Physical Exercise and Brain Functions in Older Adults

Guest Editors: Louis Bherer, Kirk I. Erickson, and Teresa Liu-Ambrose
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Editorial

Physical Exercise and Brain Functions in Older Adults

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Studies suggest that regular physical activity can help maintain and enhance brain functions in older adults. However, we still do not understand how physical activity impacts the rate of cognitive decline. One major issue is whether physical activity broadly defined (i.e., activity that is part of one’s daily life involving bodily movements and the use of skeletal muscles) or structured exercise (i.e., physical activity that is planned, structured, and purposive to improve physical fitness) leads to the same benefits in preventing age-related cognitive decline. More studies are needed to appreciate the level of change or protection provided by physical activity, the basic mechanisms by which this change occurs, and whether physical activity can be beneficial despite chronic medical conditions and neurological or geriatric syndromes.

This special issue presents original research results that bring additional support to the notion that physical exercise is an efficient nonpharmaceutical approach that can be used to enhance and maintain cognitive functions in healthy older adults and patients suffering from mild cognitive impairment. In a paper, we propose a brief review of the main impacts of exercise on cognition in older adults, frail patients, and those with mild cognitive impairment and dementia. Another paper of this special issue brings important knowledge in this regard. L. S. Nagamatsu et al. showed that physical activity helps improve verbal and spatial memory in older adults with probable mild cognitive impairment. In this study, eighty-six women aged 70–80 years with subjective memory complaints completed one of three interventions for 6 months: resistance training, aerobic training, or balance and tone (control). Both exercise groups showed significant improvements in memory performance, which was not observed in controls.

An original study of this special issue explored the benefits of swimming on cognition in older adults. A. Abou-Dest et al. compared three groups of sixteen volunteer participants (young adults, sedentary older adults, and older adults who regularly practice swimming) on a battery of cognitive tasks. They reported that in older adults, regular swimming was related to better performance on executive functions but not on information processing speed. The selective benefit of exercise on executive control tasks was also reported after only 3 months of exercise intervention in a study of this special issue by D. Predovan et al. compared to controls, the training group showed significant improvements in physical capacity and enhanced Stroop performance, but only in the inhibition/switching condition, and the increase in aerobic capacity induced by the training regimen correlated negatively with reaction time in the inhibition/switching condition of the Stroop task at posttest. Importantly, the reported gains in cognitive performance were observed after only three months of physical training. The complex interaction between bodily exercise and cognition also calls into question the impact that mobility and gait might have on cognition in older adults. P. Plummer-D’Amato et al. addressed this issue in a contribution to this special issue. Studying how gait difficulty and cognitive task difficulty impact cognitive-motor interference in aging, they showed that gait task difficulty influences dual-task effects on gait speed, especially in older
adults, and that this effect is influenced by the difficulty of the cognitive task.

Another paper of the special issue brings up important issues on the potential moderators of physical activity on brain functions. R. L. Leckie et al. demonstrated how genes (APOE, BDNF, and COMT) along with dietary omega-3 fatty acid and docosahexaenoic acid (DHA) are potential moderators of the effect of physical activity on brain health. R. L. Leckie et al’s proposal calls for further studies on the role of genes and dietary factors in the relationship between physical exercise and cognitive functions in older adults populations. All together, the studies published in this special issue bring additional scientific support to the notion that physical activity and exercise are a promising approach to alleviate the age-related impact on the body and mind. By doing so, they also support the promotion of health policies that should target inactivity in individuals of all ages and with any medical condition who are able to safely participate in physical activity.

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Louis Bherer
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Review Article

A Review of the Effects of Physical Activity and Exercise on Cognitive and Brain Functions in Older Adults

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Studies supporting the notion that physical activity and exercise can help alleviate the negative impact of age on the body and the mind abound. This literature review provides an overview of important findings in this fast-growing research domain. Results from cross-sectional, longitudinal, and intervention studies with healthy older adults, frail patients, and persons suffering from mild cognitive impairment and dementia are reviewed and discussed. Together these findings suggest that physical exercise is a promising nonpharmaceutical intervention to prevent age-related cognitive decline and neurodegenerative diseases.

1. Introduction

Chronological aging, or senescence, is associated with an increased risk of chronic conditions and diseases such as cognitive impairment, cardiovascular disease, and metabolic syndrome. Due to prolonged life expectancy, age-related diseases have increased in alarming proportions in recent decades [1]. An increasing body of studies have suggested that lifestyle factors have a significant impact on how well people age. For example, Fratiglioni et al. [2] reported that three lifestyle factors can play a significant role in slowing the rate of cognitive decline and preventing dementia: a socially integrated network, cognitive leisure activity, and regular physical activity. In this review and others [3, 4], it is argued that out of these lifestyle factors, physical activity has the most support as protective against the deleterious effects of age on health and cognition. Broadly defined, physical activity refers to activity that is part of one's daily life involving bodily movements and the use of skeletal muscles. Physical exercise is a subcategory of physical activity that is planned, structured, and purposive to improve specific physical skills or physical fitness. Evidence suggests that physical activity and exercise can to some extent lower the risk of adverse outcomes associated with advancing age.

Physical activity maintained throughout life is associated with lower incidence and prevalence of chronic diseases such as cancer, diabetes and cardiovascular and coronary heart diseases [5, 6]. Recent studies suggest that physical exercise also protects against dementia [7]. Yet, despite this promise, the ways in which physical activity impacts the rate and prevalence of cognitive decline is still under investigation. Furthermore, several open issues call for further research, such as the dose-response relationship, the level of change or protection provided by physical activity, the biological and/or psychological mechanisms by which these effects occur and whether physical activity can be beneficial despite chronic medical conditions, neurological syndromes such as dementia, and the physical limitations observed in frail patients. Although recent advancements in neuroimaging techniques and genetics have opened new research avenues, more studies are required to provide definitive answers to these important questions. This literature review aims to provide an overview of studies that have attempted to assess whether and how physical activity and exercise positively
impact older adults at any age and with various physical and psychological conditions.

2. Aging and Neurocognitive Functions

It is generally assumed that age brings it declines in performance in a multitude of cognitive tasks that require a variety of perceptual and cognitive processes (for extensive reviews of the literature see [3, 8, 9]). More specifically, processing speed declines early in the course of aging, which has recently been associated with loss of white matter integrity [10]. Working memory, or the ability to maintain and consciously manipulate information, is also highly age-sensitive. The age-related difference in working memory tends to be greater if executive control processes such as inhibition, updating, and manipulation are required, and even greater if the memory load (i.e., the number of items to be maintained) is high. These deficits have sometimes been associated with reduced task-related activation in older compared to younger adults in frontal regions of the cerebral cortex. Other studies also reported higher task-related activation in older adults, a phenomenon possibly associated with compensation for age-related changes in brain structure and functions [9].

Older adults also tend to show reduced inhibition compared to younger adults. As a result, they are more distracted by irrelevant information and more affected by proactive interference (i.e., interference induced by current learning on further encoding of new information). Furthermore, episodic memory declines in late adulthood, likely due to poor encoding strategies, less use of environmental support, and deficits in binding new information with existing knowledge during encoding.

Structural and functional brain imaging studies have provided insights into potential brain mechanisms of cognitive aging. For instance, changes in brain volume occur faster in adults after 50 years of age, with an annual decline of 0.35% compared to 0.12% in young adults (see [11, 12] for reviews). Ventricle dilatation can approximate 4.25% per year at 70 years of age compared to 0.43% in young adults. The volume of the hippocampus, a cerebral structure that plays a major role in memory formation, is also sensitive to age, with an annual decline of 0.86% per year (from 26 to 82 years), 1.18% per year after 50 years, and 1.85% per year after 70 years. Yet, rate of change is difficult to appreciate due to the lack of longitudinal studies. In a recent study, Raz et al. [13] followed participants over 30 months and observed that the hippocampus, the entorhinal cortex, the orbital-frontal cortex, and the cerebellum showed volumetric changes after only 15 months, while other brain structures showed shrinkage after 30 months, including the caudate nucleus, the prefrontal subcortical white matter, and the corpus callosum. However, some brain structures showed almost no change (the primary visual cortices, the putamen, and the pons). In addition, aging is associated with overall changes in white matter integrity (e.g., leukoaraiosis), with greater changes occurring after the seventh decade, and localized preferentially in the frontal and prefrontal regions [11]. These changes are more pronounced in patients with vascular diseases such as hypertension and type-2 diabetes.

Cerebral metabolism is also altered by age, with a reduction in regional cerebral metabolic rate for glucose, oxygen, and blood flow. Although it is frequently assumed that structural changes are associated with a decline in brain metabolism, recent evidence suggests otherwise. For example, Chen et al. [14] observed that, in some brain regions, age-associated reductions in cerebral blood flow could occur independently of regional atrophy [14].

3. Physical Activity and Cognition in Healthy Seniors

Several studies support the notion that physical activity is a significant moderator of age-related cognitive decline. In cross-sectional studies, age-related differences in cognitive performance observed when older adults are compared to younger participants are reduced if the comparisons involved higher-fit individuals rather than sedentary older adults [15–19]. As a whole, these cross-sectional studies suggest that cardiorespiratory fitness is associated with more efficient cognitive functions.

In longitudinal studies, older adults that participate in physical activity show less cognitive decline over two- to 10-year follow-up periods. For instance, in a study by Barnes et al. [20] cardiorespiratory fitness assessed at baseline predicted cognitive performance six years later in a variety of cognitive domains (working memory, processing speed, attention, and general mental functioning). In nationally representative samples of noninstitutionalized persons aged 50 years and older and across 11 European countries (Austria, Germany, Sweden, Denmark, Switzerland, the Netherlands, Belgium, France, Spain, Italy, and Greece) Aichberger et al. [21] reported that individuals who participated in any type of regular physical activity showed less cognitive decline after 2.5 years, especially when they engaged in vigorous activities more than once a week.

The impact of physical activity on cognition in older adults is more strongly supported by results from intervention studies, which generally show that older adults who have completed a physical activity program that produces significant increases in cardiorespiratory fitness (indexed by direct measures or estimation of VO_{2,max}) often show enhanced cognitive performance. Dustman et al. [22] compared middle-aged and older individuals who completed a four-month aerobic training program to age-matched controls who participated in strength and flexibility exercises and controls who did not exercise. Only the aerobic training group showed improved cardiorespiratory function, along with improvements on a simple RT task. Similar results were obtained in women aged 57 to 85 years old following a three-year physical training program [23]. Hawkins et al. [24] reported that, in older adults, a 10-week aquatic fitness program led to greater improvement in task conditions that tap dual-task and switching abilities compared to conditions that do not require executive or attentional control processes. In Kramer et al’s [25] study, older adults who completed a six-month aerobic training program (walking) showed a significant improvement in cognitive performance,
unlike those who completed a stretching program. Cognitive improvement was greater in tasks that tapped attentional control or executive control functions and was correlated with improvement in VO$_{2\text{max}}$. In another study, Albinet et al. [26] reported that 12 weeks of aerobic training lead to enhanced performance in executive control and increased heart rate variability in older men and women aged 65–78. These results suggest that aerobic exercise may be an important cardiac and brain protective factor as people age. The greater improvement induced by aerobic training in executive control compared to other cognitive domains has also been confirmed by several meta-analyses (see [27] but see [28] for different conclusions).

The selective benefit of aerobic exercise for tasks that tap executive control was also observed in another recent study [29], where 57 older adults completed a 10-month training program (aerobic versus strength and flexibility). The positive effect on executive control was observed after aerobic training only. In another study, Renaud et al. [30] observed that only 12 weeks of aerobic training induced a significant improvement in cardiorespiratory capacity (estimated VO$_{2\text{max}}$) along with enhanced motor response preparation, such that participants maintained response preparation over time more efficiently after the training program. These results provide additional support for the notion that improving aerobic fitness may enhance attentional control mechanisms in older adults. In a meta-analytic review of randomized-control trials of aerobic exercise on neurocognitive functions, Smith et al. [31] examined 29 studies conducted between 1966 and 2009 (including more than 2,000 participants and 234 effect sizes). They found that individuals who were randomly assigned to aerobic exercise training showed modest improvements in attention, processing speed, executive function, and memory, with less convincing effects on working memory. These results, along with those from Colcombe and Kramer [27], suggest a selective effect of aerobic exercise on neurocognitive functions. However, not all studies reported a significant correlation between improvement in cardiorespiratory fitness outcomes and cognitive improvement (see [28, 32] meta-analysis), which suggests that physiological mechanisms supporting cognitive enhancement remain to be fully understood.

Studies reported above highlight that aerobic exercise enhances cognitive function. However, recent evidence now suggests that other types of exercise training, such as resistance training, may also benefit cognition. Cassilhas and colleagues [33] demonstrated that six months of either thrice-weekly moderate or high intensity resistance training improved memory performance and verbal concept formation among 62 community-dwelling senior men aged 65 to 75 years. Liu-Ambrose and colleagues [34] demonstrated that an individualized home-based program of balance and strength retraining significantly improved selective attention and conflict resolution as measured by the Stroop Test after six months among seniors aged 70 years and older with a recent history of falls. The finding of this study is notable given that many have hypothesized that the cognitive and neural benefits of exercise must occur within the context of social engagement for it to be effective [35]. Liu-Ambrose and colleagues [36] also demonstrated that 12 months of either once-weekly or twice-weekly progressive resistance training improved Stroop Test performance among 155 community-dwelling senior women aged 65 to 75 years. Enhanced selective attention and conflict resolution were also associated with increased gait speed. Clinically, improved gait speed predicts a substantial reduction in both morbidity [37] and mortality [38, 39]. These results illustrate the clinical significance of cognitive gains induced by resistance training. Therefore, it seems that in addition to endurance training, resistance training should be seriously considered as a potential modifier of cognitive functions in older adults. Recent studies also suggest that motor learning and coordinative exercise could also be used to enhance cognitive function in this population (see [40]).

4. Physical Activity and Brain Structures and Functions in Older Adults

The biological mechanisms by which cognition is enhanced through physical exercise training remain to be completely elucidated, although the number of studies that have tried to identify these mechanisms has increased in the last 10 years. For the most part, the studies that support the notion that physical exercise has an impact on brain functions have focused on direct biological effects of exercise using both animal and human models. However, as suggested by Spirudo et al. [41] exercise may enhance cognition indirectly by improving health conditions (stress, sleep) and reducing chronic diseases (coronary heart diseases) that impact neurocognitive functions.

The evidence for the direct effects of exercise on the brain first came from animal studies. In a comprehensive literature review,Lista and Sorrentino [42] suggest that the basic neurobiological mechanisms associated with exercise can occur at two levels, supramolecular and molecular. At the supramolecular level, physical activity has been found to induce angiogenesis or the physiological process by which new blood vessels grow from preexisting vessels [43, 44]. Physical activity has also been associated with neurogenesis, or neural cell proliferation, in the hippocampus in elderly rats [45]. Although the functional significance of this effect remains unclear, there is evidence that newly formed neurons can integrate into a neural network and become functional [46]. Exercise-induced synaptogenesis has also been reported [47, 48].

The molecular mechanisms by which exercise induces angiogenesis, neurogenesis, and synaptogenesis have received growing attention in the last few years. Again, the evidence comes mainly from animal studies that showed exercise-associated changes in molecular growth factors such as brain-derived neurotrophic factor (BDNF), which plays a crucial role in neuroplasticity and neuroprotection, and increased production of insulin-like growth factor 1 (IGF-1), which is involved in both neurogenesis and angiogenesis. Moreover, neurotransmitter systems also seem to be modulated through exercise (see [42]). Until very recently, evidence for the molecular and supramolecular effects of exercise came exclusively from animal studies.
However, a very innovative study [49] recently showed that greater exercise-related increases in BDNF were associated with increased hippocampal volume. If reproduced, these results would confirm that physical exercise induces genuine neurotrophic effects on brain structures and functions at the molecular, supramolecular, and structural levels.

In humans, several studies using structural and functional brain imaging, or electrophysiological measures of brain activity, suggest that physical exercise induces transient and permanent changes at the structural and functional levels in the aging brain [50–54]. Using voxel-based morphometry (VBM), or detailed image segmentation of high-resolution brain scans, Colcombe et al. [55] reported that a higher cardiorespiratory fitness level ($\overline{\text{VO}}_2\text{max}$) was associated with a reduced loss of grey and white matter in the frontal, prefrontal, and temporal regions in older adults. In another study, Erickson et al. [56] performed a region-of-interest analysis on magnetic resonance images in 165 non-demented older adults and found that higher fitness levels were associated with larger left and right hippocampi that further correlated with better spatial memory performance. These findings suggest that aerobic fitness is associated with changes in brain structures that translate into better cognitive function in older adults (see also [49, 57]).

Even more striking evidence of the benefit of fitness on brain functions comes from functional brain imaging studies (fMRI). It has been shown that enhanced cardiovascular functions after aerobic training are associated with greater task-relevant activity in brain areas recruited in an attentional control task [58]. Similarly, 12 months of resistance training in community-dwelling senior women led to functional changes in two regions of the cortex previously associated with response inhibition processes, the anterior portion of the left middle temporal gyrus, and the left anterior insula extending into lateral orbital frontal cortex [36]. These hemodynamic effects co-occurred with improved task performance. Moreover, Voss et al. [59] found changes in functional connectivity after aerobic exercise training in older adults. They observed that 12 months of training leads to increased connectivity in regional connections that support both the default-mode network and the frontal executive network, suggesting that physical exercise has a restorative effect on large-scale brain circuitry. Changes in these large-scale brain networks have received increasing attention in aging neuroscience, as they indicate massive changes in brain systems.

A complete understanding of the potential for physical activity to protect the brain from the effects of age would require investigating the indirect influences of exercise on cognition. There is growing evidence that exercise has indirect beneficial effects on cognition through its impact on factors that are known to alter neurocognitive integrity [60]. Spirduso et al. [60] suggest three groups of potential mediators in the relationship between exercise and cognition: physical resources, chronic diseases or states, and mental resources. It has been shown that physical exercise enhances mental resources by reducing depression [61], anxiety, and chronic stress and improving self-efficacy [62]. The effect of physical activity on cognitive function might also be mediated by physical resources such as diet [63] and sleep [64, 65]. It remains to be seen whether these factors in fact mediate the positive effects that exercise has on cognitive and brain health.

