, Yassa, Lacy, & Stark, 2013; Toner, Pirogovsky, Kirwan, & Gilbert, 2009). Therefore, interventions capable of stimulating the hippocampus, and more specifically the DG, may be able to mitigate this age-related decline in high-interference memory.

Inflammaging and brain health

Accompanying the age-related deterioration of the memory system is dysfunction of the immune system. With age, the immune system undergoes several modifications, a process referred to as immunosenescence (Gruver, Hudson, & Sempowski, 2007), which increases the

susceptibility to infection and auto-immune disorders, as well as decreases vaccine efficacy (Effros, 2007; McElhaney, 2005). Accompanying immunosenescence are elevated levels of circulating inflammatory markers, such as interleukin-6 (IL-6), interleukin-1-beta (IL-1β), tumour necrosis factor-alpha (TNF-α), and C-Reactive Protein (CRP), which produce chronic low-grade (i.e., low level) inflammation (Franceschi et al., 2000). This phenomenon, termed inflammaging, is a major risk factor for morbidity and mortality in older adults (Franceschi et al., 2000), and serves as a potential mechanism contributing to cognitive decline and Alzheimer's disease (Figure 1) (Di Benedetto et al., 2017; Goldeck, Witkowski, Fülop, & Pawelec, 2016).

The elevated levels of circulating inflammatory molecules that accompany aging can communicate with the central nervous system (CNS) through three major pathways to promote neuroinflammation: the humoral pathway, the neural pathway, and the cellular pathway (Miller & Raison, 2016). The humoral pathway involves cytokine passage through regions in the brain with more permeable blood brain barriers (BBB), such as the circumventricular organs, as well as the transport of cytokines into the brain via transport molecules on the BBB (Quan & Banks, 2007). The neural pathway involves the binding of cytokines to peripheral afferent nerves, such as the vagus nerve, which then send signals to the brain to initiate inflammatory processes (Quan & Banks, 2007). Lastly, the cellular pathway involves the trafficking of activated immune cells, such as monocytes, into the brain vasculature and parenchyma via chemokines (D'Mello, Le, & Swain, 2009; Miller & Raison, 2016). Together, these pathways make up the neuroimmune axis and represent the mechanisms through which the immune system is capable of modifying the inflammatory profile of the brain.

Microglia, the brain's resident immune cells, also play an important role in creating a neuroinflammatory profile. Under basal conditions, microglia are relatively quiescent and carry

out various functions that help to maintain brain homeostasis, such as surveying the environment and removing debris. Microglia are also involved in detecting heightened levels of inflammation in the periphery and responding by releasing pro-inflammatory cytokines (Cherry, Olschowka, & O'Banion, 2014). With age, microglia develop a "primed" profile that has been characterised by increased basal expression of inflammatory markers, as well as an exaggerated inflammatory response following activation of the immune system (Norden, Muccigrosso, & Godbout, 2015).

The resultant neuroinflammation has detrimental effects on neuronal health and disrupts brain homeostasis, which contributes to cognitive decline in aging (Figure 1) (Di Benedetto et al., 2017). Inflammatory mediators in the brain have been shown to inhibit hippocampal neurogenesis (Ekdahl, Claasen, Bonde, Kokaia, & Lindvall, 2003; Koo & Duman, 2008; Vallières, Campbell, Gage, & Sawchenko, 2002) and impair the production and function of neurotrophic factors, such as brain derived neurotrophic factor (BDNF) (Guan & Fang, 2006; Tong, Balazs, Soiampornkul, Thangnipon, & Cotman, 2008) and insulin-like growth factor-1 (IGF-1) (Venters et al., 1999), which are essential for the growth, survival, and development of neurons (Cotman et al., 2007). In rodents, activation of the peripheral immune system by administration of lipopolysaccharide (LPS), a cell-wall component of Gram-negative bacteria, has been shown to elicit an inflammatory response in the hippocampus, inhibit hippocampal neurogenesis (Monje, Toda, & Palmer, 2003), and decrease BDNF levels in various brain regions, including the hippocampus (Guan & Fang, 2006). Taken together, these findings suggest that the systemic inflammation observed in older adults can elicit neuroinflammation, which has detrimental effects on brain health at both the cellular and molecular level.

Cellular and molecular impairments within the brain following an inflammatory insult provide a mechanism for the observed relationship between inflammation and cognition in older

adults (Figure 1). A large body of literature supports the notion that the inflammatory profile of the brain changes with age. In rodents, the aged brain exhibits higher levels of inflammatory markers at rest compared to their younger counterparts (Godbout et al., 2005; Scheinert et al., 2015; Ye & Johnson, 1999). Furthermore, administration of LPS has been shown to induce an exaggerated inflammatory response in both the circulation and brain of aged mice, when compared to younger mice (Chen et al., 2008; Godbout et al., 2005), which manifests as impaired performance on memory tasks (Chen et al., 2008). In humans, circulating inflammatory markers have been associated with impaired cognitive function (Bettcher et al., 2012; Dik et al., 2007; Marsland et al., 2015; Tegeler et al., 2016), with higher levels of inflammation predicting subsequent cognitive decline (Marioni et al., 2009; Rafnsson et al., 2007; Weaver et al., 2002; Yaffe et al., 2003). Extending these findings, Marsland et al. (2015) demonstrated that circulating IL-6 and CRP are associated with lower cortical grey and white-matter volumes, as well as lower hippocampal volume. Since changes in brain morphology precede cognitive decline and may contribute to reduced cognition (Kramer et al., 2007; Persson et al., 2012; Raz et al., 2005), these findings suggest that the relationship between peripheral inflammation and cognition may be mediated by changes in brain morphology (Marsland et al., 2015). Thus, interventions that target the immune system and are capable of reducing inflammation are of interest for the aging population and may help to alleviate cognitive decline.

Physical activity and memory

The evidence presented herein will discuss the relationship between physical activity and cognition, with a focus on memory, in older adults. Physical activity is defined as any bodily movements produced by skeletal muscle that results in an increase in energy expenditure beyond resting levels (Caspersen et al., 1985). A subcategory of physical activity is exercise, which is

any activity that is planned, structured, repetitive, and is completed for the purpose of enhancing or maintaining physical fitness (Caspersen et al., 1985). Physical fitness is a set of health-related qualities that people have and/or aim to achieve, such as cardiorespiratory fitness and body composition (Caspersen et al., 1985). Furthermore, cardiorespiratory fitness represents the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity and thus cardiorespiratory fitness can be considered a physiological indicator of habitual physical activity (Caspersen et al., 1985). While physical activity, exercise, and cardiorespiratory fitness represent different concepts, they are related to one another and will be discussed in this thesis.

Observational evidence

A physically active lifestyle is beneficial for maintaining cognitive function with advancing age. Meta-analyses and systematic reviews of epidemiologic studies conclude that higher levels of physical activity are associated with a reduced risk of cognitive decline and dementia (Beydoun et al., 2014; Blondell, Hammersley-Mather, & Veerman, 2014; Sofi et al., 2011). Additionally, of the several modifiable risk factors for Alzheimer's disease, including diabetes, hypertension, obesity, smoking, depression, and education, the risk factor contributing to the largest proportion of Alzheimer's disease cases in the United States, and third largest worldwide, is physical inactivity (Barnes & Yaff, 2011). Thus, physical activity represents an important and promising area of study for maintaining cognition with age.

Physical activity may enhance cognitive function primarily through its impact on cardiorespiratory fitness. The cardiorespiratory fitness hypothesis proposes that fitness is a physiological mediator that explains the cognitive benefits associated with participating in physical activity (Colcombe et al., 2004; Kramer et al., 1999; McAuley et al., 2004). In older adults, greater cardiorespiratory fitness is associated with better global cognition, as well as

better domain-specific cognitive function, including memory (Freudenberger et al., 2016). While improved cardiorespiratory fitness benefits multiple cognitive domains, this thesis will focus on high-interference memory due to its reliance on hippocampal circuitry and vulnerability to age-related decline (Leal & Yassa, 2015). In young adults, the beneficial effects of physical activity on high-interference memory are mediated by cardiorespiratory fitness (Suwabe, Hyodo, Byun, Ochi, Fukuie, et al., 2017), providing support for the cardiorespiratory fitness hypothesis. In older adults, greater cardiorespiratory fitness is also associated with improved performance on a high-interference memory task (Bullock et al., 2018), as well as measures of brain integrity, such as improved cerebral blood flow (Dougherty et al., 2019) and larger hippocampal volumes (Dougherty et al., 2017; Erickson et al., 2009). Together, these results suggest that cardiorespiratory fitness is an important factor influencing brain health and prompts specific benefits for memory performance.

Exercise training

While long-term prospective studies have consistently demonstrated the cognitive benefits associated with physical activity, findings from randomized-controlled trials implementing exercise have been mixed. Meta-analytical studies and systematic reviews in young, middle-aged, and older adults have found an overall positive effect of exercise training and cardiorespiratory fitness gains on various cognitive domains, including memory (Colcombe & Kramer, 2003; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018; Smith et al., 2010); while other studies in older adults have concluded that there is insufficient evidence to support this proposed relationship (Angevaren et al., 2008; Snowden et al., 2011; Young, Angevaren, Rusted, & Tabet, 2015). One meta-analysis even found a negative relationship between cardiorespiratory fitness gains and cognitive performance, such that larger improvements in fitness were predictive

of lesser improvements in cognitive performance (Etnier, Nowell, Landers, & Sibley, 2006). One potential reason for these equivocal findings is the lack of consistency in cognitive measures used across studies (Voss et al., 2019; Young et al., 2015). For example, the review conducted by Young et al., (2015) included results from over 40 cognitive tests, which tested different aspects of cognitive function. It is difficult to interpret results from a battery of cognitive measures this large as different tasks have differing levels of sensitivity, thus grouping them together may obscure their true relationship with exercise. Therefore, it has been recommended that researchers in the field agree on a smaller set of cognitive measures to allow for better comparison across studies (Young et al., 2015).