5. Physical Activity and Cognition in Frail Older Adults

With increasing age, and specifically with advanced age (i.e., over 75 years), many individuals eventually develop one or more of a group of related medical problems referred to as geriatric syndromes. Perceptual limitations (vision and hearing problems), urinary incontinence, falls, delirium, and dementia are examples of geriatric syndromes. These syndromes are characterized by having more than one cause and by involving several different body systems. An emerging symptom that appears particularly relevant to our purpose is frailty, as it apparently limits physical activity and exercise. Frailty is defined as a complex health state of increased vulnerability to stressors due to impairments in multiple systems. It has been associated with adverse outcomes such as disability, falls, hospitalization, and death [66]. With aging, the prevalence of frailty increases from 7% in older adults aged between 65 and 74 years to 18% between 75 and 84 years and 37% at age 85 years and older [67]. Physical inactivity is a major risk factor for frailty [66]. It is important to note that frailty is not a contraindication for physical activity. On the contrary, it may be one of the most compelling reasons to prescribe physical exercise [68].

Results from longitudinal studies show that physical activity and exercise can prevent frailty in older adults. In a recent study, 2,964 older adults were followed for five years to determine the relationship between physical activity and the risk of becoming frail [69]. Results showed that individuals who regularly exercised at baseline were less likely to develop frailty within a five-year period than sedentary individuals, even after adjusting for baseline health conditions and demographic characteristics.

Intervention studies also suggest that physical activity can improve several frailty syndrome components, especially sarcopenia (reduction in skeletal muscle mass) and functional impairment [68]. Moreover, in a recent randomized controlled trial that assessed the impact of a three-month physical training intervention on quality of life in 77 physically frail persons aged 75 years and older [70], it was observed that functional exercises twice a day to improve balance and lower extremity muscle strength, in addition to strength training twice a week, helped to improve psychological well-being associated with physical functioning, emotion, and mental health. To our knowledge, only one study has shown that physical exercise training can help improve cognition in frail older adults. Langlois et al. [71] recently observed that three months of training in frail older adults resulted in significant improvement in both physical capacity and cognitive performance (executive functions, processing speed, and working memory) as well as quality of life associated with leisure activities and satisfaction with physical capacity.
6. Physical Activity and Cognition in Older Adults with Mild Cognitive Impairment and Dementia

According to the Alzheimer's Association [72], one in eight people aged 65 and older (13%) and 43% of people 85 and older have Alzheimer's disease. Currently, there is no cure for Alzheimer's disease. However, research has suggested that physical activity and exercise can significantly reduce the risk of developing it. In a recent cross-sectional study that compared 198 subjects with mild cognitive impairment (MCI) to 1,126 with normal cognition, Geda et al. [73] observed that moderate activity during midlife was associated with a 39% lower risk of having mild cognitive impairment in later life. Late-life moderate exercise was associated with a 32% lower risk for MCI. Burns et al. [74] explored the effect of exercise on cognitively impaired individuals and found an association between direct measures of cardiorespiratory fitness (VO

peak) and cognition (neuropsychological test battery) in normal older participants and patients in the early stage of Alzheimer's dementia (AD). Results showed that cardiorespiratory fitness was modestly reduced in patients with AD compared to participants without dementia. Although no significant association was found between cardiorespiratory fitness and cognition in participants without dementia, higher fitness levels in early AD participants were associated with larger brain volume (less brain atrophy), even when controlling for age, sex, dementia severity, and physical frailty.

In a longitudinal study exploring the association between midlife physical activity and late-life cognitive function and dementia, Chang et al. [75] observed that being active (around 5 hours per week) was associated with higher scores in processing speed, memory, and executive functions, even after controlling for demographic and cardiovascular factors. Moreover, participants who reported being active were significantly less likely to have dementia in later life. In a prospective study following 1,740 persons older than 65 years without cognitive impairment for a period of 6.2 years, Larson et al. [7] reported reduced dementia incidence for individuals who exercised three or more times a week (13 per 1,000 person-years) compared to those who exercised fewer than three times a week (19.7 per 1,000 person-years), demonstrating a 32% reduced risk for dementia.

Interestingly, correlations have also been reported between muscle strength and a lower risk of AD and a slower rate of cognitive decline. Having followed 900 community-based older persons without dementia at baseline, Boyle et al. [76] showed a lower rate of global cognitive decline, MCI and AD in older adults with higher muscle strength. The protective effects remained after adjustment for several covariates, including body mass index, physical activity, pulmonary function, vascular risk factors, vascular diseases, and apolipoprotein E4 status. Furthermore, in a recent meta-analysis of prospective studies that covered 15 prospective studies (12 cohorts) and 33,816 nondemented individuals, 3,210 of which showed cognitive decline during the one- to 12-year followup, Sofi et al. [77] observed that physical activity significantly and consistently prevented cognitive decline. Individuals who were highly physically active showed 38% less risk of cognitive decline, and those who did low-to-moderate level exercise also showed a significantly 35% reduced risk.

Results from intervention studies are scarce. A meta-analysis of randomized controlled trials (2,020 participants; 30 trials) [78] reported beneficial effects of physical activity on physical fitness (effect size = 0.69) and cognitive function (effect size = 0.57) in adults with cognitive impairment (MCI and dementia). However, other studies have reported modest benefits [79] or no appreciable effect [80] of physical activity on cognition in patients with cognitive impairment. A recent randomized clinical study evaluated the impact of a six-month aerobic exercise intervention in individuals with mild cognitive impairment [81]. Thirty-three older adults (17 women) with amnestic mild cognitive impairment ranging in age from 55 to 85 years were randomized to either a high-intensity aerobic exercise (75–85% of heart rate capacity) or a stretching control group. Results showed beneficial effects of aerobic exercise, especially in speed of processing and executive functioning, although in some tests, gender differences in cognitive improvement were observed, despite comparable gains in cardiorespiratory fitness in men and women. In a randomized controlled study, Kemoun et al. [82] examined the benefits of a 15-week physical activity program in 31 subjects (mean age of 82 years). They reported that a physical activity program can slow cognitive decline and improve quality of walking in elderly persons with dementia. A more recent study assessed the cognitive impact of a Tai-Chi intervention group (n = 171) compared to a stretching and toning group (n = 218) in older adults with cognitive impairment [83]. Results showed that both groups improved in global cognitive function, delayed recall, and subjective cognitive complaints. However, improvements in balance, visual span, and Clinical Dementia Rating scores were observed in the intervention group only. Future studies are needed to specify whether interventions should involve aerobic or strength training exercises or both to improve cognition in MCI patients. Nagamatsu et al. [84] recently reported that patients who completed six months of aerobic or strength training exercise showed improved spatial memory performance, but only the aerobic group showed a correlation between physical capacity after intervention and spatial memory performance. The mechanisms by which exercise impacts cognition in this population thus deserve further study.

7. Conclusions

In recent decades, an increasing number of studies have suggested that people should adopt physical activity and exercise as part of their lifestyle to alleviate the negative impact of aging on the body and the mind. However, we still do not understand how physical activity impacts the rate of cognitive decline. One major issue is whether physical activity broadly defined (i.e., activity that is part of one’s daily life involving bodily movements and the use of skeletal muscles) or structured exercise (i.e., physical activity that is planned, structured, and purposive to improve physical fitness) leads to the same benefits in preventing age-related cognitive decline. Physical exercise often differs from physical
activity by being more controlled in terms of intensity and duration, while physical activity studies tend to incorporate a large variety of unspecified activities. Future studies are required to understand the intensity, duration, and types of exercise that better enhance cognitive functions in older adults. Although recent advancements in brain imaging techniques and genetics have opened new research avenues, more studies are required to find definitive answers to these questions. Further research is needed to better document the impact of other forms of exercise, as well as the dose-response relationship that governs the positive impact of exercise on brain functions. Hopefully, ongoing randomized trials such as the AIBL Active Trial [85] and the brain-in-motion trial [86] designed to address the relationship between physical exercise intervention and brain function in at risk individuals will help answer these questions.

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Review Article

Sarcopenia, a Neurogenic Syndrome?

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Sarcopenia is an aging-associated condition, which is currently characterized by the loss of muscle mass and muscle strength. However, there is no consensus regarding its characterization hitherto. As the world older adult population is on the rise, the impact of sarcopenia becomes greater. Due to the lack of effective treatments, sarcopenia is still a persisting problem among the global older adults and should not be overlooked. As a result, it is vital to investigate deeper into the mechanism underlying the pathogenesis of sarcopenia in order to develop more effective therapeutic interventions and to inscribe a more uniform characterization. The etiology of sarcopenia is currently found to be multifactorial, and most of the pharmacological researches are focused on the muscular factors in aging. Although the complete mechanism underlying the development of sarcopenia is still waiting to be elucidated, we propose in this article that the primary trigger of sarcopenia may be neurogenic in origin based on the intimate relationship between the nervous and muscular system, namely, the motor neuron and its underlying muscle fibers. Both of them are affected by the cellular environment and their physiological activity.

1. Introduction

Sarcopenia (Greek: sarx means “flesh,” penia means “loss”) is an age-related geriatric syndrome first described on a meeting in 1988 by Dr. Rosenberg as a phenomenon whereby the age-related decline in lean body mass affects ambulation, mobility, energy intake, overall nutrient intake and status, independence, and breathing [1]. More recently, sarcopenia is characterized by the gradual loss of muscle mass, muscle strength, and muscle function/quality in aging [2, 3]. However, there are studies indicating that sarcopenia should be referred only as the age-related loss in muscle mass whilst the age-related loss in muscle strength should be isolated as a new condition called “dynapenia” based on the evidences indicating that the loss of muscle mass and strength are two distinct processes with different pathophysiology [4].

Hitherto, there is no consistent data among a variety of prevalence studies probably due to the difference in study sample, definition of sarcopenia, and the assessment tool used [3]. For example, for the population of over 80 years old, American study of New Mexico Elder Health Survey has found that there were >40% of women and 50% of men who were sarcopenic whilst the NHANES III database study reveals that 11% of women and 7% of men were sarcopenic. Also, the Italian study of InCHIANTI cohort reveals that 15% of women and 70% of men were sarcopenic [3]. In summary, the prevalence of this syndrome depends on age, sex, race [3, 5–7], morbidity [7, 8], nutrition [9], and physical activity [10, 11].

Some studies indicate that sarcopenia leads to functional limitations, impaired mobility, disability, falls, and fractures, which in turn lead to the loss of independence, frailty, and increased risk of mortality [11–13]. In contrast, some studies indicate that the parameter of muscle mass may not relate to the functional status and mortality [4]. No matter whether sarcopenia may affect both the quality and quantity of life of individuals or not, there are no effective treatment for sarcopenia and its related outcomes yet. Pharmacological interventions currently present are not effective and possess a considerable level of side effects. These include hormonal (e.g., growth hormones, testosterone, estrogens, tibolone) and nonhormonal (e.g., losartan, telmisartan) interventions [14]. Hitherto, only exercise training except endurance training, especially by power training [11, 14], and with adequate nutrition [9] seems to be the relatively effective intervention with the least side effects. Together with the inconformity
of sarcopenia characterization among different studies, it is imperative to explore deeper into the mechanism or etiology of sarcopenia which in turn will provide further insight into the development of more effective therapy as well as a better understanding of the rationale that leads to a better characterization of sarcopenia.

In this article, we aimed to provide another perspective on sarcopenia and propose that sarcopenia may be neurogenic in nature despite its muscle-related features. In the following sections, we will discuss first the definition of sarcopenia, followed by the effects and overview of the physiological factors that link up the nervous and muscular system.

2. Definition of Sarcopenia

Despite the characterization of sarcopenia varied among different studies [2–4, 15, 16], the major impact of sarcopenia is the age-related progressive decline in muscle mass. Under normal circumstances, when a healthy individual is trying to perform a particular physical activity, the relevant muscles on the corresponding part of the body will start to generate strength or force by neural action potential-induced contraction. The part of the body moves only when the overall strength produced overcomes the weight exert by the corresponding body part and the resistance forces induced by the activity. It is commonly assumed that if every muscle fiber of a single type has the same rate of force generation and produces the same force, then the muscle strength shall be positively correlated with the number of muscle fibers present in the muscle. Thus, the loss of muscle mass shall at least partly contribute to the loss of muscle strength which in turn contribute to the decline in muscle function due to the impaired ability to overcome resistance forces involved in the physical activity. In fact, the association between muscle mass and strength was supported by early cross-sectional studies until recent longitudinal studies demonstrated that there may be a disassociation between age-related changes in muscle mass (sarcopenia) and strength (dynapenia), and there are distinct mechanisms accounting for each component [15, 16]. These recent evidences not only bring a new terminology “dynapenia” into the field but also a reconsideration of the mechanism and etiology that underlies the problems as well as examining the problem from other perspectives. However, according to the original definition of sarcopenia [1],

> no decline with age is as dramatic or potentially more significant than the decline in lean body mass. In fact, there may be no single feature of age-related decline more striking than the decline in lean body mass in affecting ambulation, mobility, energy intake, overall nutrient intake and status, independence and breathing. Irwin H. Rosenberg, 1988

Notwithstanding, the focus is on the decline of lean body mass, and if scrutinized carefully, the statement is actually referred to a phenomenon that relates to both the body mass and function but not the strength. Thus, “sarcopenia” in 1988 is defined as the change of body functions and behavior due to the loss of lean body mass. However, as strength is an independent predictor of body functions including falls and mortality [4, 16], it eventually replaces the body function and becomes part of the definition of sarcopenia in some studies [2, 3]. Since the definition of sarcopenia plays a central role in its research affecting the significance of its related research findings thereafter, we should have a consensus regarding this definition. Recently, some studies have pointed out the disassociation between the muscle mass and muscle strength [4, 15, 16] and have introduced the concept of “dynapenia” into the field; the strength parameter should be isolated from the definition of sarcopenia once again. However, when reading the original Albuquerque statement, it should be noted that Dr. Rosenberg has actually used the term “lean body mass” which includes the mass of muscles, blood, bones, and other nonfat tissues. All these tissues could experience aging and contribute to the decline in body function at a certain degree. Even the prefix “sarco” is commonly used to depict the muscles, and the Greek translation for “sarco” is only flesh whilst the one for muscle is “myxa”. As a result, the term “myopenia” may be more appropriate for the current pathological condition of the age-related decline in muscle mass.

Virtually all diseases and pathological conditions involve a change in body physiology in which a phenotype is determined by a myriad of molecular factors that weave different molecular cascades in an interlacing fashion. Interestingly, one physiological factor may link up to several diseases (e.g., inflammation involved in both Alzheimer’s disease and Parkinson’s disease) and one sort of disease may also have several underlying physiological factors (e.g., amyotrophic lateral sclerosis has several subtypes and each of which is associated with a different gene or protein). In the case of sarcopenia, although muscle wasting and muscle atrophy are main features of its pathology, it is not unique at least Cachexia has a similar characteristics and consequence as sarcopenia [8, 17]. The certain degree of pathological overlapping suggests that at least some underlying molecular mechanisms are common to/shared between these pathologies. For instance, inflammation where proinflammatory cytokines and ubiquitin-proteasome degradation pathway are upregulated [17]. Despite the similarity and overlapping characteristics with cachexia, sarcopenia is a separate clinical condition with a certain degree of discrepancies. Sarcopenia is a chronic muscle wasting condition associated with a low grade systemic inflammation which is not necessary to be the pathological trigger whilst cachexia is an acute muscle wasting condition that only develops under an overlying inflammation [8, 17]. In summary, it may be more appropriate to account the loss of muscle mass in subtypes or in a way similar to the definition of amyotrophic lateral sclerosis. For example, the subtype with a muscle-in-origin etiology shall call “type I sarcopenia” whilst the subtype with a neuron-in-origin etiology shall call “type II sarcopenia”. Or from the other perspective, the term “sarcopenia” shall be a pronoun for all types of chronic muscle mass decline and each of its subtypes is defined by one sort of etiological mechanism. For instance, the one shared with cachexia shall be called “cachexic sarcopenia” whilst the one shared...
with amyotrophic lateral sclerosis shall be called “Hawking’s sarcopenia.”

3. Commonly Accepted Etiology of Sarcopenia

Currently, the body physiology or the etiology of sarcopenia is believed to be affected by but not restricted to five main features: (1) aging, (2) genetics, (3) morbidity, (4) nutrition, and (5) activity. Nevertheless, it is certain that muscle mass, strength, function, and quality are determined by at least three cardinal physiological systems: (1) neurological system [15], (2) muscular system [15], and (3) circulatory system. Thus, it is not surprising that any diseases or conditions that affect or alter these physiological systems may contribute to the development of dynapenia and sarcopenia, for example, genetic factors, neurodegenerative diseases, hormonal dysregulatory diseases, autoimmune diseases, inflammation, malnutrition, physical injuries, and inactivity [5, 8, 12]. As the muscle function relies on the status of motor units (each of which consisted of a motor neuron, motor neurites (axons), neuromuscular junctions (NMJ), and muscle fibers) in addition to the circulation factors, the pathology of sarcopenia may be neurogenic, musculogenic (term created to differ from “myogenic”), synaptogenic (from NMJ), and/or vasculogenic (from blood vessels) (Figure 1).

3.1. Muscular Factors. Aging is a sympletic (“sym”: together; “plektos”: braid) natural process of matters and contributes significantly to sarcopenia. For skeletal muscle, aging leads to a decline in muscle function. At the systemic level, both the upper and lower limbs of men and women have an age-associated sequential loss in muscle power, muscle strength, and muscle mass, starting from the age of 40 years, 30 years, and 24 years, respectively [19]. The age-related loss of muscle power is more rapid than the parallel loss of muscle strength which in turn is more rapid than the loss of muscle mass [12, 19]. The loss in muscle power and muscle strength is at least partly attributable to the reduction in muscle mass. At the molecular level, the loss of muscle power and muscle strength is further associated with a reduction in the amount of Ca\(^{2+}\) available for the mechanical response in muscles [20] and with a reduction in Ca\(^{2+}\) release in response to the mechanical action of muscles due to the age-associated reduction in dihydropyridine receptors at the t-tubule and sarcoplasmic reticulum membrane which in turn results in uncoupling of Ca\(^{2+}\) release channels or ryanodine receptors in type II muscle fibers [15, 19, 20]. On the myocellular level, skeletal muscle fibers are basically two types. Type I fibers are slow and oxidative which mainly operate in the weight bearing/antigravity functions, whilst type II fibers are fast and glycolytic which are mainly involved in the explosive actions (e.g., sprinting). Patients with sarcopenia manifested a reduction in the number of both type I/slow-twitch and type II/fast-twitch muscle fibers and an atrophy specific to the type II fibers (being more prominent in IIB fibers than IIA fibers) [12, 19]. This may be resulted from a hypotrophic or hypercatabolic state of muscle fibers which may be a cause or an effect of the denervation of motor units and/or the loss of motor neurons [21]. These are the common features of aging and are being more prominent in type II than type I fibers. However, the hypercatabolic state of muscle fibers may also attribute to the reduction in the number of satellite cells [22]. In other words, the loss of muscle mass is also partly attribute to the diminished ability of muscle self-repair due to the decreased number and impaired function of satellite cells [2, 22]. At the cellular level, aging is associated with a reduction in cell density of the satellite cell population in type II fibers as well as a diminished satellite cell proliferation capacity or a replicative senescence, which may relate to the shortening of telomeres [2, 22, 23].