Despite the high degree of variation in cognitive measures employed across studies, high-interference memory is a hippocampal-dependent ability that has consistently demonstrated exercise-induced improvements. In young adults, 6 weeks of high-intensity interval training (HIIT) has been shown to improve high-interference memory (Déry et al., 2013; Heisz et al., 2017). Additionally, even *acute* bouts of mild and moderate-intensity exercise in young adults are capable of augmenting high-interference memory performance (Suwabe et al., 2018; Suwabe, Hyodo, Byun, Ochi, Yassa, et al., 2017). A recent study in our laboratory investigated the effect of moderate-intensity continuous training (MICT) and HIIT on high-interference memory in older adults and found HIIT, but not MICT, improved high-interference memory (Kovacevic, 2017). This was the first study to examine the effect of exercise training, as well as the role of exercise intensity, on this memory domain in older adults, highlighting an important future direction. Taken together, these findings portray the robust influence of exercise training on high-interference memory.

Potential mechanisms underlying the relationship between physical activity and memory

Neurogenesis

One potential mechanism by which physical activity is able to enhance memory is neurogenesis. In both adult and aged mice, exercise has been shown to induce hippocampal neurogenesis (van Praag, 2005; van Praag, Christie, Sejnowski, & Gage, 1999), with greater amounts of neurogenesis being correlated with improved high-interference memory (Creer, Romberg, Saksida, van Praag, & Bussey, 2010). Furthermore, mice with ablated neurogenesis exhibit impaired performance on high-interference memory tasks, demonstrating a functional role for hippocampal neurogenesis in high-interference memory (Clelland et al., 2009). While measuring hippocampal neurogenesis directly is not yet feasible in humans, researchers have discovered potential markers of neurogenesis in humans. Pereira et al. (2007) found that aerobic exercise training increased cerebral blood volume (CBV) in the DG of both mice and middle-aged humans and that, in mice, the increase in CBV was correlated with the amount of neurogenesis, suggesting CBV may be a useful *in vivo* correlate of neurogenesis in humans. In older adults, aerobic exercise-induced improvements in cardiorespiratory fitness are correlated with increased hippocampal CBV, which suggests that the aged brain retains the plasticity to undergo these changes (Maass et al., 2015) and thus could be partly responsible for the memory benefits provided by engaging in physical activity.

Inflammation

Regular engagement in physical activity has anti-inflammatory effects (Gleeson et al., 2011) and is thus thought to be a potential treatment strategy to counteract inflammaging and memory decline (Figure 2) (Di Benedetto et al., 2017). Cross-sectionally, physically active older adults have lower levels of pro-inflammatory cytokine IL-6 and higher levels of anti-inflammatory cytokine IL-10 compared to their inactive counterparts (Jankord & Jemiolo, 2004).

Additionally, exercise training in the older adult population is able to reduce levels of circulating pro-inflammatory cytokines IL-6, TNF-α, and CRP, while also increasing anti-inflammatory cytokine IL-10 (Monteiro-Junior et al., 2018; Santos et al., 2012). In aged rats, aerobic exercise reverses the impairments in hippocampal-dependent memory caused by peripheral LPS injection, while also preventing the infection-induced increase in hippocampal IL-1β (Barrientos et al., 2011). Even without a peripheral immune challenge, aerobic exercise training improves memory performance and decreases hippocampal IL-1β in aged rodents (Speisman, Kumar, Rani, Foster, & Ormerod, 2013). This animal- and human-based evidence supports the notion that physical activity may be able to improve cognitive function by modulating the immune and neuroimmune profiles of older individuals.

Neurotrophic factors

Neurotrophic factors, such as BDNF and IGF-1, are also thought to be involved in facilitating the beneficial effects of physical activity on cognitive function (Figure 2) (Cotman et al., 2007; Voss et al., 2019). Evidence from both human and animal studies have demonstrated the role of BDNF in synaptic plasticity, neurogenesis, and cell survival (Cotman et al., 2007; Sleiman & Chao, 2015). Exercise is able to induce BDNF mRNA and protein expression in the rodent hippocampus following short (days) and long (months) training periods (Freitas et al., 2018; Neeper, Góauctemez-Pinilla, Choi, & Cotman, 1995; Voss et al., 2019; Voss, Vivar, Kramer, & van Praag, 2013) and can remain elevated for up to 2 weeks following training cessation (Berchtold, Castello, & Cotman, 2010). When the ability of BDNF to bind to its receptor, TrkB, in the hippocampus is blocked, the exercise-induced benefits on learning and memory are eliminated (Vaynman, Ying, & Gomez-Pinilla, 2004). Furthermore, when the gene encoding the TrkB receptor is ablated in adult hippocampal neural progenitor cells, mice

demonstrate impaired hippocampal neurogenesis (Li et al., 2008). These findings highlight the importance of BDNF in the exercise-cognition relationship.

In humans, an acute bout of exercise transiently increases circulating BDNF, with greater increases seen in individuals who exercise regularly (Szuhany, Bugatti, & Otto, 2015). While we cannot be certain that the levels of BDNF in the blood directly reflect that within the brain, it is estimated that the human brain contributes 70-80% to circulating BDNF at rest and during exercise (Rasmussen et al., 2009), suggesting that circulating BDNF concentration may serve as a proxy for BDNF in the brain. Resting concentrations of circulating BDNF have also been shown to increase in response to exercise training of two or more weeks in duration (Dinoff et al., 2016; Szuhany et al., 2015). Critically, greater changes in the resting concentrations of BDNF are correlated with larger changes in hippocampal volume following one year of aerobic exercise training (Erickson et al., 2011). Since BDNF is thought to play a role in exercise-induced neurogenesis, the increased hippocampal volume may be due to enhanced cell proliferation and dendritic branching (Erickson et al., 2011). Furthermore, higher levels of circulating BDNF are associated with larger hippocampi and better memory performance in older adults (Erickson et al., 2010). Nonetheless, cross-sectional studies introduce a degree of discrepancy. Some studies do find that more physically active individuals have higher levels of circulating BDNF at rest (Correia et al., 2011; Zoladz et al., 2008), but others report null results (Flöel et al., 2010). Several studies have also reported a negative relationship between cardiorespiratory fitness and circulating BDNF, such that those with higher fitness levels have lower levels of BDNF (Cho et al., 2012; Currie, Ramsbottom, Ludlow, Nevill, & Gilder, 2009; Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014; Jung, Kim, Davis, Blair, & Cho, 2011).

The reason for this discrepancy in the literature remains unclear and highlights the need for further investigation.

IGF-1 is also thought to have pro-cognitive effects due to its role in supporting synaptic plasticity, synapse density, neurotransmission, and neurogenesis (Fernandez & Torres-Alemán, 2012; Trejo et al., 2007). IGF-1 gene expression is increased in the hippocampus following a short period (5 days) of exercise in rodents (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006). IGF-1 is also produced in the periphery, transported across the blood brain barrier (Reinhardt & Bondy, 1994), and taken up into the cortex and hippocampus following an exercise bout in rodents (Carro, Nuñez, Busiguina, & Torres-Aleman, 2000). In fact, infusion of IGF-1 into the systemic circulation of sedentary rats produces many of the same benefits as exercise, including enhanced hippocampal neurogenesis (Aberg, Aberg, Hedbäcker, Oscarsson, & Eriksson, 2000; Trejo, Carro, & Torres-Aleman, 2001). When the entrance of peripheral IGF-1 into the brain is blocked, a complete inhibition of exercise-induced hippocampal neurogenesis occurs (Trejo et al., 2001). Furthermore, blocking IGF-1 receptors in the hippocampus, and thus preventing IGF-1 downstream signalling cascades, during a short period of voluntary exercise prevents the exercise-induced increase in BDNF mRNA and protein, as well as impairs performance on a hippocampal-dependent memory test (Ding et al., 2006). These results suggest that IGF-1 and BDNF may work in concert, converging on similar downstream signaling pathways, to facilitate the effects of physical activity on hippocampal plasticity and memory.

Similar to BDNF, an acute bout of exercise results in transient increases in circulating IGF-1 concentrations (Cappon, Brasel, Mohan, & Cooper, 1994; Hornum, Cooper, Brasel, Bueno, & Sietsema, 1997; Kostka, Patricot, Mathian, Lacour, & Bonnefoy, 2003; Schwarz, Brasel, Hintz, Mohan, & Cooper, 1996). In contrast, the effect of exercise training on resting

concentrations of IGF-1 appears to be less consistent. A recent systematic review investigating the relationship between exercise training, IGF-1, and cognition in older adults was unable to establish a consensus on this relationship due to mixed results, with IGF-1 levels increasing, decreasing, or remaining unchanged in response to exercise training (Stein et al., 2018). Cross-sectionally, higher levels of cardiorespiratory fitness are associated with higher levels of circulating IGF-1 in young adults, as well as older adults (Haydar, Blackman, Tobin, Wright, & Fleg, 2000; Kelly et al., 1990; Nindl, Santtila, Vaara, Hakkinen, & Kyrolainen, 2011; Poehlman & Copeland, 1990). IGF-1 levels have also been shown to correlate with cognitive performance in older adults (Arwert, Deijen, & Drent, 2005; Okereke et al., 2007; Rollero et al., 1998), with higher levels of IGF-1 predicting less subsequent cognitive decline (Kalmijn, Janssen, Pols, Lamberts, & Breteler, 2000).