3.2. Neurological Factors. On the neurological side, the loss of muscle power and muscle strength is associated with the age-related changes in motor units and in the degree of coactivation of antagonist muscles, respectively [19]. At the cellular level, aging is associated with a reduction in motor axon conduction velocity and the number of myelinated axons. Further, it is associated with a reduction in motor unit reinnervation after denervation, and with a reduction in the number of motor units and motor neurons specific to the type II muscle fibers [19, 21]. As the fast-twitch motor units are the determinant of the degree of power exerted by muscles, their loss in aging contributes to the loss in muscle power [19]. In fact, under normal aging process, a preferential denervation of type II muscle fibers occurs and these denervated fibers are then reinnervated by the axonal sprouting from slow motor neurons in a process called motor unit remodeling. However, if denervation outpaces reinnervation, then a population of denervated fibers will undergo atrophy and degeneration [24] due to the loss of trophic factors [25]. This process contributes to the loss of muscle mass at least partly by apoptosis [26]. At the molecular level, rat studies have shown that progressive denervation during aging have disrupted the precise overlapping between the presynaptic nerve terminal and the postsynaptic acetylcholine receptor (AChR) clusters at the NMJ [27]. Also, denervated muscles have elevated the expression of proapoptotic/atrophic factors including bax, caspase 3, 7, 8, and 10 [26] along with a reduction in the trophic factor signals including TrkB signaling via BDNF and NT-4/5 [27]. These in turn increase the apoptotic potential of myocytes. Thus, denervation seems to be the trigger for muscle loss.

3.3. Circulation Factors. Blood circulation is vital to the whole body and thus may also contribute to the pathology. Aging is associated with the changes in microcirculation and ultrastructure of the vascular endothelium [28], a decline in vascular endothelial functions [29], and a decline in exercise-induced blood flow which may be partly resulted from an age-related reduction in vasodilatory capacity and capillarization [28]. The reduced blood flow leads to a reduction in the exchange of oxygen, energy sources, metabolites, and heat between blood and the body cells. This results in a less trophic environment for the cells in the corresponding region [28].
4. Common Pathophysiology Shared between the Aging Nervous System and the Aging Muscular System

According to most of the studies, contributors to the loss of muscle mass in sarcopenia are explained mainly by, but not limited to: (1) mitochondrial dysfunction, (2) elevation of oxidative stress, (3) inflam-aging, (4) altered rate of protein turnover, (5) decreased hormones, growth factors, and proteins that maintain proper cellular functions, (6) declines in intake of essential nutrients, and (7) declines in physical activity [5, 12, 19, 21]. Interestingly, most of these contributors are not unique to the muscular system. They may also applicable to the nervous system.

4.1. Mitochondrial Dysfunction. Mitochondrial dysfunction may arise from the age-related decline in mitochondriogenesis [14, 30] and mitochondrial function. Both of which may be associated with an increase in the mitochondrial DNA damage by oxidative stress, changes in the mitochondrial respiratory chain enzymes, and changes in the mitochondrial proapoptotic proteins. Mitochondrial dysfunction results in an impaired mitochondrial oxidative function and energy production. These in turn affect cell viability through necrosis and/or apoptosis of both myocytes and neurons [21, 31].

4.2. Elevation of Oxidative Stress. Elevation of oxidative stress is commonly seen in aged animal cells with an increase in the oxidative species (e.g., $H_2O_2$ species, MDA/4-HAE, nitrotyrosine, catalase [32], iNOS [17]) and a decrease in the antioxidative species (e.g., MnSOD [32], G6PDH [33]). Also, accumulation of the oxidative stress-induced advanced age glycation end-product (AGE) and lipoxidation end-products (ALE) on the extracellular and intracellular proteins during aging impairs the activities of these proteins [21]. The consequence of an elevated oxidative stress in muscles...
is the iNOS-mediated downregulation of a set of myogenic proteins including CKM and MyoD [17], and the concomitant inhibition of general protein translation by both the phosphorylation of eIF2α and the inhibition of mTOR [17]. Additionally, aging upregulates the iNOS which correlates with an increase in caspase 2 and JNK signaling activity, this suggests the involvement of JNK-mediated apoptotic signaling [33]. In the perspective of the nervous system, oxidative stress may lead to an alteration in the balance between mitochondrial fission and fusion as well as an activation of the apoptotic pathway in neurons [34].

4.3. Inflamm-Aging (Aging-Associated Chronic Inflammation). Inflammation is intimately linked to the oxidative stress. Inflamm-aging is an age-related elevation of the baseline level of proinflammatory markers and cytokines (e.g., TNF-α, IL-6, CRP) [10]. The most representative cytokines are TNF-α and IL-6. TNF-α induce apoptosis directly through its interaction with the death domain receptors which in turn leads to the activation of procaspase 8 [21, 26]; and indirectly through the activation of its downstream effectors, NF-κB, which activity is also elevated by aging [17]. Activated NF-κB upregulates MSTN/GDF8 [35], iNOS, and MuRF1 [17], these factors play a negative role in the trophic state of myocytes. Additionally, IL-6 plays a similar role by downregulating IGF-1 [2]. As a result, the anabolic potential of myocytes including the satellite cells is impaired due to (1) reduced expression of proteins involved in myogenesis and other relevant muscle growth processes (e.g., MRF, myogenin, MyoD, and CKM) [17, 26]; (2) elevated expression of MSTN which exerts its effect on muscle growth by regulating the Activin receptor-mediated pathway, MAPK pathway, and Akt/mTORC1/p70S6K pathway [5]. Additionally, MSTN induces reactive oxygen species (ROS) production via NADPH oxidase and TNF-α. The elevated TNF-α in turn induces further MSTN production and the higher levels of MSTN promotes proteasome-mediated catabolism of intracellular proteins [35]. In addition to the muscular system, both oxidative stress and inflammation have great impacts on the nervous system as they are commonly disclosed in the neurodegenerative diseases [34, 36].

4.4. Altered Rate of Protein Turnover. Altered protein balance is one of the major features in aging cells. In myocytes, there is an age-associated change in expression of dystrophic factors (e.g., Id1, Id2 and Id3, etc.) [26] and trophic factors (e.g., MGF, etc.) [19]. Similarly, the expression profile of dystrophic/proapoptotic factors (e.g., bax and procaspase 3, etc.) [37] and trophic factors (e.g., CNTF, etc.) [19] in neurons are also altered by aging. The fate of a cell is determined by the balance between the rate of positive metabolism and the rate of negative metabolism which are positively correlated to the level of trophic signal (e.g., growth factor-mediated pathways) and atrophic/dystrophic signal (e.g., proapoptotic factor-mediated pathways), respectively. Thus, when the rate of negative metabolism exceeds the rate of positive metabolism, the cell will undergo atrophy and finally death by apoptosis. In the case of aging myocytes, despite the mechanism is not clear, the loss of multinucleated myocyte nuclei is suggested to be caused by apoptosis regulated by AIF-mediated caspase-independent DNA fragmentation. Unlike single-nucleated neurons, apoptosis of one single nucleus of the myocyte may not result in cell death [21]. Instead it will undergo an atrophy due to the decrease of the nuclear domain [19]. Together with the “use it or lose it” perspective (discuss in later section), this may explain the more remarkable reduction in the size of type II muscle fibers than that of the type I muscle fibers in sarcopenia. Additionally, this also suggested that myocytes may have a greater potential to resist death than neurons. At the transcription level, miRNAs may also contribute to the age-related alteration in protein turnover as they are capable of regulating protein expression. Many miRNA candidates altered their expression level during aging in both myocytes and neurons [38–40].

4.5. Decreased Hormones, Growth Factors, and Functional Proteins. Hormones, growth factors, and proteins that maintain proper cellular functions are associated with the trophic state of myocytes. Aging is associated with a decline in sex hormones in both male and female, for example, androgen and estrogen [2]. On the neurological side, the alteration in sex hormone levels may also affect brain functions as circulating sex hormones can penetrate the blood-brain barrier [41]. Additionally, aging is associated with a decline in growth factors and their relevant regulators affecting both myocytes and neurons, for example, (1) GH, which regulates the synthesis of IGF-1 [19] and the survival of neurons [42]; (2) IGFs, which stimulate amino acid and glucose transport and are important trophic factors to both myocytes [5, 12] and neurons [43–45]. IGF-1 regulates growth, differentiation, and regeneration of myocytes [12] by inducing hypertrophy pathways (e.g., PI3K and MAPK pathways) [5] whilst IGF-2 is associated with the proliferative action in adult muscles [12]; (3) CNTFs, which are important hypertrophic factors for both myocytes and neurons [12] and may play a role in the re-innervation of muscle fibers by motor neurons after muscle and nerve injury [5]. Apart from the growth factors, aging is also associated with a reduction in stress-induced expression of HSP70, which normally functioned as chaperones and expressed by both myocytes and neurons [21, 23]. HSP70 reduces the apoptotic potential of a cell by inhibiting the formation of apoptosome and functioning as an antagonist of AIF [21]. Thus, the age-associated decline in these candidates may have a serious consequence on both the muscular and nervous systems.

4.6. Malnutrition. Aging is commonly associated with a decline in the ability to utilize exogenous amino acids. This may be due but not limited to: (1) reductions in transmembrane amino acid transport for protein synthesis; (2) alterations in the whole body amino acid turnover which results in a reduced availability of substrate for protein synthesis; (3) alterations in the endogenous hormonal response; and/or (4) alterations in the response of muscle to the hormonal stimuli after meal intake [47]. The current recommended daily
nutrition intake for the prevention of sarcopenia and frailty is 24–36 kcal and 0.8–1.2 g high quality protein per kg body weight [9]. Essential amino acids, in particular the branched-chain amino acids (BCAA) especially Leucine, are potent anabolic signals for protein accretion [47, 48], which requires ∼0.7 kcal/g of muscle protein synthesized [47]. Therefore, lacking such nutrients may alter the protein turnover and thus contribute to the development of sarcopenia [8].

4.7. Disuse Atrophy. Physical inactivity, induced by either sedentary lifestyle or immobility due to illness/injury, is a trigger of muscle disuse atrophy [18]. At the molecular level, physical inactivity is associated with an inhibition of the IGF-1 hypertrophic signaling and a concomitant upregulation of proteasomal (ubiquitin) and lysosomal (autophagy) degradation signaling via FOXO proteins [18, 49]. This contributes to a reduced trophic state in myocytes. In contrast, increased physical activity level by resistance training enhances the muscle mass, muscle strength, and balance which in turn reduces the risk of physical limitation and/or the onset of frailty [11, 21]. The effect of exercise training is dose dependent. The higher the intensity involved in the training, the better the yield of the effect. Training at 60%–85% of the individual maximum voluntary strength can increase the muscle mass whilst more than 85% can also increase the rate of force development. The addition of a sensorimotor component to the exercise training program may also help improving the postural control in older persons [50]. In addition to the muscles, the influence of exercise training to the nervous system is also well described [51]. Interestingly, although having a positive impact on both muscle mass and strength, exercise trainings do not prevent the age-related impairment in muscle features. Recent studies reported that both the muscle size and functions are impaired in aged sprint-trained athletes. Similar to sarcopenia, type II muscle fibers were suffered from a more remarkable impairment than type I muscle fibers [52].

5. Use It or Loss It

On the neurological perspective, physical inactivity reflects a reduced activity of the corresponding motor units. Unused or seldom used neurons will undergo disuse degeneration which in turn results in a further disuse degeneration of its synaptically connected cells [53]. Thus, it is possible that the age-associated progressive denervation and the age-associated loss of muscle fibers are due to the disuse atrophy and degeneration of the NMJ and/or the motor neurons. This "use it or loss it" doctrine at least partly explains why there are more prominent type II motor unit atrophy and degeneration in sarcopenia and why sedentary individuals are more susceptible to sarcopenia. As sedentary individuals have less explosive actions, the frequency of usage and/or length of activation of the fast motor unit (type II fibers) is lesser than that of the slow motor unit (type I fibers) which is frequently engaged in the antigravity functions. Thus, the potential of disuse atrophy and degeneration for type II fibers is higher. In fact, age-related denervation, loss of motor units, and motor neurons are all being more prominent in the type II fibers in comparison to the type I fibers [19, 54]. Further, space flight studies reported that the loss of muscle mass, strength, and power are more prominent in the type I fibers than those of the type II fibers under microgravity [55]. These may be explained by the “use it or lose it” doctrine again. As gravity is reduced, the usage of slow motor unit is lesser than that of the fast motor unit. Hence the potential of disuse atrophy and degeneration for the type I fibers is higher. It is interesting to note that after the space flight, the type II fibers were also lesser. This may due to the reduction in gravity which leads to the reduction in resistance force for activity, and the type II motor units were then using lesser strength, energy, or power for the same work. As a result, they were susceptible to the disuse issue but to a lesser degree.

6. The Origin of Sarcopenia

Contributors to the development of sarcopenia discussed so far are common to both myocytes and neurons. Thus, the aforementioned contributors may be the systemic/general factors which may not necessary be the primary trigger in the etiology of sarcopenia but rather they may play a role in exacerbating the development process of sarcopenia upon triggering. Apparently, sarcopenia is linked to the interplay of assorted molecular cascades which involve a complex relationship between a variety of nucleic acids and proteins. Therefore, it is also possible that the pathology is originated from these multiple independent or synergistic triggers. Additionally, morbidity factors including neurodegenerative diseases and other pathological conditions may also have a direct or indirect role in the development of sarcopenia, that is, sarcopenia as a complication of other diseases.

By putting these pictures together, the development of sarcopenia may originate either from the following: (1) muscle fiber atrophy and degeneration which in turn leads to the denervation and loss of motor neuron (musculogenic); (2) synapse atrophy and degeneration of the NMJ which in turn leads to the atrophy and degeneration of muscle fibers (synaptogenic); (3) motor neuron atrophy and degeneration which in turn leads to the atrophy and degeneration of muscle fibers (neurogenic); (4) all of these. On the other hand, the exercise-induced hypertrophy of muscles may be explained either by (1) hypertrophy of the muscle fiber which in turn reinforces and stabilizes the synapses (muscle-induced); (2) hypertrophy of the synapses at the NMJ by synaptic facilitation through reinforcing signals and this in turn potentiates the trophic status of the muscle fibers (nerve induced); (3) both. Interestingly, the nervous system-based ideas seem more feasible due to (Figure 2) the following: (1) the trophic state of the muscle is determined by the net protein balance and some myogenic factors, e.g. myogenin, are strongly regulated by the electrical activity [25]; (2) some trophic factors, e.g. NT-4/5 and TrkB, are innervation dependent [56]; (3) some neurotrophic factors,CNTF, nourishes both the muscular and nervous system [57]; (4) the loss of muscle mass and strength albeit having different onset time, both of them are well maintained or decline slowly until the
7. One Picture Has Two Sides

Nature is amazing and sometimes surprising, this makes science even challenging and fascinating especially when analyzing a particular phenomenon with a different or even antagonistic logic. For example, although hypertrophic state is commonly considered to be important for the survival of cells, chronic hyperactivity of growth-promoting pathways may not possess any positive impacts. Animal studies reported that hyperactivation of the mTOR pathway, which originally promotes accretion and regulates initiation of translation, does not reverse the atrophy observed in obese muscles [59]. In contrast, when treated with the AMPK-agonists which inhibit the mTOR pathway, the translation capacity and the mass of obese muscle increased [59]. Thus, hyperactivity of mTOR may lead to a secondary resistance to the growth stimuli probably due to the negative feedback of a homeostatic effect [17]. Interestingly, some human studies reported that the muscle mass is higher in obese old persons than those with lesser obesity [60, 61]. This may be due to the decreased levels of SHBG which in turn results in an increased level of circulating androgens [61].

When we considered food intake as an important factor for the prevention of sarcopenia, caloric restriction without being malnutrition may have a positive impact on cells [59]. Animal studies shown that caloric restriction attenuates the progressive functional decline of organs [21]. At the cellular level, caloric restriction is associated with a decreased damage of peripheral nerve during aging by increasing the expression of chaperones and autophagic machineries [24]. It also ameliorates the loss of muscle mass, decreases abnormalities in the electron transport chain and diminished apoptotic potential in muscles [21]. Further, it is associated with neuronal protection against degeneration in animal CNS [62]. However, more ongoing investigations in humans are required to determine its efficacy in reality.

Every picture has two sides, like the above examples, although the nervous system may have an important vital role for the muscular system, the muscular system is also playing an important vital role for the nervous system as the muscle fibers are supplying the NGF-like factors to the motor neuron for its survival [63]. Thus, when considering the motor unit holistically, the common musculogenic model of sarcopenia is also valid.
8. Conclusion

Sarcopenia is an age-associated condition which links to multiple etiological factors ranging from external factors (physical activities, nutrients, and diseases) to internal factors (interplay between different cells, epigenetic profile of the cells, and congenital genetic configuration of an individual).

In this article, we propose that sarcopenia may be neurogenic in origin due to the intimate relationship between the nervous system and the muscle cells. By summarizing the aforementioned evidences, it seems that the pathological importance at the presynaptic side (nerve side) precedes the postsynaptic side (muscle side). This presumption is in agreement with the age-associated degeneration of motor neurons [21]. Further, the age-associated denervation is more likely to be triggered by the disuse atrophy of synapse or even motor neurons. This is consistent with the fact that individuals with a sedentary life style or physical inactivity are usually more susceptible to sarcopenia compared to the physical active ones. However, more investigation is required in order to validate this belief. For example, to perform an in vitro experiment on the primary muscle cells which cultured with the necessary nervous-system-derived factors and observe whether the change in these factors would significantly affect the potential for sarcopenia development. But before that, a consensus for the definition of sarcopenia must be committed.

Conflict of Interests

The authors declare that they have no conflict of interests.

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References


Research Article

Physical Activity Improves Verbal and Spatial Memory in Older Adults with Probable Mild Cognitive Impairment: A 6-Month Randomized Controlled Trial

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We report secondary findings from a randomized controlled trial on the effects of exercise on memory in older adults with probable MCI. We randomized 86 women aged 70–80 years with subjective memory complaints into one of three groups: resistance training, aerobic training, or balance and tone (control). All participants exercised twice per week for six months. We measured verbal memory and learning using the Rey Auditory Verbal Learning Test (RAVLT) and spatial memory using a computerized test, before and after trial completion. We found that the aerobic training group remembered significantly more items in the loss after interference condition of the RAVLT compared with the control group after six months of training. In addition, both experimental groups showed improved spatial memory performance in the most difficult condition where they were required to memorize the spatial location of three items, compared with the control group. Lastly, we found a significant correlation between spatial memory performance and overall physical capacity after intervention in the aerobic training group. Taken together, our results provide support for the prevailing notion that exercise can positively impact cognitive functioning and may represent an effective strategy to improve memory in those who have begun to experience cognitive decline.