Since inflammation has been shown to impair neurotrophic factor signaling within the brain, physical activity presents a potential intervention strategy for maintaining brain health into advancing age, as it promotes an anti-inflammatory environment and induces neurotrophic factor expression, both of which are conducive to improved cognitive function (Figure 2). Currently, there is limited research in humans investigating the influence of physical activity on both inflammation and neurotrophic factors, as well as their relationship to memory. The inflammation and neurotrophic factor literature is quite separate in humans, highlighting an important gap to address in the literature. A greater understanding of the mechanisms by which physical activity improves memory opens the possibility of designing feasible and effective interventions for reducing the magnitude of age-related cognitive decline.

Purpose

The purpose of the present study was to investigate the relationship between cardiorespiratory fitness, an indicator of habitual physical activity levels, and high-interference memory in older adults, as well as examine inflammatory markers and neurotrophic factors as potential underlying mechanisms. As an exploratory analysis, this study aimed to evaluate whether the relationship between cardiorespiratory fitness and high-interference memory was sequentially mediated by inflammation and neurotrophic factors. Participants completed a sub-maximal cardiorespiratory fitness assessment and high-interference memory was evaluated using a hippocampal-dependent task. Serum blood samples were collected at rest to measure peripheral concentrations of inflammatory markers, including IL-6, IL-1β, TNF-α, and CRP, as well as neurotrophic factors BDNF and IGF-1.

Hypotheses

It was hypothesized that cardiorespiratory fitness would be positively associated with high-interference memory. Additionally, it was hypothesized that greater cardiorespiratory fitness would be correlated with lower levels of inflammatory markers and higher levels of neurotrophic factors, and that inflammatory markers would be inversely correlated with neurotrophic factors. Better high-interference memory was also hypothesized to be correspondent with lower levels of inflammatory markers and higher levels of neurotrophic factors. Lastly, as an exploratory analysis, it was hypothesized that the relationship between cardiorespiratory fitness and high-interference memory would be sequentially mediated by inflammatory markers and neurotrophic factors.

METHODS

Participants

A sample size estimate was computed using G*Power software (Version 3.1; www.gpower.hhu.de), based on Suwabe et al.'s (2017) medium effect size of the relationship between cardiorespiratory fitness and high-interference memory in young adults (r = .323). According to G*Power, 72 participants were required with an alpha of .05 and a power of .80. Participants were recruited through posters and local news outlets in Hamilton and surrounding areas. Eligibility criteria included being 65 years of age or older, free from cognitive impairment, auto-immune disease, type II diabetes mellitus, and obesity (class II; BMI > 35), non-smoker, and not currently taking hormone replacement therapy or beta-blockers. Fulfillment of these criteria was assessed through verbal or written confirmation via phone or email. Eligible participants were required to gain written informed consent from their physicians to participate in the sub-maximal cardiorespiratory fitness assessment prior to enrolling in the study. This study received clearance from the Hamilton Integrated Research Ethics Board. Following study completion, participants were compensated $30 for their participation.

Materials

Cardiorespiratory fitness

The Rockport 1-mile walk test (Kline et al., 1987) was used as a cardiorespiratory fitness assessment to predict peak oxygen uptake (VO_2 peak). The Rockport 1-mile walk test has been validated in older adults, with Rockport-derived estimates of VO_2 peak correlating highly with direct measures of VO_2 peak determined by traditional graded exercise test protocols (Colcombe et al., 2004; Fenstermaker, Plowman, & Looney, 1992; Kline et al., 1987; McAuley et al., 2011). Participants walked on an indoor track and were instructed to complete the 1-mile walk as quickly as possible, without running. A trained research assistant supervised the test and recorded heart rate at each minute interval and at completion (measured using Polar FT1 heart

rate monitors), as well as the time taken to complete the 1-mile walk. Cardiorespiratory fitness was estimated using the following equation:

Predicted VO_2 peak = 132.853 – (0.0769 x weight in pounds) – (0.3877 x age in years) + (6.315 for males only) – (3.2649 x time in minutes) – (0.1565 x heart rate at completion)

The first eleven participants that enrolled in this study completed the Rockport 1-mile walk test on the indoor track located in the David Braley Athletic Centre at McMaster University. This track was subsequently closed to the public. Thus, the remainder of participants completed the Rockport 1-mile walk test on the indoor track located in the Physical Activity Centre of Excellence at McMaster University.

Body composition

Body composition was assessed using air displacement plethysmography (BOD POD, Cosmed USA Inc.). Prior to each testing session, the BOD POD was calibrated according to the manufacturer's guidelines using a cylinder of known volume (50.053 L). Participants were asked to avoid food, water, and exercise for at least 2 hours prior to testing. Participants were tested wearing form-fitted clothing, such as swimsuits or compression shorts, and swimming caps. Participants were also instructed to remove all jewellery, eyeglasses, and any other types of accessories. Height was measured to the nearest 0.5 cm using a stadiometer and body mass was measured to the nearest 0.001 kg using the BOD POD calibrated electronic scale. Then, participants entered the BOD POD chamber, where they were asked to sit still and breathe normally. Body volume was measured twice; if the first and second measurements were not consistent, a third measurement was taken. Thoracic gas volume was predicted using standard prediction equations based on sex, age, and height; this value was then incorporated into the calculation of body volume, as per the manufacturer's recommendations (McCrory, Gomez,

Bernauer, & Mole, 1995). Percent body fat was calculated from body density determined by the BOD POD using the Siri equation (Siri, 1961).

Global cognition

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) was used to assess global cognition as a descriptive characteristic of overall cognitive status. The MoCA assesses multiple domains of cognition, including visuospatial abilities, executive function, memory, attention, concentration, working memory, language, and orientation. The minimum score on the MoCA is 0 and the maximum score is 30, with a higher score indicating better cognitive function (Nasreddine et al., 2005). A recommended cut-off score of 23 has been suggested for differentiating healthy aging from Mild Cognitive Impairment (Carson, Leach, & Murphy, 2018).

Memory

An adapted version of the Mnemonic Similarity Task (MST) (Kirwan & Stark, 2007; Stark, Stevenson, Wu, Rutledge, & Stark, 2015; Stark et al., 2013) was used to assess high-interference memory. This task involved an incidental study phase during which participants were presented 60 full colour images of everyday objects against a white background on a computer screen for 2 seconds each. A blank screen preceded each trial for 500 milliseconds. The images were shown individually and in random order for each participant. Participants were asked to classify each image as either indoor or outdoor using the "1" and "2" key, respectively, on the number pad to aid in encoding and maintain focus. Immediately after completion of the study phase, participants completed a test phase where they were instructed to classify objects as either "Old" (repetitions), "Similar" (lures), or "New" (foils) using the "1", "2", and "3" keys, respectively, on the number pad. "Old" objects were objects previously presented in the study

phase, “Similar” objects were highly similar, but not identical, to objects presented in the study phase, and “New” objects were objects that were not previously presented. The test phase consisted of 90 trials presented in random order: 30 repetitions, 30 lures, and 30 foils. In this phase, each image was presented on the computer screen until the participant responded.

High-interference memory was assessed as the ability to correctly identify lure items as “Similar”. Performance on the task was quantified as the proportion of “Similar” responses to lure images minus the proportion of “Similar” responses to foil images, which corrects for any bias the participant may have to use the “Similar” response overall (Stark et al., 2013). This formula can be seen below:

High-interference memory = [p(“Simiar”|Lure image) – p(“Similar”|Foil image)]

Data were inspected to ensure task comprehension; participants who did not use all target keys were assumed to have not understood task instructions and thus, were removed from all high-interference memory analyses. One participants data from the MST was removed for this reason.

Activity tracking

Participants were equipped with a Fitbit Flex 2 as a descriptive characteristic of habitual physical activity levels (Fitbit Inc., San Francisco, CA). Participants were instructed to wear the device on their non-dominant wrist during waking hours for a period of 7 days. The validity of the Fitbit for measuring steps has been demonstrated previously in a sample of community-dwelling older adults (Paul et al., 2015). Fitbit tracker data was extracted from the Fitbit app interface as the number of steps taken each day. Step counts from the Fitbit were averaged over the 7-day period to compute average steps/day.

Inflammatory markers and neurotrophic factors

Peripheral blood samples were collected in the morning, between 8:00 – 11:00 AM, following 12 hours of fasting. Participants were also instructed to avoid engaging in vigorous exercise, as well as to avoid consumption of alcohol and caffeine, for 24 hours prior to their scheduled visit. Serum samples were collected into BD Vacutainer Serum tubes (BD, Franklin Lanes, NJ). The tubes were allowed 30 minutes to clot at room temperature and were then centrifuged at 1000 xg for 15 minutes at 4ºC. The supernatant was aliquoted into 1.5 mL Eppendorf tubes and stored at -20ºC until analysis.