1. Introduction

Cognitive decline is one of the most pressing health care issues of the 21st century. Currently worldwide, one new case of dementia is detected every seven seconds [1] and the number of people affected is projected to be over 80 million by 2040 [1]. Thus, the societal value of developing effective intervention strategies cannot be overstated [2]. To date, pharmacological interventions for dementia have remained medically challenging at best. As a result, there has been growing interest in exercise training as an alternative intervention strategy.

The primary aim of our current study was to investigate the efficacy of exercise as an intervention strategy to improve memory performance in older adults who have already begun to experience cognitive decline—namely, those with mild cognitive impairment (MCI). MCI is characterized by cognitive decline that is greater than expected for an individual’s age and education level, but does not significantly interfere with everyday function (i.e., instrumental activities...
of daily living) [3]. Importantly, MCI is a well-recognized risk factor for dementia; longitudinal studies report that seniors with MCI develop Alzheimer’s disease at a rate of 10–30% annually [4, 5], compared to 1-2% of seniors without MCI [5]. Thus, MCI represents a critical window of opportunity to intervene and alter the trajectory of both cognitive and functional decline in seniors.

Exercise is a promising strategy for improving cognitive functions. Previous research has found that both resistance training [6, 7] and aerobic training [8] positively impact cognitive functioning and result in functional plasticity in healthy older adults. Furthermore, emerging evidence also suggests that exercise training has cognitive benefits for seniors with MCI. For example, a 24-week home-based physical activity program improved performance on the Alzheimer Disease Assessment Scale-Cognitive Subscale in seniors with probable MCI [9]. Additionally, a six-month aerobic training program improved selective attention and conflict resolution, processing speed, and verbal fluency in senior women with amnestic MCI [10].

Expanding upon the existing body of knowledge on exercise and cognitive functions, we found that twice-weekly progressive resistance training in our six-month intervention improved associative memory—or the memorization of two items in conjunction—in senior women with probable MCI [11]. These findings were further corroborated by our neuroimaging results, where resistance training was associated with increased activation over time in key cortical regions that subserve associative memory. Importantly, other research groups have found complementary evidence for a relationship between physical activity and memory in seniors with MCI [12]. However, a comparison has not been conducted between resistance and aerobic training for their propensity to improve various forms of memory in older adults who are showing signs of memory decline.

For our study reported here, we analyzed the secondary outcome measures of our randomized controlled trial that was previously published [11]. Our current analysis was primarily designed to examine the efficacy of both resistance training and aerobic training to improve memory performance in senior women with probable MCI. To this end, we examined the impact of exercise on two distinct forms of memory: (1) verbal memory and learning and (2) spatial memory. The second aim of our study was to determine whether memory performance at the end of the trial might be associated with physical performance measures. While research on the effects of resistance training on cognitive function has been limited, preliminary evidence does suggest that different forms of exercise (e.g., aerobic versus resistance training) alter distinct cognitive processes [6, 11]. Consistent with this idea, Cassilhas and colleagues [13] recently reported differences in underlying molecular mechanisms between the two types of exercise for how they may improve cognitive function; whereas resistance training appeared to increase levels of serum IFG-1, aerobic training increased levels of brain-derived neurotrophic factors (BDNF) in the hippocampus. Therefore, we hypothesized that both types of exercise training would yield beneficial—although potentially divergent—impacts on memory.

2. Methods

2.1. Study Design. We conducted a 26-week, single-blinded, randomized trial of exercise (NCT00958867) with assessments at baseline, mid-point, and trial completion. Details of the trial have been reported elsewhere [11].

2.2. Participants. Our study only included women due to sex differences in cognitive response to exercise [14]. From April 2009 to August 2009, we recruited participants using advertisements in local media and a memory clinic. Individuals were screened by a standardized telephone interview and by a 30-minute in-person assessment. Women who lived in Vancouver, Canada, were eligible for study entry if they (1) were aged 70 to 80 years; (2) were living independently in their own home; (3) scored ≥24/30 on the Mini-Mental State Examination (MMSE); (4) scored ≥26/30 on the Montreal Cognitive Assessment (MoCA) [15]; (5) answered “yes” to the question “do you have any difficulty with your memory?” [9]; (6) scored ≥6/8 on the Lawton and Brody [16] Instrumental Activities of Daily Living; (7) had a visual acuity of at least 20/40, with or without corrective lenses; and (8) obtained their physician’s clearance to start a supervised exercise program. We excluded those who (1) had a current medical condition for which exercise is contraindicated; (2) had participated regularly in resistance training or aerobic training in the last six months; (3) had a neurodegenerative disease and/or stroke; (4) had a diagnosed psychiatric condition (e.g., depression); (5) had a diagnosis of dementia of any type; (6) did not speak and understand English fluently; or (7) were on oestrogen replacement therapy.

In Figure 1, the CONSORT (Consolidated Standards of Reporting Trial) flowchart shows the number and distribution of participants. Ethical approval was obtained from the Vancouver Coastal Health Research Institute and the University of British Columbia’s Clinical Research Ethics Board. All participants provided written informed consent.

2.3. Descriptive Variables. Current level of physical activity was determined by the Physical Activities Scale for the Elderly (PASE) self-report questionnaire [17]. The 15-item Geriatric Depression Scale [18] screened for depression. The Functional Comorbidity Index was calculated to estimate the degree of comorbidity associated with physical functioning [19]. We used the Lawton and Brody [16] Instrumental Activities of Daily Living Scale to subjectively assess ability to perform daily activities.

2.4. Verbal Memory and Learning. The Rey Auditory Verbal Learning Test (RAVLT) [20] assessed verbal memory and learning. Participants were asked to list 15 common words five times. Immediately after each time, they were required to recall as many words as possible. After the fifth trial, an interference list was presented, after which participants had to spontaneously recall the original words. Finally, participants were required to spontaneously recall the original words after a 20 minute delay. Scores were calculated as the total number of words recalled (1) across the five trials
2.5. Spatial Memory. Spatial memory was assessed using a computerized task developed in-house by one of our co-authors along with her collaborators. This task was chosen because it has previously been found to modulate with physical activity [21–23] and allows for the collection of reaction times and accuracy—rather than just working memory span which other spatial memory tasks provide. Our spatial memory task required participants to recall the spatial location of dots presented on a screen. Specifically, one, two, or three dots appeared at randomly selected locations on the screen for 500 ms. Next, a fixation-cross appeared for 3 s. At the end of the delay, a single red test dot was presented on the screen, either at the same location as one of the previous black dots (match), or at a new location (nonmatch). Subjects...
Table 1

<table>
<thead>
<tr>
<th>Variablea</th>
<th>BAT (n = 28)</th>
<th>AT (n = 30)</th>
<th>RT (n = 28)</th>
<th>Total N = 86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>75.1 (3.6)</td>
<td>75.6 (3.6)</td>
<td>73.9 (3.4)</td>
<td>74.9 (3.5)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>158.2 (7.3)</td>
<td>159.2 (5.9)</td>
<td>158.7 (7.0)</td>
<td>158.7 (6.7)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.4 (14.0)</td>
<td>64.8 (12.8)</td>
<td>65.2 (10.7)</td>
<td>65.4 (12.4)</td>
</tr>
<tr>
<td>Physical activity scale for the elderly</td>
<td>133.2 (78.1)</td>
<td>121.6 (52.9)</td>
<td>151.8 (74.9)</td>
<td>135.2 (69.5)</td>
</tr>
<tr>
<td>Education, No (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than grade 9</td>
<td>0 (0)</td>
<td>2 (2.3)</td>
<td>0 (0)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Grade 9 to 12 without certificate or diploma</td>
<td>5 (5.8)</td>
<td>3 (3.5)</td>
<td>2 (2.3)</td>
<td>10 (11.6)</td>
</tr>
<tr>
<td>High school certificate or diploma</td>
<td>7 (8.1)</td>
<td>7 (8.1)</td>
<td>7 (8.1)</td>
<td>21 (24.4)</td>
</tr>
<tr>
<td>Trades or professional certificate or diploma</td>
<td>5 (5.8)</td>
<td>2 (2.3)</td>
<td>3 (3.5)</td>
<td>10 (11.6)</td>
</tr>
<tr>
<td>University certificate or diploma</td>
<td>8 (9.3)</td>
<td>8 (9.3)</td>
<td>8 (9.3)</td>
<td>24 (27.9)</td>
</tr>
<tr>
<td>University degree</td>
<td>3 (3.5)</td>
<td>8 (9.3)</td>
<td>8 (9.3)</td>
<td>19 (22.1)</td>
</tr>
<tr>
<td>Geriatric depression scaleb</td>
<td>1.0 (1.8)</td>
<td>1.1 (1.8)</td>
<td>1.4 (2.0)</td>
<td>1.2 (1.8)</td>
</tr>
<tr>
<td>Functional comorbidities indexc</td>
<td>2.6 (2.2)</td>
<td>2.9 (1.5)</td>
<td>3.0 (1.9)</td>
<td>2.8 (1.8)</td>
</tr>
<tr>
<td>Instrumental activities of daily livingd</td>
<td>78 (0.5)</td>
<td>78 (0.5)</td>
<td>77 (0.8)</td>
<td>78 (0.6)</td>
</tr>
<tr>
<td>Montreal cognitive assessmente</td>
<td>22.5 (2.8)</td>
<td>22.2 (2.8)</td>
<td>21.4 (3.4)</td>
<td>22.1 (3.0)</td>
</tr>
<tr>
<td>Minimental state examinationf</td>
<td>27.1 (1.7)</td>
<td>27.4 (1.5)</td>
<td>27.0 (1.8)</td>
<td>27.2 (1.6)</td>
</tr>
<tr>
<td>Exercise class compliance, %</td>
<td>59 (14.8)</td>
<td>60 (18.7)</td>
<td>54 (14.7)</td>
<td>57 (16.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BAT: balance and tone; AT: aerobic training; RT: resistance training.

a Unless otherwise indicated, data are expressed as mean (SD). Percentages (%) have been rounded and may not total 100.
b Maximum was 15 points.
c Maximum was 18 points.
d Maximum was 8 points.
e Maximum was 30 points.
f Maximum was 30 points.

2.6. Choice Reaction Time. Choice reaction times were collected to use as a covariate in our statistical analyses for computerized tasks measuring reaction times to account for differences in basic processing speed secondary to memory performance [24]. Participants were required to indicate whether a number (1, 2, 3, 4, 5, 7, 8, 9) presented on a computer screen was higher or lower than the number “5”. Numbers were presented individually for 1500 ms in the centre of the screen, and the same number did not repeat twice in a row. Using one hand, they were required to press one button with their index finger if the correct answer was “higher” than five and another button with their middle finger if the number was “lower” than five. Participants were instructed to respond as quickly and accurately as possible.

2.7. Physical Performance. General balance and mobility was assessed using the Short Physical Performance Battery, which is a composite score of the following tasks: (1) tandem standing; (2) four-metre walk (gait speed); and (3) chair stands. General cardiovascular capacity was assessed using the Six-Minute Walk Test, where the total distance walked at participants’ usual pace in six minutes was measured in metres.

2.8. Randomization. The randomization sequence was generated by (http://www.randomization.com) and was concealed until interventions were assigned. This sequence was held independently and remotely by the Research Coordinator. Participants were enrolled and randomized by the Research Coordinator to the twice-weekly exercise groups: resistance training (RT), aerobic training (AT), or balance and tone (BAT).

2.9. Exercise Intervention. The exercise protocol has been reported elsewhere [11]. Briefly, classes began one month after baseline assessments and were held at a fully equipped gym in a research centre. Classes were led by certified fitness instructors who received additional training from the study investigators. The classes were 60 minutes in duration (10-minute warm-up, 40 minutes of core content, and 10-minute cool-down). Attendance was recorded daily, which
was used to calculate compliance (i.e., percentage of total classes attended). Strategies were implemented to promote participant engagement [6, 25].

2.9.1. Resistance Training. For the RT program, both a Keiser Pressurized Air system and free weights were used [6]. The Keiser-based exercises consisted of biceps curls, triceps extension, seated row, latissimus dorsi pull downs, leg press, hamstring curls, and calf raises. The intensity of the training stimulus was at a work range of six to eight repetitions (two sets). The training stimulus was subsequently increased using the 7RM method—when two sets of six to eight repetitions were completed with proper form and without discomfort. Other key strength exercises included minisquats, mini lunges, and lunge walks.

2.9.2. Aerobic Training. The AT program was an outdoor walking program. The intensity of the training stimulus was at approximately 40% of one’s age specific target heart rate (i.e., heart rate reserve; HRR) and progressed over the first 12 weeks to the range of 70% to 80% of HRR. Exercise intensity was monitored through heart rate monitors. Participants also monitored the intensity of their workouts by the Borg’s Rating of Perceived Exertion [26] and the “talk” test [27, 28].

2.9.3. Balance and Tone. The BAT program consisted of stretching exercises, range of motion exercises, balance exercises, functional and relaxation techniques [6]. Other than bodyweight, no additional loading (e.g., hand weights, etc.) was applied. This group served to control for confounding variables such as physical training received by traveling to the training centres, social interaction, and changes in lifestyle secondary to study participation.

2.10. Adverse Effects. Participants were questioned about the presence of any adverse effects, such as musculoskeletal pain or discomfort, at each exercise session. Instructors monitored participants for symptoms of angina and shortness of breath during the exercise classes.

2.11. Statistical Analysis. All analyses were “full analysis set” [29] (defined as the analysis set which is as complete and as close as possible to the intention-to-treat ideal of including all randomized participants). Data were analyzed using IBM SPSS STATISTICS (Version 20).

Performance on the RAVLT was measured using univariate ANOVAs for each outcome measure, with two planned simple contrasts to assess differences between (1) RT versus BAT and (2) AT versus BAT. Baseline scores were entered as covariates. For the spatial memory task, repeated measures ANOVAs were performed to examine changes over the course of the trial in both reaction time and accuracy, with number of items (one, two, or three) as the within-subjects factor and group as the between-subjects factor. The reaction time analysis included choice reaction time as a covariate to account for differences in processing speed [24]. Bivariate Pearson correlations were calculated to examine the relationship between memory and physical performance at trial completion within each group. For all analyses the overall alpha was set at \( P \leq 0.05 \).

3. Results

3.1. Descriptive Variables, Physical Activity, and Participants. In this trial, 86 participants were recruited and randomized (Figure 1). Baseline demographic and characteristics of the 86 participants are shown in Table 1. Physical activity levels (PASE scores) did not differ significantly between the groups at midpoint (\( P = 0.93 \)) or trial completion (\( P = 0.67 \)). Of the 86 participants, 77 completed the 26-week trial. The number of dropouts was the greatest in the AT group (Figure 1).

3.2. Verbal Memory and Learning. Table 2 shows the baseline, mid-point, and trial completion results for verbal memory and learning performance. For the RAVLT, there were no significant between-group differences at trial completion in total acquisition, recall after interference, and long delay free recall (all \( P \)’s > 0.15). However, there was a significant difference in loss after interference at trial completion between the AT and BAT groups, \( P = 0.04 \) (Figure 2). Conversely, the RT and BAT contrast for loss after interference was nonsignificant, \( P = 0.20 \). Overall, loss after interference was reduced by 43.4% and 32.5% in the AT group and the RT group, respectively. In contrast, the BAT group demonstrated a 1.45% increase in loss after interference. The improvement observed in the AT group was not present at mid-point, \( P = 0.71 \).

3.3. Spatial Memory. Table 3 shows the baseline, mid-point, and trial completion results for reaction time and accuracy.
Table 2: Mean values (SDs) for RAVLT performance.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (SD)</th>
<th>Midpoint Mean (SD)</th>
<th>Final Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 25 )</td>
<td>( n = 24 )</td>
<td>( n = 25 )</td>
</tr>
<tr>
<td>Total acquisition</td>
<td>40.88 (8.36)</td>
<td>46.79 (12.68)</td>
<td>44.36 (11.29)</td>
</tr>
<tr>
<td>Recall after interference</td>
<td>7.48 (2.50)</td>
<td>8.58 (3.89)</td>
<td>8.52 (3.50)</td>
</tr>
<tr>
<td>Loss after interference</td>
<td>3.2 (1.85)</td>
<td>3.38 (2.63)</td>
<td>2.16 (1.80)</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>7.52 (2.76)</td>
<td>8.83 (4.10)</td>
<td>7.79 (4.23)</td>
</tr>
<tr>
<td>AT</td>
<td>( n = 24 )</td>
<td>( n = 23 )</td>
<td>( n = 24 )</td>
</tr>
<tr>
<td>Total acquisition</td>
<td>39.58 (9.04)</td>
<td>47.22 (11.01)</td>
<td>43.38 (10.95)</td>
</tr>
<tr>
<td>Recall after interference</td>
<td>7.83 (3.21)</td>
<td>8.83 (3.73)</td>
<td>9.29 (3.21)</td>
</tr>
<tr>
<td>Loss after interference</td>
<td>2.79 (1.79)</td>
<td>2.87 (2.32)</td>
<td>1.58 (1.86)</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>7.46 (3.08)</td>
<td>8.91 (4.28)</td>
<td>8.13 (3.70)</td>
</tr>
<tr>
<td>BAT</td>
<td>( n = 25 )</td>
<td>( n = 24 )</td>
<td>( n = 25 )</td>
</tr>
<tr>
<td>Total acquisition</td>
<td>41.00 (8.63)</td>
<td>43.75 (9.55)</td>
<td>43.00 (9.61)</td>
</tr>
<tr>
<td>Recall after interference</td>
<td>7.60 (3.21)</td>
<td>8.83 (3.73)</td>
<td>9.29 (3.21)</td>
</tr>
<tr>
<td>Loss after interference</td>
<td>2.76 (1.92)</td>
<td>2.71 (2.05)</td>
<td>2.80 (2.58)</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>7.84 (3.33)</td>
<td>8.26 (3.68)</td>
<td>8.04 (3.36)</td>
</tr>
</tbody>
</table>

Abbreviations: BAT: balance and tone; AT: aerobic training; RT: resistance training.

Figure 3: Change between baseline and trial completion on the spatial memory task as a function of number of items presented and exercise group. Both the RT and AT groups showed improved performance compared to the BAT group for the memorization of three items. Error bars represent standard error of the mean.