Serum measurements of IL-6, IL-1β, TNF-α, CRP, BDNF, and IGF-1 were quantified using enzyme-linked immunosorbent assays (ELISAs) according to kit specifications (R&D Systems; Minneapolis, MN, USA). All standards and samples were run in duplicate. The optical density was determined at 450 nm, with wavelength correction set at 540 nm, using the Tecan Infinite M1000 PRO plate reader (Tecan Group Ltd., Männedorf, Switzerland).

Procedure

Participants visited the laboratory on three separate occasions. At the first visit, participants completed demographic questionnaires and performed the Rockport 1-mile walk test to predict their cardiorespiratory fitness. At the second visit, participants underwent the body composition assessment, completed the global cognition assessment, and received the activity tracker. Following the 7 days of activity tracking, participants returned to the laboratory for their third visit. At this visit, the serum samples were collected, and participants completed the memory task. Participants were encouraged to bring a snack to consume at the second and third visits prior to completing the cognitive tasks so as to avoid the potential influence of fasting on cognitive performance (Benau, Orloff, Janke, Serpell, & Timko, 2014).

The first eleven participants enrolled in the study visited the laboratory on two separate occasions, as opposed to three. At the first visit, these participants completed the demographic questionnaires, body composition assessment, global cognition assessment, performed the Rockport 1-mile walk test to predict their cardiorespiratory fitness, and received the activity tracker. Following the 7 days of activity tracking, participants returned to the laboratory for their second visit. At this visit, the serum samples were collected, and participants completed the memory task. These participants were also encouraged to bring a snack to consume at the first and second visits prior to completing the cognitive tasks so as to avoid the potential influence of fasting on cognitive performance (Benau et al., 2014). The study was restructured from two visits to three visits following the closure of the indoor track located in the David Braley Athletic Centre. The indoor track located in the Physical Activity Centre of Excellence had limited availability, thus the study protocol was spread across three visits to maximize the number of participants we were able to schedule on the track in the available time slots.

Statistical analysis

Data was analyzed using IBM SPSS Statistics Software 23. Descriptive statistics were computed for all study variables. For all statistical analyses, a p value (two-tailed) of $<.05$ was considered significant.

Partial correlations were conducted to verify that cardiorespiratory fitness was associated with average steps/day. Age and sex were included as covariates.

Since the primary objective of the present study was to investigate the relationship between cardiorespiratory fitness and memory in older adults, we computed partial correlations to examine the association between cardiorespiratory fitness and high-interference memory. Age, sex, and years of education were included as covariates.

To investigate the potential mechanisms related to cardiorespiratory fitness and high-interference memory, partial correlations were computed to assess the relationship of cardiorespiratory fitness with inflammatory markers (IL-6, IL-1β, TNF-α, CRP) and neurotrophic factors (BDNF, IGF-1). Age and sex were included as covariates. Partial correlations were also conducted to examine the association among inflammatory markers (IL-6, IL-1β, TNF-α, CRP) and neurotrophic factors (BDNF, IGF-1). Age and sex were included as covariates. Next, correlations were conducted to examine the association of inflammatory markers (IL-6, IL-1β, TNF-α, CRP) and neurotrophic factors (BDNF, IGF-1) with high-interference memory. Age, sex, and years of education were included as covariates.

As an exploratory analysis and to test the hypothesis that inflammatory markers and neurotrophic factors mediate the relationship between cardiorespiratory fitness and high-interference memory, a sequential mediation analysis was conducted using Model 6 in the *PROCESS* software macro v3.3 for SPSS (Hayes, 2018). Age, sex, and years of education were included as covariates for all mediations. Bootstrap procedures utilizing 10,000 simulations were computed and a 95% confidence interval that does not cross zero is indicative of a significant indirect (mediation) effect.

RESULTS

Data screening and assumptions

Data were screened for normality using the Kolmogrov-Smirnov test and through visual inspection of histograms. All analyzed data were normally distributed. Data were also screened for extreme outliers: values beyond quartiles 1 (Q1) and 3 (Q3) with a step of 1.5 times the interquartile range (IQR; i.e., values <Q1-1.5*IQR or >Q3+1.5*IQR). Two participants were identified as outliers in cardiorespiratory fitness, and five participants were identified as outliers

in inflammatory markers (IL-6: n=1, TNF-α: n=1, IL-6 and TNF-α: n=1 CRP: n=2). Thus, a total of seven participants were removed from analyses, resulting in a final sample size of 65. The serum concentration of IL-1β was only detectable in 30% of the sample; thus, IL-1β was not included in analyses.

Data were then screened for missing cells; 3.1% of the data was missing. Missing values were present in the following variables: cardiorespiratory fitness (n = 1), average steps/day (n = 4), high-interference memory (n = 5), BDNF (n = 5), IGF-1 (n = 5), IL-6 (n = 5), TNF-α (n = 5), and CRP (n = 6). The pattern of missingness was considered to be missing completely at random (MCAR), according to Little's MCAR test. Missing cells were subsequently imputed using expectation-maximization (Tabachnick & Fidell, 2007). For two participants expectation-maximization imputed values outside the physiological range for CRP (values < 0). Analyses were conducted on the original data, with missing values excluded pairwise, and on the imputed data. In all cases, analyses produced nearly identical results. Thus, results of the analyses using the original data are reported, with missing values excluded pairwise.

Descriptive characteristics

Descriptive characteristics for the study sample are presented in Table 1**.** Participants were between 65-80 years of age (M ± SD: 70.6 ± 4.0), predominantly female (41/65), and well-educated. Performance on the MoCA ranged from 17-30 (M ± SD: 25.9 ± 2.8). While seven participants fell below the recommended cut-off score of 23 for differentiating healthy aging from Mild Cognitive Impairment (Carson et al., 2018), all participants reported that they were free from any diagnosis of cognitive impairment and thus met the inclusion criteria.

Partial correlations

Partial correlations confirmed that cardiorespiratory fitness was positively associated with average steps/day ($r(56) = .478$, $p < .001$) .

Table 2 presents mean values for cardiorespiratory fitness, memory, and biomarkers and Table 3 presents partial correlations between these variables. There was no association between cardiorespiratory fitness and high-interference memory ($r(54) = -.009$, $p = .950$; Figure 3). However, cardiorespiratory fitness was negatively associated with IL-6 ($r(55) = -.316$, $p = .016$; Figure 4) and TNF-α ($r(55) = -.352$, $p < .01$; Figure 5), but not CRP ($r(54) = -.110$, $p = .419$). There was a trend towards a positive relationship between cardiorespiratory fitness and BDNF ($r(55) = .235$, $p = .078$; Figure 6), but this was not seen with IGF-1 ($r(55) = -.013$, $p = .925$).

Among the inflammatory markers, CRP was positively associated with IL-6 ($r(55) = .369$, $p < .01$) and TNF-α ($r(55) = .394$, $p < .01$), and IL-6 and TNF-α were positively correlated with one another ($r(56) = .264$, $p = .045$). There was also a negative correlation between IL-6 and IGF-1 ($r(56) = -.441$, $p < .01$; Figure 7). No additional correlations were observed among the inflammatory markers and neurotrophic factors (all $p > .05$).

High-interference memory was not associated with the inflammatory markers or neurotrophic factors (all $p > .05$).

Sequential mediation analysis

As an exploratory analysis, inflammatory markers and neurotrophic factors were tested as sequential mediators between cardiorespiratory fitness and high-interference memory (Figure 8). Cardiorespiratory fitness served as the independent variable (X), high-interference memory served as the dependent variable (Y), and each inflammatory marker (IL-6, TNF-α, CRP; M_1) and neurotrophic factor (BDNF, IGF-1; M_2) served as the mediators. Age, sex, and years of

education were entered as covariates for all mediations. All six mediation models indicated no significant indirect effect (Table 4) .

DISCUSSION

The current study aimed to examine the relationship between cardiorespiratory fitness and high-interference memory in older adults, and to explore whether inflammatory markers and neurotrophic factors underlie this relationship. An association between cardiorespiratory fitness and high-interference memory was not observed, and further analyses revealed that inflammatory markers and neurotrophic factors did not sequentially mediate any relationship between fitness and memory. However, older adults with higher cardiorespiratory fitness had lower levels of inflammatory markers IL-6 and TNF-α and a trend towards higher levels of BDNF. Furthermore, lower levels of IL-6 were associated with higher levels of IGF-1.

Cardiorespiratory fitness and high-interference memory

Our primary hypothesis was that cardiorespiratory fitness would be positively associated with high-interference memory, but we did not find evidence to support this. This is in contrast with previous literature that has demonstrated an association between the two in both younger and older adults (Bullock et al., 2018; Suwabe, Hyodo, Byun, Ochi, Fukuie, et al., 2017). A potential explanation for the non-significant relationship is the influence of other lifestyle factors, such as socially and mentally stimulating activities, on memory (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012), which we did not control for. Indeed, engagement in sociocognitive activity is associated with better memory performance in older adults (Clark, Vandermorris, & Heisz, 2015). Furthermore, older adults who engage in more socially and mentally stimulating activities demonstrate less subsequent cognitive decline (Ghisletta, Bickel, & Lövdén, 2006; Lövdén, Ghisletta, & Lindenberger, 2005; Small, Dixon, McArdle, & Grimm,

2012). Thus, it is possible that the older adults in our sample with lower levels of cardiorespiratory fitness were engaging in other lifestyle activities known to enhance memory. This is consistent with the notion of cognitive reserve (Stern, 2009)—a concept that refers to the individual differences that allow some individuals to tolerate and compensate for the age-related changes in the brain better than others (Nyberg et al., 2012; Stern, 2009). Evidence suggests that 'enriched' lifestyles involving mentally, socially, and physically stimulating activities help to support and build this cognitive reserve (Nyberg et al., 2012; Scarmeas et al., 2003). This represents an important area for future research; particularly, examining whether individuals who participate in lifestyle activities known to maintain brain health (i.e., mental, social, and physical activities) are also less vulnerable to brain pathology when it does eventually occur (Nyberg et al., 2012).

Additionally, it is important to consider the specificity of the task to target high-interference memory, especially with respect to the role of target-lure similarity. Although not coded for in the present study, target-lure similarity is the degree of mnemonic similarity between the target (i.e., image presented in the 'study phase') and the lure (i.e., highly similar image presented in the 'test phase'), with a greater degree of mnemonic similarity generating higher levels of interference. Research in young adults suggests that the relationship between cardiorespiratory fitness and performance on the MST is influenced by the degree of target-lure similarity, such that fitness is only associated with high-interference memory when there are moderate levels of interference, but not when there are low or high levels of interference (Suwabe, Hyodo, Byun, Ochi, Fukuie, et al., 2017). A similar pattern of results emerges with acute exercise, such that an acute bout of light and moderate-intensity exercise improves performance only on moderate and high similarity lures (Suwabe et al., 2018; Suwabe, Hyodo,

Byun, Ochi, Yassa, et al., 2017). Therefore, it is possible that the influence of cardiorespiratory fitness on high-interference memory was obscured because our implementation of the task did not take into account target-lure similarity.

Potential mechanisms: inflammation and neurotrophic factors

Our secondary objective was to investigate potential mechanisms underlying the relationship between cardiorespiratory fitness and high-interference memory. Although there was no association between fitness and memory, further analyses were carried out to examine how inflammatory markers and neurotrophic factors relate to both fitness and memory, as well as to one another.

Cardiorespiratory fitness was negatively associated with both IL-6 and TNF-α, such that those with higher fitness levels had lower levels of pro-inflammatory cytokines. Given that aging is associated with immunosenescence and chronic low-grade inflammation, our results support the notion that increased levels of physical activity, and thus greater cardiorespiratory fitness, may help to restore a more 'youthful' immune profile through its anti-inflammatory effects (Gleeson et al., 2011; Jankord & Jemiolo, 2004; Monteiro-Junior et al., 2018; Santos et al., 2012). Indeed, it has been suggested that many of the characteristic features of immunosenescence observed in older adults are driven by the reduced levels of physical activity that occur with advancing age (Duggal, Pollock, Lazarus, Harridge, & Lord, 2018).

Not all markers of inflammation were associated with fitness. Specifically, we did not observe an inverse relationship between CRP and cardiorespiratory fitness, despite a positive association between CRP and both IL-6 and TNF-α. Since IL-6 is the primary stimulus for the hepatic synthesis of CRP (Du Clos, 2000), it is often expected that these two inflammatory markers will respond similarly to anti- or pro-inflammatory stimuli, but this is not always the

case. A previous study in older women investigating cardiovascular risk factors found similar results as shown here, such that exercise frequency was negatively correlated with circulating IL-6, but not CRP (Bermudez, Rifai, Buring, Manson, & Ridker, 2002). That study also reported that other cardiovascular risk factors, such as alcohol use, were discordantly associated with either IL-6 or CRP (Bermudez et al., 2002). Taken together, these results suggest that IL-6 and CRP may be differentially associated with cardiorespiratory fitness, and that there may be IL-6 independent pathways that influence CRP levels.

Since the immune system is capable of communicating with the brain (Quan & Banks, 2007), it has been suggested that physical activity may promote brain health by reducing neuroinflammation (Di Benedetto et al., 2017). We hypothesized one mechanism by which lower levels of inflammation may promote memory is via its influence on neurotrophic factors (Cotman et al., 2007; Di Benedetto et al., 2017). Indeed, we found a negative correlation between IL-6 and IGF-1, such that those with higher levels of pro-inflammatory cytokine IL-6 had lower levels of IGF-1. Although prior work has demonstrated a similar relationship with frail older adults (Leng et al., 2004), disabled older women (Cappola et al., 2003), and individuals with rheumatoid arthritis (De Benedetti et al., 1997), this is one of the first studies to investigate the relationship between IL-6 and IGF-1 in healthy older adults.

With respect to hippocampal function and memory, animal models of rheumatoid arthritis with high serum levels of IL-6 have demonstrated impaired IGF-1 receptor signaling in the hippocampus, which is associated with reduced hippocampal neurogenesis and smaller hippocampal volume (Andersson et al., 2018). However, we did not find associations between IL-6 or IGF-1 with high-interference memory in our healthy older adult sample. In fact, none of our inflammatory markers or neurotrophic factors were associated with high-interference

memory. One potential explanation for this is that the sample of older adults participating in this study were less immunosenescent than the general population, and thus had overall lower levels of inflammatory markers. The nonsignificant associations between inflammatory markers and neurotrophic factors with memory may also come back to the idea of cognitive reserve; specifically, within our sample of healthy older adults, potential underlying brain pathologies caused by inflammation may have not yet accumulated to the point of compromised memory function. This reasoning is consistent with prior work, which has demonstrated that higher levels of inflammation at baseline are associated with an increased rate of memory decline at follow up, despite a nonsignificant association between inflammation and memory at baseline (Mooijaart et al., 2013). Thus, it is possible that if the present study tracked this sample of older adults over time, those with higher inflammation may exhibit more accelerated memory decline.

Although we found a reciprocal relationship between inflammation and IGF-1, the same was not observed for BDNF. It is important to note that much of the work investigating the relationship between inflammation and BDNF has been conducted *in vitro* or in animal models and has measured hippocampal BDNF expression (Calabrese et al., 2014; Patterson, 2015). Our measurements of BDNF were derived from the circulation and thus we cannot be certain the extent to which peripheral BDNF represents central BDNF.

Furthermore, we only observed a trending positive correlation between cardiorespiratory fitness and BDNF, consistent with many prior studies (though not all, see Cho et al., 2012; Currie et al., 2009; Huang et al., 2014; Jung et al., 2011) that have reported higher resting levels of BDNF in physically active and exercise-trained subjects (Correia et al., 2011; Szuhany et al., 2015; Zoladz et al., 2008). Another methodological consideration with BDNF measurements in humans is whether it is quantified in plasma or serum. Plasma samples represent BDNF that

circulates freely (unbound), while serum samples represent both free (unbound) BDNF and BDNF stored in platelets (Walsh & Tschakovsky, 2018). While most of the literature investigating the relationship between exercise and BDNF has measured BDNF in the serum, it would be beneficial for studies to include measurements of BDNF in the serum, plasma, platelets, as well as determine the amount of BDNF per platelet (Walsh & Tschakovsky, 2018). The functional relevance of platelet-derived BDNF in relation to cardiorespiratory fitness and brain health is unclear, thus investigating the relative contribution of different sources of circulating BDNF to the total BDNF concentration may help to further clarify these relationships.

We also found no association between cardiorespiratory fitness and IGF-1. Although some cross-sectional studies have demonstrated a positive relationship between cardiorespiratory fitness and IGF-1 (Haydar et al., 2000; Kelly et al., 1990; Nindl et al., 2011; Poehlman & Copeland, 1990), exercise training studies have yielded varying results, with IGF-1 levels increasing, decreasing, or remaining unchanged (Stein et al., 2018). Indeed, resting concentrations of IGF-1 are susceptible to fluctuations and intra-individual variability given that the primary source of IGF-1 synthesis at rest is the liver (Berg & Bang, 2004). Liver-derived IGF-1 can be influenced by growth hormone availability, which is a hormone upstream of IGF-1 that stimulates its production, as well as nutritional factors (Berg & Bang, 2004; Nindl & Pierce, 2010). For example, if the energy and protein demands associated with a physically active lifestyle are not being fulfilled, production of IGF-1 by the liver may actually decrease (Berg & Bang, 2004; Smith, Clemmons, Underwood, Ben-Ezra, & McMurray, 1987). This introduces a source of variability that may have contributed to the nonsignificant association between cardiorespiratory fitness and IGF-1 observed in the present study.

Finally, we explored the hypothesis that inflammatory markers and neurotrophic factors mediate a relationship between cardiorespiratory fitness and high-interference memory. While the nonsignificant association between cardiorespiratory fitness and high-interference memory did not support our primary hypothesis, the absence of a relationship between the independent and dependent variable does not prevent the possibility of mediation (Hayes, 2018). That said, the results indicated that there were no sequential indirect effects of any the inflammatory markers and neurotrophic factors on high-interference memory. When interpreting these results, it is important to consider the cross-sectional nature of our study. Specifically, the hypothesized mediation model follows a temporal dynamic, which we were unable to capture with the present study design.

An additional factor that may have obscured potential relationships between fitness, inflammation, neurotrophic factors, and memory is that we only captured resting levels of circulating BDNF and IGF-1. The influence of resting concentrations of BDNF and IGF-1 on brain health is not entirely understood. Since acute exercise transiently increases both circulating BDNF (Rojas Vega et al., 2006; Schmidt-Kassow et al., 2012) and IGF-1 (Schwarz et al., 1996), it may be that these acute increases in neurotrophic factors, rather than their resting concentrations, mediate the structural and functional changes that occur in the brain with regular exercise, such as increased hippocampal volume and enhanced memory (Erickson et al., 2011; Maass et al., 2016, 2015).