3.4. Correlations between Memory and Physical Performance.

Changes in physical performance as a function of exercise group have been previously reported [11]. In this study, faster reaction times at trial completion compared to baseline during the three-item condition on the spatial memory task were associated with better performance on the SPPB in the AT group (Figure 4). This was confirmed via a significant negative correlation between the two variables, \( r(13) = -0.57, P = 0.04 \). Spatial memory reaction times and SPPB were not significantly correlated in the RT or BAT groups (\( P = 0.20 \) and \( P = 0.79 \), resp.). Furthermore, reaction times were not associated with performance on the Six-Minute Walk Test (all \( P’s > 0.17 \)). There were no significant correlations between spatial memory for either mid-point or trial completion (\( P = 0.83 \) and \( P = 0.14 \), resp.).
Table 3: Mean values (SDs) for spatial memory performance.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Midpoint</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One item</td>
<td>981.02 (141.18)</td>
<td>941.05 (167.40)</td>
<td>952.57 (193.75)</td>
</tr>
<tr>
<td>Two items</td>
<td>1036.40 (176.36)</td>
<td>997.00 (196.59)</td>
<td>948.09 (219.19)</td>
</tr>
<tr>
<td>Three items</td>
<td>1092.71 (148.86)</td>
<td>1072.64 (189.75)</td>
<td>1006.69 (189.75)</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One item</td>
<td>0.76 (0.17)</td>
<td>0.82 (0.14)</td>
<td>0.74 (0.17)</td>
</tr>
<tr>
<td>Two items</td>
<td>0.81 (0.16)</td>
<td>0.81 (0.13)</td>
<td>0.75 (0.19)</td>
</tr>
<tr>
<td>Three items</td>
<td>0.72 (0.15)</td>
<td>0.78 (0.13)</td>
<td>0.73 (0.17)</td>
</tr>
<tr>
<td>Choice reaction time, ms</td>
<td>895.26 (158.07)</td>
<td>880.42 (149.10)</td>
<td>889.41 (163.19)</td>
</tr>
<tr>
<td>AT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One item</td>
<td>958.77 (161.91)</td>
<td>927.12 (179.21)</td>
<td>896.51 (172.92)</td>
</tr>
<tr>
<td>Two items</td>
<td>1013.56 (198.95)</td>
<td>982.32 (146.48)</td>
<td>951.22 (165.06)</td>
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<tr>
<td>Three items</td>
<td>1093.65 (186.34)</td>
<td>1039.24 (172.98)</td>
<td>1002.91 (195.64)</td>
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<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One item</td>
<td>0.73 (0.11)</td>
<td>0.79 (0.13)</td>
<td>0.77 (0.12)</td>
</tr>
<tr>
<td>Two items</td>
<td>0.75 (0.15)</td>
<td>0.84 (0.10)</td>
<td>0.84 (0.09)</td>
</tr>
<tr>
<td>Three items</td>
<td>0.71 (0.11)</td>
<td>0.78 (0.10)</td>
<td>0.74 (0.09)</td>
</tr>
<tr>
<td>Choice reaction time, ms</td>
<td>877.82 (128.62)</td>
<td>894.49 (130.15)</td>
<td>910.08 (164.62)</td>
</tr>
<tr>
<td>BAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One item</td>
<td>993.26 (155.19)</td>
<td>968.55 (179.74)</td>
<td>952.00 (178.40)</td>
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<td>1007.27 (187.55)</td>
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<tr>
<td>Three items</td>
<td>1084.62 (215.32)</td>
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<td>Accuracy</td>
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<tr>
<td>One item</td>
<td>0.73 (0.14)</td>
<td>0.74 (0.14)</td>
<td>0.79 (0.12)</td>
</tr>
<tr>
<td>Two items</td>
<td>0.76 (0.13)</td>
<td>0.76 (0.15)</td>
<td>0.79 (0.12)</td>
</tr>
<tr>
<td>Three items</td>
<td>0.71 (0.14)</td>
<td>0.68 (0.15)</td>
<td>0.74 (0.10)</td>
</tr>
<tr>
<td>Choice reaction time, ms</td>
<td>864.91 (111.95)</td>
<td>885.06 (169.32)</td>
<td>838.30 (101.36)</td>
</tr>
</tbody>
</table>

Abbreviations: BAT: balance and tone; AT: aerobic training; RT: resistance training.

Maximum was 1.00.

RAVLT performance and either of the physical performance measures (all P’s > 0.37).

3.5. Adverse Events. Adverse effects included episodes of shortness of breath that resolved with rest (n = 2) and noninjurious falls (n = 4). Results of the Chi Square test indicated no significant between-group differences (P = 0.54) in the proportion of participants reporting adverse events.

4. Discussion

We analyzed our secondary data from a six-month intervention to examine the effects of aerobic training and resistance training on two distinct forms of memory. Our specific aims were to evaluate whether either type of exercise would improve verbal memory and learning and/or spatial memory and to determine whether an association might exist between postintervention memory performance and physical measures. In this regard, we report three key findings. First, we found that twice-weekly aerobic training for six months remembered significantly more items in the loss after interference condition on the verbal memory test. Second, our results suggest that both types of exercise improved reaction times during the spatial memory test compared to the control group. Last, spatial memory performance appears to be positively associated with physical performance in the aerobic training group after the intervention. The results of our present study extend those from our previous work [11], where we found that resistance training significantly improved associative memory. Within this context, several noteworthy points of discussion follow.

To begin with, our finding that aerobic exercise significantly improved verbal memory and learning is consistent with previous reports. Specifically, Pereira and colleagues...
found that three months of aerobic exercise improved performance on the RAVLT. While the benefits of aerobic activity on verbal memory and learning in our study were only observed after six months—compared to three months in the study by Pereira et al. [30], differences in study design may account for this apparent discrepancy. For example, participants in the study by Pereira et al. [30] were young, healthy adults who engaged in aerobic activity four times per week; this is contrasted with older adults in our study who were already experiencing cognitive decline and exercised twice per week. This suggests that a higher dose of exercise may result in observable changes in memory more quickly. It is worth mentioning that in our study, the resistance training group also showed a greater reduction in loss after interference after the trial compared with the control group, although this change was not significant. Nevertheless, future studies with larger sample sizes may discover that resistance training does yield similar benefits to aerobic training for verbal memory performance.

Second, we found that both of our experimental exercise groups showed improved reaction time performance for recalling the spatial location of three items, as compared to the balance and tone group. Task performance on the spatial memory test has been shown to systematically decline as a function of load [31]. That the between-group difference was solely observed for three items—the most difficult condition for the spatial memory task—suggests that exercise distinctively improves higher-level cognitive processing required for more complicated tasks. These findings directly support those from previous studies, where both resistance and aerobic training improved executive functioning—such as selective attention and conflict resolution, as measured by the Stroop task [6, 8, 11].

Third, in light of our initial findings regarding improved associative memory performance after six months of twice-weekly resistance training, the results of our present study suggest that different types of exercise may selectively target distinct cognitive processes—and their underlying neural correlates. To recapitulate, we previously reported that resistance training resulted in improved associative memory performance and increased functional activation in three key regions of the cortex: the right lingual and occipital-fusiform gyri and the right frontal pole [11]. In contrast, here we found that both types of exercise training led to improved spatial memory. Importantly, spatial memory has neural underpinnings in the hippocampus [21, 32], thus suggesting that both forms of exercise training may impact hippocampal structure and/or function. Indeed, it has been established that the hippocampus is the structure most sensitive to exercise-induced change via neurogenesis and cell proliferation. For example, aerobic exercise has been found to increase hippocampal volume and levels of BDNF—a neurotrophic factor involved in cell growth and survival and memory promotion [21]. Thus, while there are multiple potential mechanisms to account for the relationship between cognitive functions and physical activity, such as increased cerebral blood flow [33], reduced neuroinflammation [34], and contribution of white matter hyperintensities [35], we can speculate that underlying changes in hippocampal structure and/or function may be a mediating observed relationship between spatial memory and physical performance.

Finally, the link between physical activity and cognitive functioning is further supported by the significant correlation we have reported between our measure of overall physical performance and spatial memory in the aerobic training group. Notably, these results correspond to our previous findings that improvements in conflict resolution and selective attention, as measured by Stroop performance, were significantly correlated to improved gait speed after 12 months of resistance training [6]. That these two studies found relationships between different types of exercise (aerobic versus resistance training) and two different measures of cognitive function further supports the notion presented above that the two types of exercise may target distinct molecular pathways [13]—and thus, modify different subtypes of cognitive function. However, in combination, evidence from these two studies demonstrate that higher levels of physical performance are associated with better cognitive performance. Given that there are multiple ways to improve general physical performance levels, our results therefore suggest that individuals may gain cognitive benefits from a wide variety of exercise options. Future work is needed to explore this possibility.

The conclusions of our study are tempered by our exclusion of men and those older or younger than 70–80 years old. Additionally, our study was only powered to compare the resistance training versus the control group and the aerobic training versus the control group; therefore, we were unable to directly compare changes in performance between our two exercise groups. Hence, future research on how our results may apply to the broader population with larger sample sizes is warranted.

In sum, our study provides preliminary evidence that multiple benefits for memory can be observed after six months of exercise training. However, the mechanisms behind how resistance training and aerobic training may differentially impact cognition remain unclear; thus future work should be aimed at further understanding the contribution of each type of exercise to cognitive functioning, functional plasticity, and brain structure. Furthermore, while our study did find performance improvements after six months, we did not see comparable changes after only three months using a twice-weekly exercise protocol. Therefore, the dose-response relationship of exercise needs to be elucidated so that future recommendations for the most effective program can be translated to health care practitioners and the public.

Disclosure

T. L. Ambrose had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

All authors have no conflict of interests to declare.
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References


Research Article
Swimming as a Positive Moderator of Cognitive Aging: A Cross-Sectional Study with a Multitask Approach

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This study examined whether regular swimming in older adults was related to better cognitive functioning and whether there were any global or selective positive effects of this physical activity (PA) on cognition. The cognitive performances of three groups of sixteen volunteer participants (young adults, sedentary older adults, and older adults who regularly practice swimming) were evaluated using a multitask approach. All participants performed a battery of ten tasks: two reaction time tasks assessing information processing speed and eight experimental tasks assessing three executive functions (EFs), (behavioral inhibition, working memory updating, and cognitive flexibility). The results showed that young adults performed significantly better than older adults on all examined cognitive functions. However, in older adults, regular swimming was related to better performance on the three EFs, but not on information processing speed. More precisely, five experimental tasks out of the eight tapping EFs were shown to be sensitive to positive effects from swimming practice. Finally, the demonstrated benefits of swimming on EFs were not necessarily linked to better cardiorespiratory fitness. The present findings illustrate the validity of using a multitask approach in examining the potential benefits of regular PA on cognitive aging.

1. Introduction

The growth of the proportion of the population aged 65 and older in the industrialized world, as well as in developing countries, has profound implications for public health and the economic costs of medical care. Cerebral and cognitive decline, as a function of aging, represents a predominant cause of autonomy loss in aging populations. According to the prefrontal-executive theory [1], executive functions (EFs) and their underpinning prefrontal and frontal brain structures are particularly sensitive to the effects of normal and pathological aging [2, 3]. Therefore, the preservation of these brain areas and their associated cognitive functions is of particular importance. Chronic physical activity (PA), aimed at improving cardiorespiratory health, has been proposed to be a good, practical, and powerful candidate to overcome cerebral and behavioral declines [4–6]. Accordingly, the principal aim of the present study was to examine the potential benefits of an understudied form of PA—regular swimming (one of the most popular and accessible forms of PA for older adults)—on EF performance in a population aged 65 to 80 years old.

Executive functions involve higher-order functions of control and coordination allowing behavioral adaptation to complex or novel situations for which automatisms or routines are inappropriate. As such, EFs refer to a set of cognitive processes involved in goal and strategy formulation, planning and monitoring, mental flexibility, and behavioral inhibition [7, 8]. This multicomponent or fractionated view implies that EFs may be composed of different executive processes that are at least partially independent, yet are sufficiently correlated to represent a unique construct. In this line, an authoritative model was developed by Miyake and colleagues [9], who proposed that EFs can be fractionated into at least three separable processes; cognitive flexibility (shifting between multiple tasks or mental sets), behavioral inhibition (suppression of dominant, automatic, or prepotent responses when necessary), and updating of
Working memory (substitution of old information by new more relevant information in working memory). This three-factor structure of EFs has been frequently postulated in the literature and replicated in older populations [2, 10, 11]. Although caution is still needed when choosing the tasks used to assess this construct, all three EFs have been quite constantly shown to be impaired in older people, even after having controlled for other confounders such as level of education and information processing speed [2].

In contrast to the prefrontal-executive theory, the processing speed theory [12] assumes that age-related cognitive declines are accounted for by generalized slowing of cognitive processing due to a diffuse or global deterioration of white matter integrity throughout the whole brain with aging. A meta-analysis by Colcombe and Kramer [13] showed that the effect size of the positive effects of chronic exercise is significantly smaller on information processing speed than on executive functions. It is then very interesting to compare the effects of aging and physical activity on these two functions in the same experiment.

In contrast to this negative view of cognitive aging, a new line of research has developed works that examine how keeping a physically active lifestyle can maintain or even improve cognition and brain functions. In recent years, using various methodologies, several studies have shown that older adults who maintain a physically active way of life by participating in regular PA or chronic exercise outperform their sedentary counterparts in cognitive performance, exhibit higher brain plasticity [14, 15] and are more efficiently protected against neurological diseases and dementia [16, 17]. Moreover, randomized controlled trials have demonstrated that short physical training programs (from 3 months to 1 year) improve cognitive performance, particularly EFs, in sedentary older adults with no pathology of the central nervous system [18–21] or dementia [22, 23]. Narrative and meta-analytic reviews tend to show that this positive effect may be particularly selective to attentional, controlled cognitive functions involving EFs (see [4, 13, 24]) and that the PA programs should involve a strong proportion of aerobic exercises (see [4, 13, 25]). Moderate-to-vigorous PA induces improvements in cardiorespiratory fitness (indexed by maximal oxygen uptake, VO₂max) and leads to a cascade of neurophysiological mechanisms such as the release of neurotrophic factors that facilitate neurogenesis and/or angiogenesis [19, 26–28], two mechanisms known to be associated with higher brain plasticity, which ultimately leads to improvements in cognitive performance. It is important to note that, on the one hand, the putative links between neurophysiological mechanisms and efficiency of cognitive processes are not yet fully understood and, on the other hand, the possible mechanisms explaining these links are most likely not exclusive. A number of reviews on this topic suggest a concomitant increase in cardiorespiratory fitness, brain plasticity, and cognitive performance, but inconsistent results have been reported concerning the last point. For instance, some authors have been unable to show cognitive improvements after an aerobic exercise program that was sufficient to increase VO₂max [29]. Others have shown that not all EFs are enhanced after a PA program and that the improvement in cognitive performance, when effective, was not related to the improvement in cardiorespiratory fitness [21, 25]. Finally, Liu-Ambrose et al. [30] recently reported the results of a randomized controlled study showing that a 12-month resistance training program (involving strength exercises twice a week) induced the same improvements in EF performance and functional plasticity as an aerobic program. These findings emphasize the need to further study the relationships between PA and cognitive performance in the aged population. In the present study, we were particularly interested in one understudied aerobic physical activity: swimming. To the best of our knowledge, only one study was designated to explicitly test the specific relationship between water aerobics and cognitive improvements in older adults [31]. In this study, Hawkins and collaborators examined the influence of a 10-week program of basic swimming skills on variations of two experimental tasks involving processing speed, attentional switching, and dual-task time-sharing. They found that subjects who trained in water aerobics showed significantly larger improvements on the executive control tasks than a nontrained control group. Interestingly, similar performance improvements were demonstrated for both groups in the nonexecutive tasks. Thus, it is important to verify whether this isolated finding can be generalized and to determine if swimming benefits are global or selective to some executive processes given the fractionated reality of EFs. To that end, we employed a clear theoretically driven framework to examine the potential mediator role of VO₂max in this relationship.

The objectives of the present study were twofold. First, we wanted to replicate our team’s previous results on age-related declines in EF and processing speed performance [2] by comparing the performances of younger and older adults on various tasks that assess information processing speed and the three postulated EFs, inhibition, working memory updating, and shifting. Second, assuming these age-related cognitive declines, we wanted to determine the selectivity of the relationship between swimming and the three EFs and information processing speed, in our sample of older adults. An important feature of this experiment was to combine the use of two or three cognitive tasks that are well-known for tapping each of the cognitive functions of interest with a multivariate approach. This procedure was shown to accurately assess the construct of EF and to reveal age-related executive declines in a previous pool of participants [2]. Swimming was chosen for three main reasons. (1) It is an understudied aerobic activity in the field of cognitive aging, and it solicits all the muscle groups and increases cardiorespiratory fitness. (2) It is one of the most accessible and practiced PAs in the elderly and is rated as the second most popular PA in France for the age range 65 and older [32]. (3) It is less traumatic on joints than walking or jogging. Several reviews have described the beneficial effects of water-based exercise on physical fitness parameters, such as aerobic capacity and strength in the elderly [33–35]. The elderly take a particular interest in water activity because it reduces the fear of falling, limits tolerance for weight-bearing activities, and enhances adherence and participation [36].
2. Methods

2.1. Participants. Thirty-two older adults aged 65 to 80 years (16 sedentary people and 16 swimmers) and 16 younger adults (18–30 years), all of whom were free of neurological and cardiovascular disease, participated in this study. The older participants were recruited from senior community centers, civic groups, and aquatic centers through the use of flyers and newspapers. All the older participants were screened by their personal physicians who rated them as being in good health and signed a medical certificate indicating no contraindications for cardiorespiratory fitness testing. Younger participants were recruited from the University of Poitiers.

Inclusion criteria for older adults were as follows: (a) being aged between 65 and 80 years; (b) having adequate mental status as indicated by a score strictly greater than 25 on the Mini Mental State Examination (MMSE) [37]; (c) for the sedentary group, leading a sedentary lifestyle with no participation in any structured PA as assessed by a validated PA questionnaire, the Dijon Score of Physical Activity (DSPA) [38]; (d) for the active group, leading a physically active lifestyle as assessed first by a history of regularly swimming at least twice a week for at least two years but no other regular PA. Secondly, the DSPA was also administered for the active group to ensure a significant difference in the amount of physical activity between the two groups. Inclusion criteria for younger adults were being aged from 18 and 30 years. The exclusion criteria were the following: (a) using medication that could affect cardiovascular health or cognitive functions; (b) cardiorespiratory or neurological disease; (c) major surgery within one year prior to testing. All participants gave written informed consent and the study was approved by the local ethics committee. The demographic and physical characteristics of all participant groups are displayed in Table 1. The active older adults (swimmers) had been practicing swimming for two to 43 years (M = 2.56 years; SD = 0.79), two to five times a week. The mean session duration was between 45 and 100 minutes (M = 64.38 min; SD = 15.37).