Strengths and limitations

The present study addressed an important gap in the literature by exploring inflammatory markers and neurotrophic factors in the context of cardiorespiratory fitness and high-interference memory in healthy older adults. The inclusion of various inflammatory markers and neurotrophic

factors in the present study should be viewed as a strength as the results help to inform specific pathways that should be investigated further in the context of human brain health, such as the association between IL-6 and IGF-1. In humans, the literature has largely focused on inflammation and neurotrophic factors as separate mechanisms, but evidence from animal models suggests these mechanisms interact via downstream signaling pathways (Cotman et al., 2007). Specifically, animal studies demonstrate that exercise reduces inflammatory markers within the hippocampus (Barrientos et al., 2011; Speisman et al., 2013) and stimulates neurotrophic factor expression (Ding et al., 2006; Neeper et al., 1995), and that exercise can blunt the inflammation-induced impairments on neurotrophic factor expression (Barrientos et al., 2011). These exercise-induced effects then promote enhanced memory functions (Cotman et al., 2007; Voss et al., 2013). However, as discussed throughout this thesis, findings in humans have been much less consistent for a variety of reasons, including the limitations discussed below.

The memory task implemented in the present study can be seen as both a strength and a limitation. The MST tasks pattern separation and can be viewed as a stress test for the hippocampus (Voss et al., 2019). Since this task is able to specifically tap into hippocampal-dependent processes, it has been proposed to be the most sensitive to early deteriorations in the hippocampal system that may occur before larger, more advanced memory impairments (Voss et al., 2019). Despite these strengths, the present study did not incorporate target-lure similarity into the MST, as noted above. We attempted to address this limitation post hoc by sorting each lure stimuli into bins based on the degree of mnemonic similarity to the target image (Yassa, Lacy, et al., 2011). Unfortunately, the stimuli presented in our MST did not completely match up with those used by Yassa et al. (2011), thus we were unable to complete the binning process. Since the degree of target-lure similarity has been shown to influence the relationship between

cardiorespiratory fitness and high-interference memory (Suwabe, Hyodo, Byun, Ochi, Fukuie, et al., 2017), as well as the effects of acute exercise on high-interference memory (Suwabe et al., 2018; Suwabe, Hyodo, Byun, Ochi, Yassa, et al., 2017), failing to incorporate this into the MST may have obscured the results.

The cross-sectional design of the current study is a limitation, as we cannot establish causality with regards to the observed relationships between fitness, inflammation, and neurotrophic factors. Additionally, this study implemented a sub-maximal cardiorespiratory fitness assessment, known as the Rockport 1-mile walk test (Kline et al., 1987). While this test has been validated in older adults (Colcombe et al., 2004; Fenstermaker et al., 1992; Kline et al., 1987; McAuley et al., 2011), a traditional graded exercise test to maximal exertion would have provided a more valid measure of one's cardiorespiratory fitness levels.

Lastly, the sample of older adults in the present study were relatively healthy and well educated, which may not be representative of the older adult population, thus limiting the generalizability of these findings.

Future directions

Future research is needed to explore the relationship between inflammatory markers and neurotrophic factors in humans, and whether physical activity is able to promote favourable changes in these biomarkers to enhance memory function. Studies investigating both the acute effects of exercise on relevant biomarkers, as well as the long-term changes associated with exercise training and physical activity participation, are required to gain a better understanding of potential mechanisms and to establish causality. By examining both the short and long-term effects of exercise, researchers can elucidate the relevance of acute exercise-induced changes in biomarkers, as well as resting concentrations of biomarkers, on memory. Furthermore, where

possible, imaging techniques should be implemented to investigate associated neurobiological mechanisms. Incorporating imaging data alongside behavioural tests of memory will also provide an opportunity to investigate the cognitive reserve theory and identify variables that may contribute to this reserve.

Conclusions

The present study demonstrated that greater cardiorespiratory fitness is associated with lower levels of inflammation and a trend towards higher levels of BDNF. Furthermore, older adults with lower inflammation have higher levels of IGF-1, providing evidence for a reciprocal relationship between inflammation and neurotrophic factor production. Although we did not observe a relationship between fitness and high-interference memory in our sample of older adults, the results suggest that cardiorespiratory fitness may promote favourable changes in inflammatory markers and neurotrophic factors that could help to support brain health with advancing age.

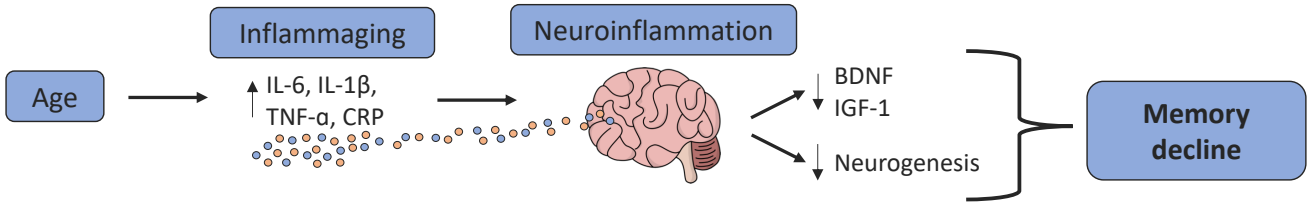


Figure 1. Potential mechanisms underlying age-related memory decline. Aging is associated with elevated levels of circulating inflammatory markers, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), and C-reactive protein (CRP); a phenomenon termed inflammaging. These inflammatory markers can communicate with the central nervous system to promote neuroinflammation. Within the brain, inflammatory markers impair the production and function of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), and inhibit hippocampal neurogenesis, resulting in memory decline.

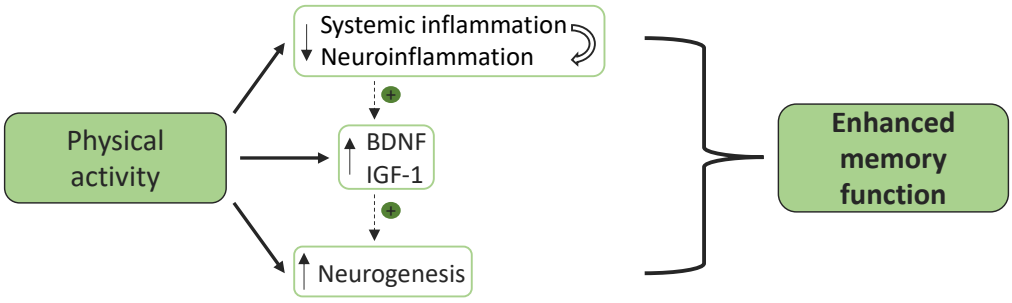


Figure 2. Potential mechanisms underlying the beneficial effects of physical activity on memory. Physical activity reduces inflammation in the periphery and within the brain, induces neurotrophic factor expression, including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), and stimulates hippocampal neurogenesis. The anti-inflammatory environment achieved through regular physical activity supports the production and function of neurotrophic factors, which in turn promotes the physical activity-induced increase in neurogenesis. The result is enhanced memory function.

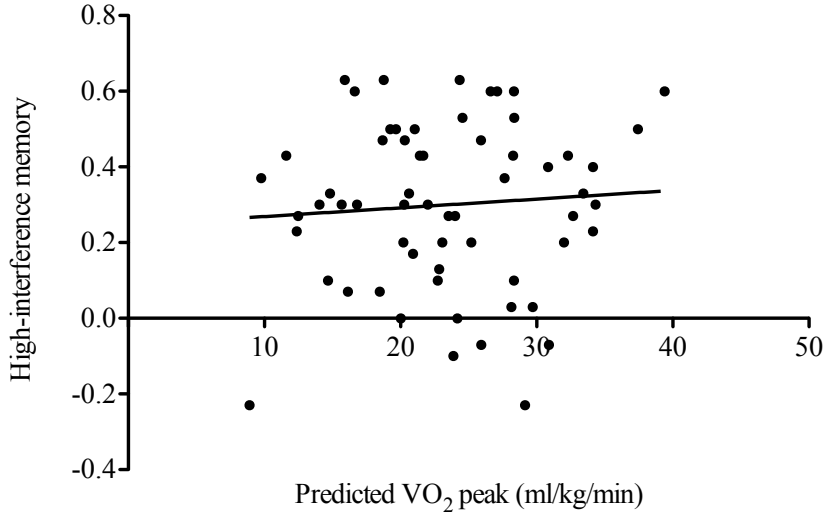


Figure 3. The association between predicted VO_2 peak and high-interference memory. There was no correlation between predicted VO_2 peak and high-interference memory after controlling for age, sex, and years of education ($r(54) = -.009$, $p = .950$). The scatterplot has not been adjusted for these covariates.

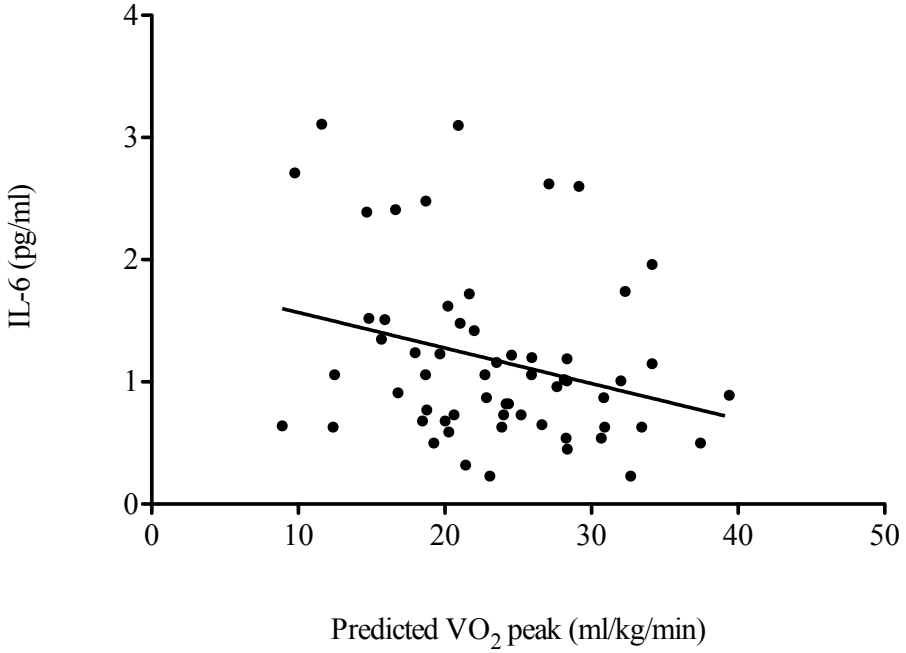


Figure 4. The association between predicted VO_2 peak and IL-6. A negative correlation was observed between predicted VO_2 peak and IL-6 after controlling for age and sex ($r(55) = -.316$, $p = .016$). The scatterplot has not been adjusted for these covariates.

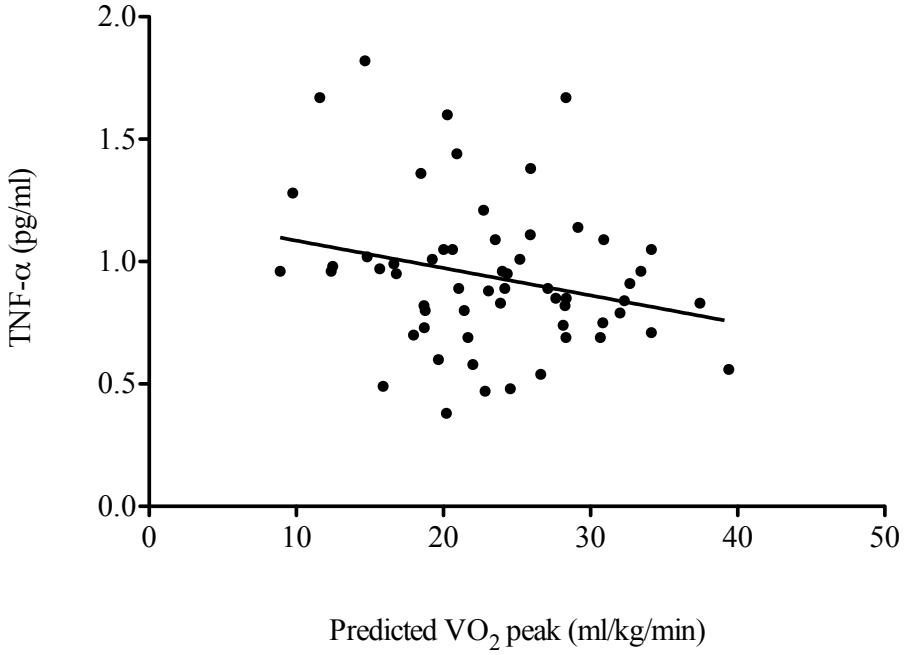


Figure 5. The association between predicted VO_2 peak and TNF-α. A negative correlation was observed between predicted VO_2 peak and TNF-α after controlling for age and sex ($r(55) = -.352$, $p < .01$). The scatterplot has not been adjusted for these covariates.

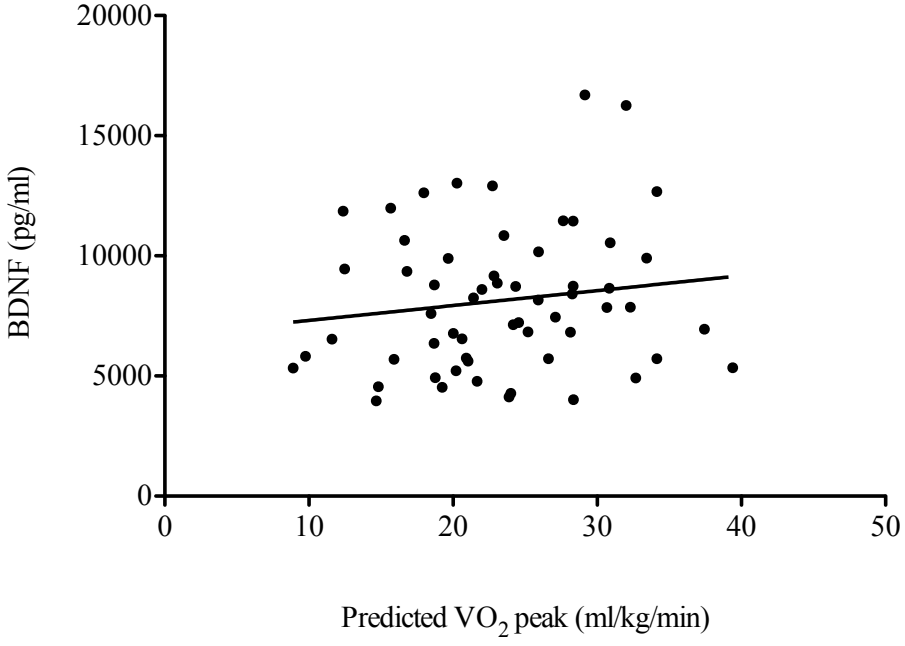


Figure 6. The association between predicted VO_2 peak and BDNF. A trending positive correlation was observed between predicted VO_2 peak and BDNF after controlling for age and sex ($r(55) = .235$, $p = .078$). The scatterplot has not been adjusted for these covariates.

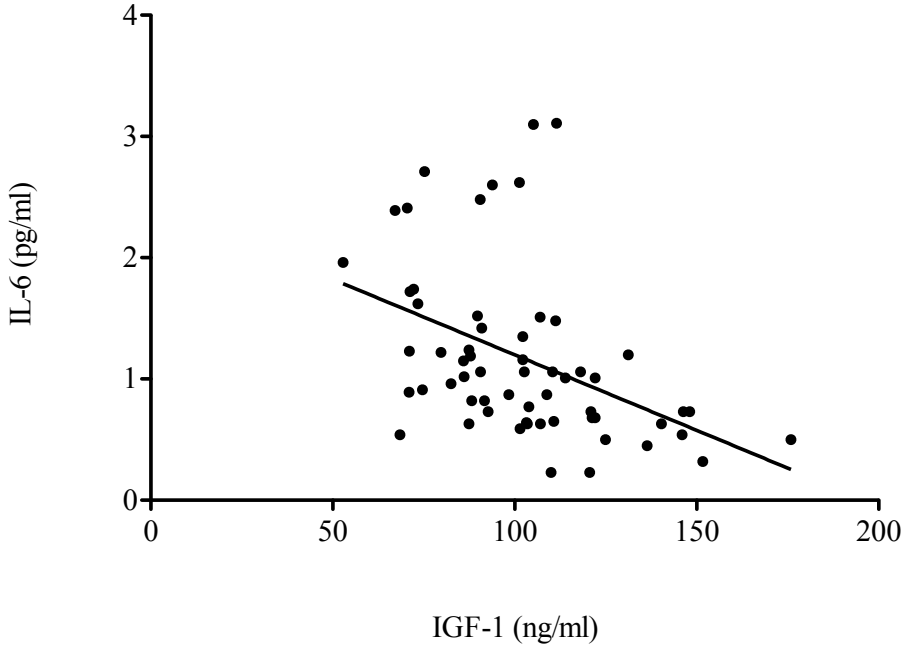
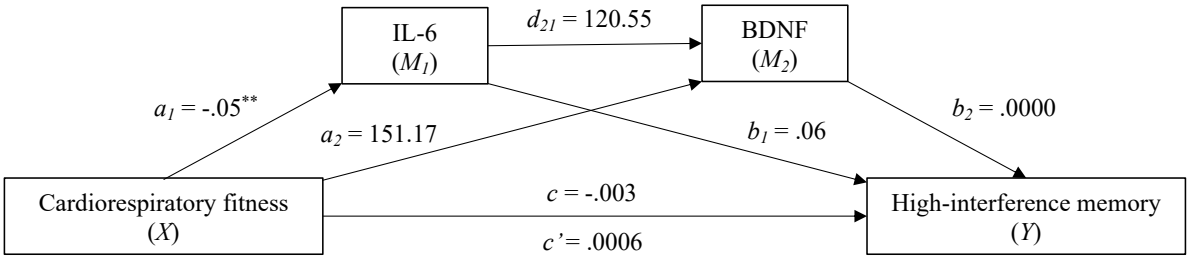
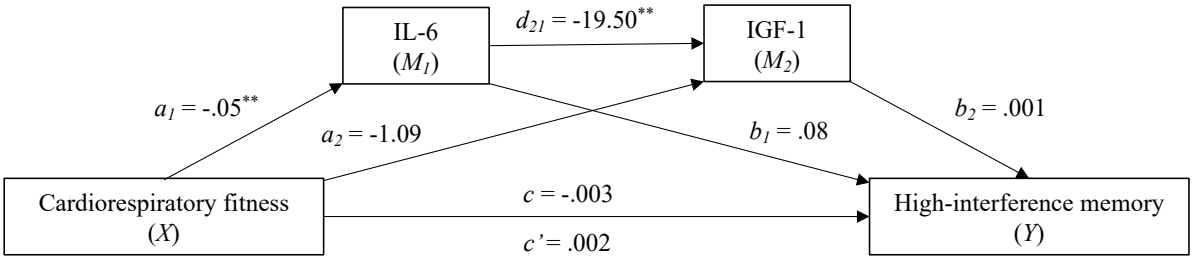


Figure 7. The association between IGF-1 and IL-6. A negative correlation was observed between IGF-1 and IL-6 after controlling for age and sex ($r(56) = -.441$, $p < .01$). The scatterplot has not been adjusted for these covariates.