2.2. Evaluation of Cardiorespiratory Fitness. For the older participants, VO2max was estimated by the Rockport Fitness Walking test [39]. This submaximal field test has been shown to accurately estimate VO2max in populations similar to the one in the present study [39, 40]. Participants were required to walk one mile (1609 m) as quickly as possible, and heart rate was continuously recorded by a Polar RS 800 beat-to-beat recorder (Polar Electro, Oy, Kempele, Finland). VO2max was calculated using the equation developed by Kline and collaborators.

2.3. Evaluation of Information Processing Speed. Information processing speed was measured through two reaction time tasks: an auditory simple reaction time (SRT) task and a visual 2-Choice Reaction Time (CRT) task [2]. SRT and CRT were used as the main dependent variables and the error rate in the CRT task enabled checking for possible speed-accuracy tradeoffs.

2.4. Evaluation of Executive Functions. Each of the three EFs was assessed via 2 or 3 different experimental tasks. All tasks were the same as those used in a previous study from our laboratory that involved a different sample of younger and older adults [2]. We refer the reader to this paper for a full description of the procedure and tasks used.

2.4.1. Inhibition

The Stroop Task. In this computerized version of the Stroop task, the dependent variable was the difference in mean RTs (ms) between incongruent trials (e.g., the word RED written in blue) and neutral trials (e.g., XXXXX written in blue) for correct responses. The error rate in incongruent and neutral conditions was also controlled to check for any possible speed-accuracy tradeoffs.

The Stop-Signal Task. In this task, participants were required to respond as quickly as possible to a visual stimulus by pressing the corresponding key, unless an auditory tone rang out requiring to abort (or inhibit) the prepotent motor response. The dependent variable selected for the multivariate analyses of variance (MANOVAs) was the rate of successful inhibition calculated as the probability (P) between 0 and 1) of successful inhibition. The stop-signal reaction time (SSRT) has also been calculated according to Logan’s race model [41]. This variable was not included in the MANOVAs for two reasons: (1) SSRT correlated moderately with SRT and CRT (r = .41 and .50, resp.), while P(I) did not (see Table 2); (2) SSRT did not correlate with the interference score measured in the Stroop task and the adjacency score measured in the RNG task, two variables reflecting inhibition (r = .13 and r = -.06, resp.), while P(I) correlated significantly with the adjacency score (see Table 2).

The Random Number Generation (RNG) Task. In this task, participants were required to generate and say aloud series of random numbers from one to nine at the rate of one digit per second. The dependent variable that reflected inhibition for this task was the Adjacency score (A in %), ranging from 0% (no neighboring pairs, i.e., good performance) to 100% (only neighboring pairs, i.e., poor performance). The RNG task necessitates inhibiting counting in ascendant or descendant series, and the Adjacency score measures the tendency of the participants to count by one.

2.4.2. Updating

The Verbal Running Span Task. In this computerized task, participants were required to recall serially the last four letters of a list of six, eight, ten, or twelve consonants that were presented visually. The dependent variable was the number of letters correctly recalled in the right order (max. = 48).

The spatial Running Span Task. Like for the previous task, in this computerized task, participants were required to recall serially the last four spatial locations of a dot in a 4 × 4
A set of cards according to three different rules that changed periodically. The dependent variable that reflected shifting for this task was the number of perseverative errors.

For the processing speed construct and for each EF component, a standardized Cronbach alpha was computed to assess how well the selected tasks measured a latent construct. Alphas for each postulated cognitive function were low to good (standardized Cronbach alphas were .77, .60, .78, and .59 for Information processing speed, Inhibition, Updating, and Shifting, resp.). Table 2 presents the results of the bivariate correlations between all cognitive tasks within the whole sample.

Table 1: Characteristics of the three groups of participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Young adults</th>
<th>Active older adults</th>
<th>Sedentary older adults</th>
<th>Young versus active older adults</th>
<th>Active versus sedentary older adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>P = 1</td>
<td>P = 1</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>9/7</td>
<td>9/7</td>
<td>9/7</td>
<td>P = 1</td>
<td>P = 1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.56 (2.56)</td>
<td>69.13 (3.88)</td>
<td>69.25 (3.25)</td>
<td>P &lt; .05</td>
<td>P = .92</td>
</tr>
<tr>
<td>MMSE (max = 30)</td>
<td>29.31 (0.01)</td>
<td>28.75 (0.93)</td>
<td>28.69 (1.08)</td>
<td>P = .06</td>
<td>P = .86</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.09 (1.25)</td>
<td>13.75 (3.11)</td>
<td>13.56 (1.93)</td>
<td>P &lt; .05</td>
<td>P = .84</td>
</tr>
<tr>
<td>DPAS (max = 30)</td>
<td>—</td>
<td>24.25 (1.48)</td>
<td>15.17 (4.37)</td>
<td>—</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>VO₂ max (mL/min/kg)</td>
<td>—</td>
<td>29.35 (5.13)</td>
<td>25.27 (4.94)</td>
<td>—</td>
<td>P &lt; .05</td>
</tr>
</tbody>
</table>

Note. M: Male, F: Female, MMSE: Mini Mental State Examination, DPAS: Dijon Physical Activity Score.

2.4.3. Shifting

The Dimension-Switching Task. In this computerized task, participants watched on the computer screen the French words for LEFT or RIGHT enclosed in a left or right arrow, and displayed above or below the center of the white screen. Depending on instructions, they were required to respond to the word or to the direction of the arrow by pressing the correct corresponding key. The dependent variable selected for this task was the global switch cost for correct responses, calculated as the difference in RT (ms) between trials from the simple blocks and task-repeat trials from the mixed blocks. The error rate in simple and mixed blocks of trials was calculated to check for any possible speed-accuracy tradeoffs. The local switch cost was also calculated but was not included for further analyses because it did not correlate with the number of perseverative errors in the Wisconsin Card Sorting Task (r = .18) while the global switch cost did (r = .32, see Table 2).

Stimulus-Response Compatibility Switching Task. In this computerized task, participants watched an arrow pointing left or right, surrounded by a frame on the computer screen. Depending on the color of the frame, participants were to press the response key located either on the side pointed by the arrow (green or blue frame), or on the opposite side (red or orange frame). The dependent measure for this task was the local switch cost for correct responses, calculated as the difference in RT (ms) between task-repeat trials and task-switch trials during the mixed blocks. The error rate for repetition and alternation trials was also computed to check for any possible speed-accuracy tradeoffs. The global switch cost has not been computed in this task because the number of trials in the simple blocks was too small; the simple blocks have only been used to familiarize participants to the rules of mapping between stimuli and responses.

The Wisconsin Card Sorting Test (WCST). In this computerized version of the WCST, participants were required to sort a set of cards according to three different rules that changed periodically. The dependent variable that reflected shifting for this task was the number of perseverative errors.

For the processing speed construct and for each EF component, a standardized Cronbach alpha was computed to assess how well the selected tasks measured a latent construct. Alphas for each postulated cognitive function were low to good (standardized Cronbach alphas were .77, .60, .78, and .59 for Information processing speed, Inhibition, Updating, and Shifting, resp.). Table 2 presents the results of the bivariate correlations between all cognitive tasks within the whole sample.

2.5. Procedure. After careful screening for inclusion and exclusion criteria, older participants were first evaluated for cardiorespiratory fitness on one day. Second, each participant was tested individually in a quiet experimental room in two sessions on different days separated by a minimum of two days and a maximum of seven days. Each session lasted approximately 1.5–2 hours. The two sessions were counterbalanced across participants and, within each session, all tasks were counterbalanced across participants. Participants were given short breaks between each experimental task.

2.6. Statistical Analyses. The data on cognitive performance were analyzed in three ways. First, a series of one-way multivariate planned analyses of covariance (MANCOVAs) was conducted on each set of dependent variables reflecting a specific cognitive function (speed of information processing, behavioral inhibition, updating of working memory, and shifting), contrasting young adults and seniors with level of education (number of years) as a covariate. This first series of planned MANCOVAs was conducted in order to test the effect of age on each cognitive function. The level of education was entered as a covariate because younger adults showed a higher level of education than older adults (see Table 1). When the effect of age on a cognitive function was significant, we conducted a series of planned analyses of covariance (ANCOVAs) on each cognitive function task, contrasting young adults and seniors with level of education as a covariate. Second, a series of one-way multivariate planned analyses of variance (MANOVAs) was conducted on the same sets of dependent variables only in older adults, contrasting regular swimmers and sedentary people. This second series of planned MANOVAs was conducted in order
to test the effect of physical activity level on each cognitive function. When the result of the MANOVA was significant, we performed a series of planned analyses of variance (ANOVAs) on each of the individual tasks composing cognitive function. Finally, for the older adult sample, simple regression analyses were performed between VO2 max and EF scores when there was a significant correlation between these variables. The level of significance was set at \( P < .05 \) and Cohen's \( d \) was reported for pairwise comparisons as a measure of effect size. As proposed by Cohen [42], a "small" effect is when \( d = 0.2 \), a "medium" effect when \( d = 0.5 \), and a "large" effect when \( d = 0.8 \). For the MANOVAs and MANCOVAs, partial eta squared (Partial \( \eta^2 \)) was also reported as a measure of the percentage (when multiplied by 100) of variance explained by the treatment factors.

3. Results

3.1. Group Differences in Demographics and Global Cognition

As seen in Table 1, young adults attended more years of education than older participants (\( F(1, 46) = 12.97; P < .05 \)). In addition, as expected, older active participants were more physically active than their sedentary counterparts as revealed by a higher score on the DPAS (\( F(1, 30) = 60.75; P < .05 \)), and a higher level of VO2 max (\( F(1, 29) = 5.13; P < .05 \)), but the two groups did not differ in MMSE scores.

3.2. Effects of Chronological Age on Cognitive Functions

Results of the statistical analyses and behavioral performance as a function of age group for each cognitive function and each cognitive task are detailed in Table 3. As seen, there was a significant effect of age on each cognitive function, even after having controlled for the level of education. Subsequent ANCOVAs on each individual dependent measure revealed that the age-related effect was significant for each experimental task (see Table 3) except for three: the stop-signal task, the letter running-span, and the WCST, for which there was no significant difference between younger and older adults after having controlled for education level.

The effect of age was also examined on error rate for all the tasks that included choice reaction time measurements. A first ANOVA was conducted on error rate in the CRT task with age as between-subjects factor. There was no significant effect of age (\( F(1, 45) = 0.22; P > .63 \)), error rate was 2.81% and 2.44% for younger and older adults, respectively. A second ANOVA with age as between-subjects factor and type of trials (neutral versus incongruent) as within-subjects factor was then conducted on error rate in the Stroop task. The interaction between age and type of trials was close to significance (\( F(1, 45) = 3.40; P > .07 \)), the simple effect of age was not significant (\( F(1, 45) = 0.98; P > .32 \)) while the simple effect of type of trials reached significance (\( F(1, 45) = 12.10; P < .002 \)). Participants made significantly more errors in the incongruent condition (2.43%) than in the neutral condition (0.35%). A third ANOVA with age as between-subjects factor and type of block of trials (simple versus mixed) as within-subjects factor was conducted on error rate in the dimension-switching task. The interaction between age and type of block of trials was close to significance (\( F(1, 45) = 3.60; P > .06 \)), as well as the simple effect of age (\( F(1, 45) = 3.18; P > .08 \)), but the effect of type of block of trials reached significance (\( F(1, 45) = 26.25; P < .0001 \)). Participants made significantly more errors in the mixed block of trials (5.07%) than in the simple block of trials (1.61%). A fourth and last ANOVA with age as between-subjects factor and type of trials (alternation versus repetition) as within-subjects factor was conducted on error rate in the mixed blocks of trials of the stimulus-response compatibility switching task. The interaction between age and type of transition did not reach significance (\( F(1, 45) = 1.89; P > .17 \)), but the simple effects of age and type of transition did (\( F(1, 45) = 6.07; P < .02 \) and \( F(1, 45) = 37.10; P < .0001 \), resp.). All participants made more errors when they had to alternate (9.27%) rather than when they had to repeat the stimulus-response mapping (3.33%) and older adults (7.63%) made more errors than younger adults (3.63%). These results on error rate and those concerning RTs (see Table 3) showed that there was no speed-accuracy tradeoffs for the effect of age on cognitive functions assessed through RT tasks.

3.3. Effects of Swimming Practice on Cognitive Functions Performance in Older Adults

The results of the statistical

| Table 2: Matrix of correlations between the indices of cognitive performance, one index per cognitive task, for the whole sample. |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Dependent variable/Task | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
| (1) Auditory SRT | 1.00 |
| (2) Visual CRT | .63* | 1.00 |
| (3) \( P(I) \) | -.05 | -.02 | 1.00 |
| (4) Interference cost | .42* | .43* | .18 | 1.00 |
| (5) Adjacency score | .16 | .34* | .31* | .51* | 1.00 |
| (6) NO correct letters | -.18 | -.29* | .10 | -.26 | -.56* | 1.00 |
| (7) NO correct locations | -.30* | -.69* | -.03 | -.51* | -.63* | .64* | 1.00 |
| (8) NO perseverative errors | .23 | .30* | .04 | .40* | .58* | -.52* | -.55* | 1.00 |
| (9) Global switching cost | .08 | .54* | -.03 | .20 | .49* | -.51* | -.69* | .32* | 1.00 |
| (10) Local switching cost | .25 | .46* | .01 | .20 | .46* | -.40* | -.44* | .22 | .42* | 1.00 |

Note. SRT: Simple reaction time, CRT: Choice reaction time, \( P(I) \): Rate of successful inhibitions, *: \( P < .05 \), bold: Correlations within the same cognitive function.
Table 3: Results of the MANCOVAs, ANCOVAs, and effect-sizes contrasting young and older participants on cognitive performance, with level of education as covariate, and mean behavioral performance for each age group (SD).

<table>
<thead>
<tr>
<th>Cognitive functions</th>
<th>Cognitive tasks</th>
<th>Dependent variables</th>
<th>MANCOVA F</th>
<th>ddl</th>
<th>Wilk’s Λ</th>
<th>Partial η²</th>
<th>ANCOVA F(1,44)</th>
<th>Cohen’s d</th>
<th>Young adults M (SD)</th>
<th>Older adults M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of information processing</td>
<td>Auditory simple reaction time task</td>
<td>Reaction time (ms)</td>
<td>47.98</td>
<td>2, 43</td>
<td>.31</td>
<td>.69</td>
<td>23.06 ($P &lt; .0001$)</td>
<td>1.51</td>
<td>194 (26)</td>
<td>257 (52)</td>
</tr>
<tr>
<td>Behavioral inhibition</td>
<td>Visual choice reaction time task</td>
<td>Reaction time (ms)</td>
<td>94.89</td>
<td>3, 34</td>
<td>.77</td>
<td>.23</td>
<td>3.34</td>
<td>0.16</td>
<td>419 (15)</td>
<td>475 (53)</td>
</tr>
<tr>
<td>Behavioral inhibition</td>
<td>Stop-signal task</td>
<td>Rate of successful inhibition</td>
<td>1.13</td>
<td>3, 42</td>
<td>.29</td>
<td>0.16</td>
<td>5.96 ($P &lt; .001$)</td>
<td>1.10</td>
<td>189 (63)</td>
<td>291 (115)</td>
</tr>
<tr>
<td>Behavioral inhibition</td>
<td>Stroop task</td>
<td>Interference cost (ms)</td>
<td>12.46</td>
<td>1.10</td>
<td>0.23</td>
<td>1.10</td>
<td>189 (63)</td>
<td>291 (115)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral inhibition</td>
<td>RNG task</td>
<td>Adjacency score</td>
<td>5.96 ($P &lt; .02$)</td>
<td>0.93</td>
<td>33.50 (7.04)</td>
<td>42.27 (11.29)</td>
<td>0.93</td>
<td>33.50 (7.04)</td>
<td>42.27 (11.29)</td>
<td></td>
</tr>
<tr>
<td>Updating of working memory</td>
<td>Letter running-span task</td>
<td>NO correct responses</td>
<td>19.77 ($P &lt; .0001$)</td>
<td>2.69</td>
<td>0.11</td>
<td>0.80</td>
<td>39.19 (4.62)</td>
<td>34.28 (7.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Updating of working memory</td>
<td>Spatial running-span task</td>
<td>NO correct responses</td>
<td>36.81 ($P &lt; .0001$)</td>
<td>2.23</td>
<td>0.48</td>
<td>2.23</td>
<td>41.25 (4.84)</td>
<td>23.31 (10.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shifting</td>
<td>Wisconsin card sorting test</td>
<td>NO perseverative errors</td>
<td>3.69 ($P = 0.06$)</td>
<td>0.79</td>
<td>8.50 (2.68)</td>
<td>12.81 (7.22)</td>
<td>0.79</td>
<td>8.50 (2.68)</td>
<td>12.81 (7.22)</td>
<td></td>
</tr>
<tr>
<td>Shifting</td>
<td>Dimension switching task</td>
<td>Global switch cost (ms)</td>
<td>15.65 ($P &lt; .0003$)</td>
<td>1.74</td>
<td>192 (154)</td>
<td>606 (299)</td>
<td>1.74</td>
<td>192 (154)</td>
<td>606 (299)</td>
<td></td>
</tr>
<tr>
<td>Shifting</td>
<td>Stimulus-Response switching task</td>
<td>Local switch cost (ms)</td>
<td>9.86 ($P &lt; .0031$)</td>
<td>1.09</td>
<td>71 (57)</td>
<td>184 (135)</td>
<td>1.09</td>
<td>71 (57)</td>
<td>184 (135)</td>
<td></td>
</tr>
</tbody>
</table>

Note. RNG: Random Number Generation, in bold: Significant effect.
analyses and behavioral performance as a function of level of activity for each cognitive function and each experimental task are detailed in Table 4. The MANOVAs revealed a significant effect of swimming activity on each of the three EF components but no significant effect on information processing speed. Subsequent ANOVAs on each task tapping EFs showed that older participants who swim regularly performed significantly better in five out of eight tests. More precisely, swimmers outperformed sedentary participants on the two tasks tapping Updating, on two of three tasks tapping Shifting, and on the RNG task tapping Inhibition. When it was significant, the effect size of swimming was large (mean Cohen’s $d = 1.05$).

The effect of swimming was examined on error rate for all the tasks that included choice reaction time measurements. A first ANOVA was conducted on error rate in the CRT task with PA level as between-subjects factor. There was a significant effect of PA level on error rate ($F(1, 45) = 8.24; P < .007$); sedentary older adults made more errors in the CRT task (3.75%) than older swimmers (1.13%).

A second ANOVA with PA level as between-subjects factor and type of trials (neutral versus incongruent) as within-subjects factor was conducted on error rate in the Stroop task. There was a significant interaction between these two factors ($F(1, 45) = 8.07; P < .007$). A post hoc test showed that sedentary older adults made more errors in the incongruent condition than in the neutral condition (3.39% versus 0%, respectively; $P < .02$) while older adults who practiced swimming did not (1.24% versus 0.26% resp.; $P > .45$). A third ANOVA with PA level as between-subjects factor and type of block of trials (simple versus mixed) as within-subjects factor was conducted on error rate in the dimension-switching task. The interaction between PA level and the type of block of trials was significant ($F(1, 45) = 10.81; P = .002$). A post hoc test showed that older swimmers made more errors in the mixed than in the simple block of trials (8.68% versus 1.61%; $P < .0002$) while sedentary older adults did not (3.26% versus 1.67%; $P > .34$). The examination of RT and error data in the dimension-switching task suggests that the two groups of older adults did not use the same strategy in the more difficult condition: swimmers preferred to emphasize speed whereas sedentary people preferred to emphasize accuracy.

A fourth and last ANOVA with PA level as between-subjects factor and type of trials (alternation versus repetition) as within-subjects factor was conducted on error rate in the mixed blocks of trials of the stimulus-response compatibility switching task. The interaction between PA level and type of transition did not reach significance ($F(1, 45) = 0.61; P > .43$), but the simple effects of PA level and type of transition did ($F(1, 45) = 12.43; P < .001$ and $F(1, 45) = 33.25; P < .0001$, resp.). Older adults made more errors when they had to alternate (11.07%) rather than when they had to repeat the stimulus-response mapping (4.19%) and, overall, older swimmers (10.94%) made more errors than sedentary older adults (4.33%).

One more time, swimmers preferred to emphasize speed while sedentary participants preferred to emphasize accuracy in the more difficult condition.

### 3.4. Relationship between Cardiorespiratory Fitness and Executive Function

To examine the relationships between cardiorespiratory fitness and EF performance in older adults, we performed a series of bivariate correlations (Spearman coefficients of correlation) between each cognitive task performance and VO$_{2\text{max}}$ level. The performance of only two tasks significantly correlated with VO$_{2\text{max}}$ level: the updating of verbal information ($r = .56; P < .05$) and the global switch cost ($r = .46; P < .05$). Figure 1 depicts the scatter plots of executive performance on these tasks with VO$_{2\text{max}}$ level with their respective coefficients of determination ($R^2$).

### 4. Discussion

As has been extensively documented, age-related cerebral and cognitive declines are not uniform but quite differentiated (see [43, 44] for reviews). Similarly, most of the recent literature on aging, fitness, and cognition has shown that chronic exercise would result in selective improvements in executive functions rather than general benefits [13, 20, 21]. However, contemporary theoretical models of executive functions posit that the construct of EF is not uniform but encompasses fractionated executive subprocesses. Using this established theoretical and methodological framework, the aim of this study was to examine differences in cognitive performance as a function of chronological age and long-term regular practice of swimming by measuring younger and older adults’ information processing speed and performance on three well-known EFs, inhibition, updating, and shifting. Globally, the results revealed a clear pattern of age-related decline in all cognitive functions. On the other hand, older adults who practice regular swimming were shown to have a positive relation with improved performance on five of eight experimental tasks and all EF components. VO$_{2\text{max}}$ level was only positively related to executive performance for two tasks. These results provide a clear argument for the use of a multitask approach when studying the effects of chronic exercise on cognitive functions.

Before examining the effects of aging and swimming practice on cognitive performance, it is important to discuss the multitask approach used in this study. Because it is impossible to find a “pure” task to assess an isolated cognitive function, particularly an EF, multiple measures were used to rule out “task impurity” (see [2, 7–9]). As such, we wanted to assess the EF construct at the level of a general or latent variable, which reflects the postulated cognitive function more strongly than each individual experimental task alone. However, as revealed by the standardized Cronbach alphas and the matrix of correlations displayed in Table 2, it appears that the construct validity of our three EFs was quite low. Indeed, the correlations between tasks supposed to reflect a particular EF component were often low or even nonsignificant and sometimes smaller than the correlations between two tasks thought to assess different EF components. Such
Table 4: Results of the MANOVAs, ANOVAs, and effect-sizes contrasting active and sedentary older participants on cognitive performance and mean behavioral performance for each age group (SD).

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>Cognitive task</th>
<th>Dependent variable</th>
<th>MANOVA F</th>
<th>ddl</th>
<th>Wilk's λ</th>
<th>Partial $\eta^2$</th>
<th>ANOVA F(1,45)</th>
<th>Cohen's $d$</th>
<th>Sedentary older adults M (SD)</th>
<th>Active older adults M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of information processing</td>
<td>Auditory simple reaction time task</td>
<td>Reaction time (ms)</td>
<td>0.43 ($P = .73$)</td>
<td>2, 44</td>
<td>.98</td>
<td>.02</td>
<td>—</td>
<td>—</td>
<td>252 (40)</td>
<td>262 (64)</td>
</tr>
<tr>
<td></td>
<td>Visual choice reaction time task</td>
<td>Reaction time (ms)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>468 (49)</td>
<td>482 (57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral inhibition</td>
<td>Stop-signal task</td>
<td>Rate of successful inhibition</td>
<td>2.79 ($P = .05$)</td>
<td>3, 43</td>
<td>.84</td>
<td>.16</td>
<td>0.00 ($P = .96$)</td>
<td>0.02</td>
<td>0.44 (0.23)</td>
<td>0.44 (0.20)</td>
</tr>
<tr>
<td></td>
<td>Stroop task</td>
<td>Interference cost (ms)</td>
<td>10.04 ($P &lt; .011$)</td>
<td>7.04</td>
<td>.05</td>
<td>.16</td>
<td>0.10 ($P = .76$)</td>
<td>0.10</td>
<td>297 (132)</td>
<td>285 (99)</td>
</tr>
<tr>
<td></td>
<td>RNG task</td>
<td>Adjacency score</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>46.72 (11.09)</td>
<td>37.82 (9.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Updating of working memory</td>
<td>Letter running-span task</td>
<td>NO correct responses</td>
<td>9.61 ($P &lt; .0001$)</td>
<td>2, 44</td>
<td>.70</td>
<td>.30</td>
<td>19.50 ($P &lt; .0001$)</td>
<td>1.45</td>
<td>29.94 (6.08)</td>
<td>38.63 (5.88)</td>
</tr>
<tr>
<td></td>
<td>Spatial running-span task</td>
<td>NO correct responses</td>
<td>7.04 ($P &lt; .013$)</td>
<td>7.04</td>
<td>.04</td>
<td>.30</td>
<td>0.80</td>
<td>19.44 (8.39)</td>
<td>27.19 (10.80)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wisconsin card sorting test</td>
<td>NO perseverative errors</td>
<td>21.70 ($P &lt; .0001$)</td>
<td>3, 43</td>
<td>.58</td>
<td>.42</td>
<td>17.00 (8.05)</td>
<td>1.41</td>
<td>17.63 (2.36)</td>
<td>8.63 (2.36)</td>
</tr>
<tr>
<td></td>
<td>Dimension switching task</td>
<td>Global switch cost (ms)</td>
<td>2.65 ($P = .11$)</td>
<td>2.65</td>
<td>.08</td>
<td>.36</td>
<td>704 (267)</td>
<td>0.68</td>
<td>508 (306)</td>
<td>704 (267)</td>
</tr>
<tr>
<td></td>
<td>Stimulus-Response switching task</td>
<td>Local switch cost (ms)</td>
<td>6.24 ($P &lt; .017$)</td>
<td>6.24</td>
<td>.07</td>
<td>.36</td>
<td>232 (129)</td>
<td>0.76</td>
<td>135 (126)</td>
<td>135 (126)</td>
</tr>
</tbody>
</table>

Note. RNG: Random Number Generation, in Bold: Significant effect.
results have already been reported by previous studies from our own team [2] and others [11, 45] and raise a question of the low specificity of the tasks used to assess EFs, which will be discussed in the limitations section.

Consistent with a large body of research on cognitive and cerebral aging, we found that chronological age has a detrimental effect on information processing speed and on the three evaluated EFs. The age-related decline in the RT tasks is in agreement with numerous studies on the effect of aging on processing speed [2, 12]. The performance deficits observed in our older adults in the three EF domains also agree with the literature examining this question with a similar approach [2, 10, 11]. Our results also suggest that the deleterious effects of aging are more pronounced for processing speed (69% of the explained variance, see partial \( \eta^2 \) in Table 3) than for updating (48% of the explained variance), shifting (37% of the explained variance), and inhibition (23% of the explained variance). However, it is important to note that taking into account the educational level (as measured by the number of years of academic education) decreased the age-related effects on all the cognitive tasks and even eliminated the effects of chronological age on the letter running-span task and the WCST. This finding strengthens the importance of taking into account education as an important moderator of cognitive aging which can be interpreted in the more general context of cognitive reserve [46, 47]. As we will discuss below, it may be that PA (in the present study, swimming) could also be viewed as a proxy of cognitive reserve beyond educational level.

In the older population, the differences in cognitive performance between swimmers and sedentary people were not homogeneous across all the studied cognitive processes. First, there was no significant difference between active and sedentary participants in the measures of information processing speed, as assessed by the SRT and the CRT tasks (see Table 4). This result contrasts with some previous results [48, 49] but agrees with others [20, 21, 24], particularly with those of Hawkins and coworkers [31] in the same context of swimming practice. These contradicting findings may be due to specific differences between particular PAs practiced by different samples of participants. The impact on processing speed may be different between racket sports or hand-ball, such as in Spirduso’s study [49], and swimming such as in our study. Another, more likely possibility is linked to the assertion that chronic exercise exerts selective effects on cognitive processes involving executive control and not on less-controlled processes, such as the stimulus-driven information processing involved in basic reaction time tasks (see [13, 20, 24]). Our results favor this second possibility and strengthen this selective benefit of PA on EF processes.

Second, our results indicate prima facie that the impact of swimming practice was quite homogeneous across all three EF components, assuming that our groups only differed at the level of swimming practice. All three MANOVAs contrasting the performance between older swimmers and sedentary participants were significant for these cognitive functions. However, the percentage of variance explained by swimming practice was more important for Shifting (42%) than for Updating (30%) and Inhibition (16%), as revealed by partial eta squared (see partial \( \eta^2 \) in Table 4). Our results of a strong relationship between swimming practice and Shifting confirm the previous conclusions of Hawkins et al. [31] on the positive effect of water aerobics on attentional flexibility. However, as pointed out in the Results section, the examination of speed and accuracy measures in the two switching tasks underscores that the two groups of participants may not have used the same strategies to perform these tasks. The swimmers made more
errors and emphasized speed to the detriment of accuracy. Consequently, the speed-accuracy tradeoffs observed in the two switching tasks weaken the strength of the positive relationship between swimming practice and Shifting.

Moreover, five out of eight tasks were strongly sensitive to differences between swimmers and sedentary participants, but the performance of two tasks out of three (Stroop task and signal-stop task) assessing inhibition and one task out of three (dimension-switching task) assessing shifting did not significantly differ between regular swimmers and sedentary participants. As previously stated, we think that this result underscores the importance of using a multitask approach when studying the effects of chronic exercise on cognitive functions and may help to resolve some discrepant results in this domain. For example, the absence of significant effect of exercise training reported by other researchers on some cognitive tasks [21, 29, 50] may not reflect an absence of real effects but instead a lack of sensitivity of the experimental tasks. For instance, our results conflict with those reported by Smiley-Oyen et al. [21], because they found an effect of aerobic exercise on the Stroop task and no effect on the WCST. Several reasons can be hypothesized to explain the discrepancies, such as differences in study design, experimental tasks, modes of response, and selected dependent measures, but it is always difficult to definitively conclude which is the correct explanation. One of the strengths of the present study is to combine the use of several different experimental tasks to examine the influence of PA within the same sample not only at the level of individual tasks but also at the more general level of the explored cognitive functions. This procedure allowed us to show that regular swimming was clearly related to better executive performance on the three examined EFs, despite the absence of significant effect on three of the eight tasks. This may indicate that some tasks could be more sensitive to the effects of PA than other tasks. Additional work should verify the consistency of our results, as our findings are far from conclusive. A recent study from our group [51] used different measures of PA and explored the same executive functions with different tasks or variations of the same tasks as used in the present study and showed that PA exerted a selective effect on inhibition but not on updating or shifting and only for the oldest adults of the sample (71 years and older). These different results highlight the ability of the effects of exercise on cognitive performance according to tasks and characteristics of the participants. Clearly, more work is needed to draw a definitive conclusion on the selectivity of the effects of chronic exercise effects on EFs.

The role of cardiorespiratory fitness in the relationship between PA and cognitive performance in older adults remains under debate (see [4, 21, 25]). Accordingly, we were interested in examining the relationships between VO₂max level and cognitive performance. As shown in Figure 1, only performance on the verbal running span task and the dimension-switching task was significantly correlated with VO₂max level. Of particular interest, one must remember that there was no significant effect of PA on the global switch cost of the dimension-switching task (P = .11, see Table 4). Thus, there is only one task (the verbal running span task) showing PA-related benefits that could be mediated by cardiorespiratory fitness level and one task (the dimension-switching task) showing no relationship with swimming practice but a significant relationship with VO₂max level. These results underscore the differences between a behavioral measure assessed through questionnaires (PA) and an estimated physiological measure assessed through field test (VO₂max), and their different influences on different cognitive functions [21, 25, 51]. Distinguishing between PA and cardiorespiratory fitness, which were weakly related (r = .35; P = .054) in the present study, seems of particular importance because they may exert their influence on cognitive functioning by different mechanisms. A challenge for future studies will be to understand and characterize the mechanisms underlying these selective effects. One may hypothesize that PA could be viewed qualitatively as a proxy of cognitive reserve, as defined by Stern and collaborators [46, 47], allowing physically active older adults to make flexible and efficient use of available brain reserve and to demonstrate better cognitive performance. In other respects, better cardiorespiratory fitness could induce anatomical and neurophysiological changes in the brain [6, 14, 26–28] that could reflect and enhance brain reserve [46, 47].

There are potential limitations in the present study that should be addressed. First, the low specificity of the tasks used to assess the construct of EF in this study limits the generalizability of our conclusions and strengthens the importance of looking for and using well-designed tasks to reflect the postulated cognitive functions. Second, our cross-sectional design precludes inferences about causality in the relationship between chronic engagement in swimming and executive performance. Well-designed randomized-controlled trials are now needed, using the same multitask approach, before a definitive conclusion can be made. Third, the level of education of the participants has been taken into account as a covariate in the statistical analyses of the present study. However, other important moderators of aging related to lifestyle, such as income, socioeconomic status, food habits, previous careers, and lifelong leisure activities, have not been measured in our experiment. These different variables can explain part of the variance in cognitive aging and may lead to an overestimation of the relationship between present level of physical activity and cognitive performance in cross-sectional designs, as could have been the case in the present study.

To summarize the principal findings, this study demonstrated the validity of using a multitask approach in examining the potential benefits of regular swimming on the aging of cognitive function. Such a theoretical and methodological approach allowed us to show that chronic swimming practice is related to better executive functions in older adults and that these benefits are seen on the three EFs studied but that some tasks are less sensitive to detecting these benefits. Finally, the demonstrated benefits of PA were not necessarily linked to better cardiorespiratory fitness, showing the potential relative independence of these behavioral or physiological moderators on executive performance.
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References


Research Article

The Effect of Three Months of Aerobic Training on Stroop Performance in Older Adults

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Growing evidence supports the use of physical training interventions to improve both physical and cognitive performances in healthy older adults. Few studies have examined the impact of aerobic exercise on Stroop task performance, a measure of executive functions. In the current 3-month aerobic training study, 50 older adults (mean age = 67.96 ± 6.25 years) were randomly assigned to either a three-month physical training group or to a control group (waiting list). Training sessions were 3 times per week for 60 minutes. All participants completed pre- and post-test measures of cognitive performance using the modified Stroop task and physical performance (Rockport one-mile test). Compared to controls, the training group showed significant improvements in physical capacity (P < 0.001) and enhanced Stroop performance, but only in the inhibition/switching condition (P < 0.03).

Furthermore, the increase in aerobic capacity induced by the training regimen correlated negatively with reaction time in the inhibition/switching condition of the Stroop task at posttest (r = −0.538; P = 0.007). Importantly, the reported gains in cognitive performance were observed after only three months of physical training. Taken together, the results suggest that even short-term physical interventions can enhance older adults’ executive functions.

1. Introduction

A variety of executive function processes sustained by the prefrontal cortex decline over time [1] (e.g., response preparation [2] and task switching [3]). Recent accounts of executive functions suggest that they rely on distinct basic mechanisms [4], namely, updating (of new information), inhibition (suppressing prepotent responses) and shifting (from one mental set to another), that could be differentially altered as we age. The variability in the trajectories of cognitive decline [5] suggests that compensatory mechanisms [6] and individual factors (i.e., involvement in physical activity and cognitive reserve) [7] could minimize these deficits.

Physical activity, defined as any activity that involves bodily movements, is one individual factor that can reduce the impact of aging on executive functions [8, 9]. In goal-directed research, physical activity that was planned, structured, and repetitive improves physical fitness, defined as the ability to function efficiently and effectively in work and leisure activities and to meet unforeseen emergency situations [10]. Theoretically, the “selective improvement” hypothesis [11] argues that aerobic exercise known to increase cardiorespiratory fitness as indexed by direct measures or estimations of $V_{\text{O2 max}}$ (i.e., capacity of the body to transport and use oxygen during incremental exercise) should present the largest benefit in tasks requiring executive control processes [12, 13] (but also see [14] for the effect of resistance training).

A recent review [15] found evidence that long-term physical activity interventions have consistent effects on tasks requiring inhibition or requiring dual-task coordination, compared to tasks requiring shifting which suggests that basic executive function mechanisms may be differentially affected by physical activity. However, the consistency of the effect on dual-task coordination remains precarious as it is based on only two results [16, 17]. In the current study, we explore the effect of aerobic exercise on a complex task requiring both inhibition and shifting (dual executive...
function condition), compared to a task requiring only inhibition.

One task commonly used to explore age differences in inhibitory control processes is the Interference condition of the Stroop color-word task [18]. In this condition, the Stroop effect occurs when naming the color of the ink in which a word is written, and this happens faster and more accurately when the color denoted by the name is congruent (e.g., blue written in blue), rather than incongruent (e.g., blue written in red). When compared to younger adults, older adults demonstrate longer reaction times (RTs) and higher error rates in the incongruent condition (i.e., interference condition) [19–22].

The present study targeted sedentary older adults (i.e., no or irregular physical activity) and examined if the benefits of aerobic exercise extend to different executive processes measured by using a modified version of the Stroop task [23]. This modified version includes a switching condition in addition to the classic interference or inhibition condition. The executive component of shifting, or the ability to switch between different task sets, has demonstrated the most robust age-related deficits [24] and has been identified as an important predictor of the maintenance of independent living in elderly [25]. In accordance with Barenberg et al. [15], the aerobic exercise training benefit on executive functions should be observed in the inhibition condition. In comparison to the inhibition condition, we expect the dual executive function condition to demonstrate smaller training benefits, since the existing findings of long-term physical activity benefits on tasks requiring shifting are less consistent [15].