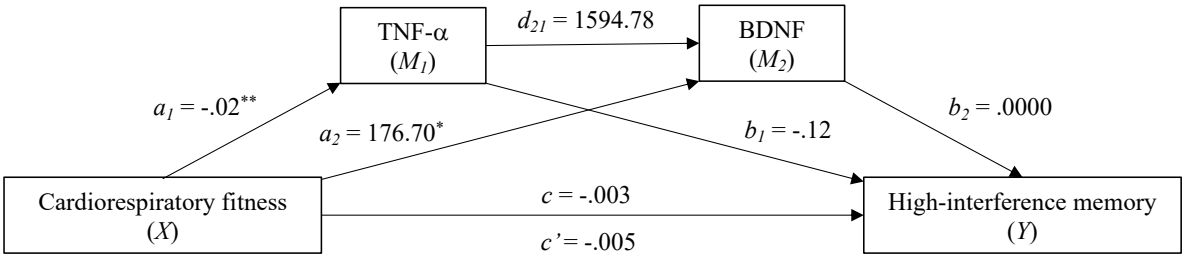
a.


IL-6
(M_1)
d_{21} = 120.55
BDNF
(M_2)
a_1 = -.05**
a_2 = 151.17
b_1 = .06
b_2 = .0000
Cardiorespiratory fitness
(X)
c = -.003
c' = .0006
High-interference memory
(Y)

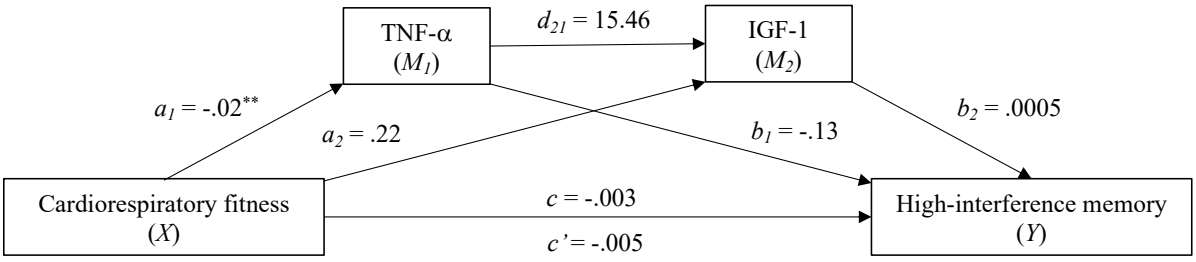
b.


IL-6
(M_1)
d_{21} = -19.50**
IGF-1
(M_2)
a_1 = -.05**
a_2 = -1.09
b_1 = .08
b_2 = .001
Cardiorespiratory fitness
(X)
c = -.003
c' = .002
High-interference memory
(Y)

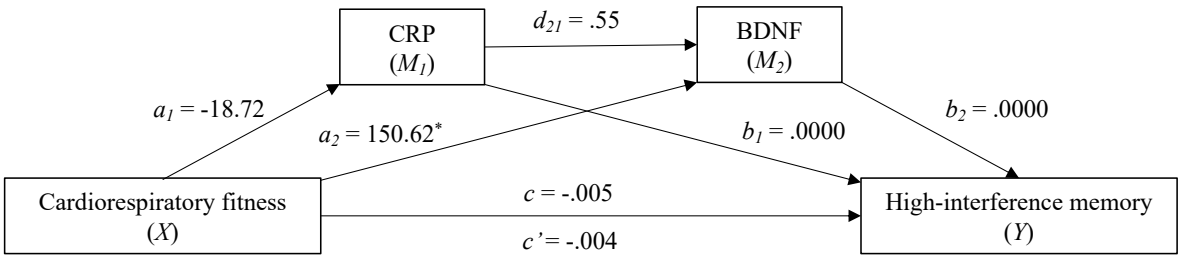
c.


TNF-α
(M_1)
d_{21} = 1594.78
BDNF
(M_2)
a_1 = -.02**
a_2 = 176.70*
b_1 = -.12
b_2 = .0000
Cardiorespiratory fitness
(X)
c = -.003
c' = -.005
High-interference memory
(Y)

d.


TNF-α
(M_1)
d_{21} = 15.46
IGF-1
(M_2)
a_1 = -.02**
a_2 = .22
b_1 = -.13
b_2 = .0005
Cardiorespiratory fitness
(X)
c = -.003
c' = -.005
High-interference memory
(Y)

e.



f.

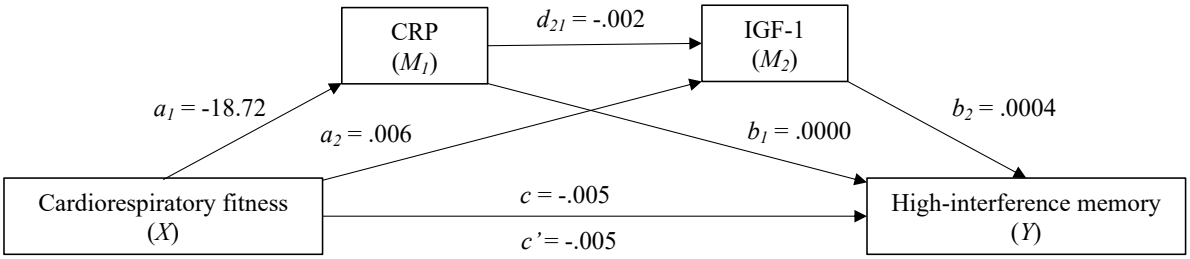


Figure 8. Sequential mediation models exploring the relationship between cardiorespiratory fitness and high-interference memory. Age, sex, and years of education were included as covariates in all mediations. There was no indirect sequential effect through (a) IL-6 and BDNF, (b) IL-6 and IGF-1, (c) TNF-α and BDNF, (d) TNF-α and IGF-1, (e) CRP and BDNF, nor (f) CRP and IGF-1. $^{*}p < .05$, $^{**}p < .01$.

Table 1. Descriptive characteristics for study sample

Variable	Mean (SD)/Frequency (%)
Age (years)	70.6 (4.0)
Sex	
Female	41 (63.1%)
Male	24 (36.9%)
Education (years)	16.7 (3.6)
MoCA	25.9 (2.8)
Body Mass Index (kg/m^2)	25.6 (2.7)
Body fat (%)	33.8 (8.1)
Average steps/day	8939.1 (4198.1)

Table 2. Mean values for cardiorespiratory fitness, memory, and biomarkers

	Mean (SD)
Predicted VO_2 peak (ml/kg/min)	23.3 (7.0)
High-interference memory	0.30 (0.22)
IL-6 (pg/ml)	1.2 (0.7)
TNF-α (pg/ml)	0.93 (0.30)
CRP (ng/ml)	1303.1 (995.0)
BDNF (pg/ml)	8088.9 (2979.9)
IGF-1 (ng/ml)	102.2 (24.6)

Table 3. Partial correlations between cardiorespiratory fitness, memory, and biomarkers

	1.	2.	3.	4.	5.	6.	7.
1. Predicted VO_2 peak	-						
2. High-interference memory	-.01	-					
3. IL-6	-.32*	.20	-				
4. TNF-α	-.35**	-.08	.26*	-			
5. CRP	-.11	.16	.37**	.39**	-		
6. BDNF	.24	-.02	.07	.13	.13	-	
7. IGF-1	-.01	.04	-.44**	.15	-.07	-.12	-

Note: Values are correlation coefficients. Partial correlations between cardiorespiratory fitness and memory, as well as between biomarkers and memory are controlling for age, sex, and years of education. Partial correlations between cardiorespiratory fitness and biomarkers, as well as between the biomarkers are controlling for age and sex. $^{*}p < .05$, $^{**}p < .01$.

Table 4. Indirect effect of cardiorespiratory fitness on high-interference memory

	95% Confidence Interval	
Indirect Effect	Lower Limit	Upper Limit
IL-6 (M_1), BDNF (M_2)	-.0008	.0010
IL-6 (M_1), IGF-1 (M_2)	-.0019	.0064
TNF-α (M_1), BDNF (M_2)	-.0019	.0010
TNF-α (M_1), IGF-1 (M_2)	-.0015	.0008
CRP (M_1), BDNF (M_2)	-.0005	.0009
CRP (M_1), IGF-1 (M_2)	-.0003	.0007

Note: In all mediation models, cardiorespiratory fitness served as the independent variable (*X*), high-interference memory served as the dependent variable (*Y*), and age, sex, and years of education were included as covariates. For the 95% confidence intervals, bootstrap procedures utilizing 10,000 simulations were computed.

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