2. Methods

2.1. Participants. Through advertisement in community centers in the Montreal area, 77 older adults were recruited. All participants completed a phone screening evaluating their physical health prior to admission in the study. The level of risk when engaging in intense physical activity and the level of physical activity over the 12 past months were assessed by the completion of the modified questionnaire of aptitude to physical activity (QAA-P) and the modifiable activity questionnaire (MAQ) [26]. Only sedentary adults, whose frequency of physical activity was less than twice per week, were enrolled.

Exclusion criteria included a history of neurological disease or major surgery in the year preceding the study, auditory or visual impairments that had not been corrected, cardiovascular disease or vascular peripheral attacks, and/or moderate to severe hypertension. In order to exclude participants with dementia or depression, a score lower than 26/30 on the Mini-Mental State Examination (MMSE) [27] and higher than 11 on the Geriatric Depression Scale (GDS) [28] resulted in exclusion. Ten participants did not meet inclusion criteria.

Assignment of the remaining 67 participants was based on the order of recruitment and on participants’ willingness to engage in a 3-month fitness training program. Therefore, 32 participants were assigned to the experimental group, and the remaining 35 were assigned to the control group who did not receive any training. After completing the screening, seven participants in the training group and ten in the control group decided not to pursue the study for personal reasons. In the training group, there were no differences in baseline characteristics between the individuals who decided not to pursue and those who remained in the study. In the control group, those who discontinued were older (P < 0.05) and had lower scores (P < 0.05) on the similarities subtest of the WAIS-III.

The remaining participants in both the aerobic exercise group (F/M = 21/4; age (years) = 67.80 ± 6.60; education (years) = 14.36 ± 4.17) and the control group (F/M = 21/4; age (years) = 67.72 ± 6.01; education (years) = 12.92 ± 2.61) completed the study. Within these 50 participants, one participant in each group was excluded from statistical analyses due to missing Stroop test data. On a five-point health-rating scale (5 = excellent), the experimental (M = 4.21, SD = 0.74) and control groups (M = 4.17, SD = 0.72) average ratings were equivalent. Table 1 presents baseline characteristics of both groups.

2.2. Procedure. During the pre-test session, the consent form was signed, and all screening tests and questionnaires were completed, along with the modified Stroop task (see description below). In the second session, a test of cardiorespiratory fitness (Rockport one-mile test, [29]) was completed. Then the training group participated in a 12-week aerobic fitness program (see below). In a post-test session, both groups were reevaluated with the same neuropsychological battery (including the Stroop task) and the Rockport one-mile fitness test. The study was completed within a 14-week period (1 week of pre-testing, 12 weeks of training, and 1 week of post-testing).

2.3. Aerobic Fitness Program. The 3-month (3 × 1 hour/week) physical exercise program was composed of stretching and cardiorespiratory exercises (fast walking and aerobic dancing). Adequate warm-up and cool-down periods and progressive and gradual increments in exercise duration and

<table>
<thead>
<tr>
<th>Table 1: Participant’s baseline characteristics.</th>
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<tbody>
<tr>
<td>Control</td>
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<tr>
<td>General characteristics</td>
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<tr>
<td>Age</td>
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<td>Education</td>
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<td>General mental ability</td>
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<td>MMSE</td>
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<td>Verbal intelligence</td>
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<td>Similarities</td>
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<td>Mood assessment</td>
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<td>GDS</td>
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<td>Fitness assessment</td>
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<td>MAQ</td>
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energy expenditure were implemented according to recommendations [30]. Duration of cardiorespiratory exercise was also gradually increased during the training program, beginning at 15 min per session and increasing until participants were exercising for 40 min per session. The training sessions were continuously supervised by two professional kinesiologists. Training session attendance was high, with participants attending 86.58% of sessions.

2.4. Pre- and Post-Test Measures: Cardiorespiratory Fitness Assessment. The Rockport one-mile test [29] was employed to evaluate cardiorespiratory fitness. This walking test provides an accurate estimation of the maximum level of oxygen consumption ($V_{O_2\text{max}}$; [29]). A strong correlation coefficient ($r = 0.88$) has been reported between the Rockport estimated $V_{O_2\text{max}}$ and a direct measure of $V_{O_2\text{max}}$ during an incremented test on a treadmill [29]. Participants wearing Polar S120 heart rate monitor (Polar Electro, Lake Success, NY, USA) were instructed to walk one mile without stopping, as fast as possible. The time required to complete the distance was manually recorded on a stopwatch. Heart rate frequency was recorded 1 min after the end of the walking test. $V_{O_2\text{max}}$ was estimated using the equation provided by [29] that takes into account participants’ weight, age, sex, cardiac frequency post-exercise, and time to walk the one-mile distance.

2.5. Pre- and Post-Test Measures: Stroop Tasks. The present study utilized a Stroop test [23] that has four different conditions. Each condition included 100 stimuli (10 items per line) printed on a 21.5 × 28 cm sheet of paper. In the first (reading) condition, the participant had to read the words printed in black (i.e., red, green, blue, and yellow). In the second condition (naming), the participant needed to name the color of the rectangles. In the third condition (interference), the participant had to name the color of the ink in which the words are written. The meaning of each word had to be ignored, since it was incongruent with the color to name (e.g., the word “green” written in red). This condition is the inhibition only condition. The last condition (Inhibition/Switching) was similar to the third condition, except that 20 color words out of the 100 items were surrounded by a small box to indicate to the participant to read the word instead of naming its color. Therefore, the participant must alternate (or switch) in the inhibition/switching condition between naming the ink color of the words and reading the words. This is considered the most complex condition as it requires two executive processes (inhibition and switching). For all conditions, participants were to respond as quickly as possible, while making the least amount of errors. Reaction times (RTs) and the number of errors (corrected and uncorrected) were the main variables of interest.

3. Results

3.1. Participant’s Baseline Characteristics. An ANOVA revealed no significant difference between groups on their level of formal education, $F(1, 46) = 2.03, P < 0.16$, MMSE, $F(1, 46) = 3.26, P < 0.08$, general verbal ability (score on the similarities subtest of the WAIS-III), $F(1, 46) < 1$, GDS, $F(1, 46) < 1$, and MAQ score, $F(1, 46) = 1.01, P < 0.32$. Training and control groups were also comparable for age, $F(1, 46) < 1$.

3.2. Cardiorespiratory Fitness Assessment. A significant group × time interaction was found, $F(1, 44) = 24.99, P < 0.001$, which confirmed that the participants in the training group showed significant improvement in the $V_{O_2\text{max}}$ estimate (see Figure 1(a)) after 3 months of physical fitness training, $F(1, 23) = 39.00, P < 0.001$, while the $V_{O_2\text{max}}$ estimate of control participants remained unchanged, $F(1, 23) < 1$. The analysis of walking time (see Figure 1(b)) also confirmed the benefits of the aerobic fitness intervention, as evidenced
by a significant group × time interaction, $F(1, 44) = 33.69, P < 0.001$. Participants in the training group walked the mile faster after the 12-week training program, $F(1, 23) = 44.44, P < 0.001$, whereas the walk time of participants in the control group did not change significantly, $F(1, 23) < 1$.

3.3. Stroop Task. At baseline, group performance on Stroop tasks (see Table 2) was equivalent as no significant differences were observed on the reading, $F(1, 46) < 1$, naming, $F(1, 46) = 2.54, P < 0.19$, interference, $F(1, 46) = 2.37, P < 0.13$, and inhibition/switching condition, $F(1, 23) < 1$. For each Stroop condition, a score measuring the amount of change due to the intervention was computed as follows: pre-test minus post-test score (see Figure 2). An MANOVA revealed a significant effect of group for the inhibition/switching condition, $F(1, 46) = 5.03, P < 0.03$. No difference was found for the reading, $F(1, 46) < 1$, naming, $F(1, 46) < 1$, and interference condition, $F(1, 46) < 1$. Follow-up univariate analyses on the change score in the inhibition/switching condition confirm the effect of the intervention on the training group, $F(1, 23) = 5.05, P < 0.03$, and no difference was found for the control group, $F(1, 23) < 1$. Furthermore, the increase in aerobic capacity correlates negatively with reaction time at post-test only in the inhibition/switching condition of the Stroop task ($r = −0.54; P = .007$) for the training group.

Table 2 presents overall error rates for each condition of the Stroop test. Analyses on error rates using a Wilcoxon signed ranks test showed that for the control and the training group, the amount of corrected errors for the interference and inhibition/switching condition remains equivalent at month 3. The amount of uncorrected errors improved in the control group only for the interference condition ($Z = −2.10, P = 0.04$), and the training group improved only for the inhibition/switching condition ($Z = −2.86, P = 0.004$).

4. Discussion

The results of the present study suggest that, in the elderly, the benefits of an aerobic training program occur primarily on executive functions and that these benefits can be seen after only three months of physical training. As a first step, we confirm based on the Rockport walk test that our trained group demonstrates improved cardiorespiratory fitness when compared to the control group after 12 weeks of physical training. In addition, the training group showed a performance improvement on the Stroop task requiring multiple executive processes, the inhibition/switching condition, as inhibition alone was not improved, we explain this in terms of improvement in the switching domain. One explanation could be the type of exercise done during the training. As previously mentioned, aerobic dance exercise was part of the training our participants received. Research [31] has already supported improved cardiorespiratory endurance after 12 weeks of low-impact aerobic dance in a group of elderly women. In addition, similar to our findings, Coubard et al. [32] evaluated executive functions after contemporary dance training and demonstrated an executive function improvement after 5.7 months of contemporary dance that was seen only in a switching condition (rule shift cards sorting test) but not in an inhibition condition (Stroop task). Together with our results, this suggests that some types of exercise might selectively improve complex tasks involving switching and/or multiple executive processes.

The absence of a specific training effect on the Interference condition is at odds with some studies, including the review of Barenberg et al. [15]. For example, in a 4-month (3 × 1 hour/week) trial, Dustman et al. [33] demonstrated that the Stroop interference condition performance only improved for those aerobically trained. Interestingly, Blumenthal et al. [34] employing an aerobic training of the same duration and intensity did not replicate this finding. The choice of control group activities does not explain these divergent findings as both studies included a group who did not exercise. A possible confounding factor is that both studies computed the Stroop effect differently. In Dustman’s study, RTs in the reading condition were subtracted from the “interference” condition, as a way to account for improved motor ability. It has been proposed [22] that these proportional interference scores minimize the effects of general slowing, which is often highlighted as a potential explanation of the magnitude of the Stroop effect in the elderly [35–37]. Therefore, the absence of an aerobic benefit in inhibition in Blumenthal’s study and our study could have been hindered by other factors that are not task specific.

Blumenthal et al. [34] acknowledged two factors that could account for the difference in the findings between their study and that of Dustman et al. [33]: (1) different sample characteristics (age and male/female ratio) and (2) differences in aerobic fitness improvement levels. In fact, Blumenthal et al. [34] reported that their participants experienced less than 50% (11.6% versus 27%) of the improvement in $V_{O2\text{max}}$ reported in Dustman study. In the current study, there were no differences in our two groups based on age or male/female ratio, and we demonstrate a significant improvement in $V_{O2\text{max}}$ in our training group, as such our findings are not confounded by these factors.
Finally, it is important to note that our results show that the improvement in cardiovascular fitness and in executive performance in our training group is correlated. The increase in cardiorespiratory fitness correlates negatively with reaction time in the inhibition/switching condition of the Stroop at post-test, suggesting that there is indeed a relationship between improved cardiorespiratory fitness and improvements in a Stroop condition requiring two executive processes. We did not find a significant correlation between cardiorespiratory fitness and the inhibition-only performance which is in line with a recent finding that suggests that an improvement in cardiorespiratory fitness is not prerequisite to an enhanced Stroop performance [38]. Smiley-Oyen et al. [38] had equivalent VO₂ peak improvements in both their aerobic (18%) and strength/flexibility exercise training groups (13%) after completing 10 months (3 × 1 hours/week) of training, and yet Stroop performance as measured by RTs and accuracy improved only in the aerobic group. This outcome highlights the possibility that the impact of aerobic exercise on the Stroop performance might not be directly mediated by changes in cardiorespiratory fitness per se. In light of this possibility, other mechanisms have been proposed such as enhancement of brain vascularization, an increased plasticity though neurogenesis, neurotrophic factors (e.g., brain-derived neurotrophic factor (BDNF)) [39], or other factors that improve neuronal viability [40, 41].

Two limitations affect the generalizability of our results. First, the method of assignment was done by self-selection, potentially placing more motivated individuals in our training group; a future study should involve a more systematic and randomized method of assignment. Second, our waiting-list control group was only assessed at pre and post time points, and as such, we cannot control for any effect of socialization that may have occurred in the training group since they came repeatedly over the 12-week period. A better approach would have been to propose a control intervention with the same training regime that includes physical activity but that does not increase cardiorespiratory fitness.

Future research is needed to clarify why in the present study participants in the training group did not improve on the Inhibition condition and why other published studies have reported improvement (Liu-Ambrose et al. [14], for instance). One promising avenue would be the use of imaging techniques as they have shown an age-related brain activation difference when performing a Stroop task [42]. Of particular interest, a recent study [43] has found distinct patterns of prefrontal activation between the inhibition condition and the inhibition/switching condition using functional near infrared spectroscopy (fNIRS). Therefore, brain imaging studies could contribute to the comprehension of the condition-related effect of aerobic training in aging that is observed with the Stroop paradigm, particularly in the inhibition/switching condition, known to be sensitive to cognitive decline in the elderly [44–47].

### Conflict of Interests

The authors have no conflict of interests to disclose.

### Acknowledgment

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### References


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**Table 2: Participant’s baseline and follow-up results (Mean (SD)) for the Stroop test.**

<table>
<thead>
<tr>
<th></th>
<th>Control Before</th>
<th>Control After</th>
<th>Training Before</th>
<th>Training After</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reaction time (s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>44.26 (6.87)</td>
<td>45.40 (6.84)</td>
<td>43.82 (6.29)</td>
<td>44.90 (6.45)</td>
</tr>
<tr>
<td>Colors naming</td>
<td>71.39 (16.69)</td>
<td>69.97 (15.83)</td>
<td>64.81 (11.40)</td>
<td>63.97 (9.06)</td>
</tr>
<tr>
<td>Interference</td>
<td>126.03 (30.39)</td>
<td>123.48 (35.81)</td>
<td>113.57 (25.49)</td>
<td>110.16 (27.41)</td>
</tr>
<tr>
<td>Inhibition/switching</td>
<td>132.55 (21.21)</td>
<td>135.04 (29.48)</td>
<td>135.56 (38.94)</td>
<td>126.24 (27.29)</td>
</tr>
<tr>
<td><strong>Error</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>0.17 (0.38)</td>
<td>0.08 (0.28)</td>
<td>0.08 (0.28)</td>
<td>0.13 (0.34)</td>
</tr>
<tr>
<td>Colors naming</td>
<td>0.92 (1.21)</td>
<td>0.92 (0.88)</td>
<td>1.38 (1.28)</td>
<td>0.75 (0.68)</td>
</tr>
<tr>
<td>Interference</td>
<td>2.17 (2.73)</td>
<td>1.71 (1.49)</td>
<td>2.08 (2.21)</td>
<td>1.75 (1.39)</td>
</tr>
<tr>
<td>Inhibition/switching</td>
<td>2.50 (2.36)</td>
<td>2.17 (1.83)</td>
<td>4.79 (4.03)</td>
<td>3.00 (3.11)</td>
</tr>
</tbody>
</table>


Review Article

Potential Moderators of Physical Activity on Brain Health

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Age-related cognitive decline is linked to numerous molecular, structural, and functional changes in the brain. However, physical activity is a promising method of reducing unfavorable age-related changes. Physical activity exerts its effects on the brain through many molecular pathways, some of which are regulated by genetic variants in humans. In this paper, we highlight genes including apolipoprotein E (APOE), brain derived neurotrophic factor (BDNF), and catechol-O-methyltransferase (COMT) along with dietary omega-3 fatty acid, docosahexaenoic acid (DHA), as potential moderators of the effect of physical activity on brain health. There are a growing number of studies indicating that physical activity might mitigate the genetic risks for disease and brain dysfunction and that the combination of greater amounts of DHA intake with physical activity might promote better brain function than either treatment alone. Understanding whether genes or other lifestyles moderate the effects of physical activity on neurocognitive health is necessary for delineating the pathways by which brain health can be enhanced and for grasping the individual variation in the effectiveness of physical activity interventions on the brain and cognition. There is a need for future research to continue to assess the factors that moderate the effects of physical activity on neurocognitive function.

1. Introduction

One in every eight US seniors over the age of 65 has been diagnosed with Alzheimer’s disease (AD), amounting to more than 5.4 million people. With the aging baby boomers, this number is predicted to double by 2050 [1]. Unfortunately, pharmaceuticals have had limited success in preventing or treating age-related cognitive dysfunction, such as AD or even normal cognitive aging. Fortunately, physical activity appears to be a promising nonpharmaceutical method to attenuate cognitive dysfunction in late life [2, 3]. Yet, there remain many unanswered questions about the effectiveness of physical activity to improve brain health, prevent dementia, and reduce age-related cognitive decline.

“Physical activity” is an umbrella term defined by the Center for Disease Control (CDC) as any activity that increases heart rate and energy expenditure from one’s basal level [4]. Examples of physical activities are walking, gardening, or even household chores such as cleaning. In turn, “exercise” is defined as a subcategory of physical activity, being any structured or repetitive activity that aims to improve fitness, endurance, or health such as strength training, purposefully running, or swimming. Both exercise and physical activity are often measured through self-report questionnaires; however, they can be assessed by identifying “fitness,” which is comprised of one’s cardiorespiratory and skeletal muscle endurance, flexibility, and balance [4]. Fitness is objectively measured by an assessment of the maximum amount of oxygen consumption by carbon dioxide expulsion or VO2 max, as this is an objective measure of cardiorespiratory strength [5]. An individual who has a very low VO2 max or reports very low levels of physical activity or exercise is considered “inactive” or sometimes referred to as “sedentary,” but precise definitions of “sedentary” has become a matter of debate [6]. As a result, cross-sectional studies compare inactive or sedentary subjects to those with greater amounts of physical activity or higher fitness levels. In contrast, intervention studies usually recruit inactive individuals with the goal of improving fitness levels by increasing physical activity through engagement in exercise.
Numerous studies, reviews, and meta-analyses have documented that greater amounts of physical activity and higher fitness levels and are associated with greater gray matter volume [7–10], greater white matter integrity [8, 11–13], elevated functional dynamics including heightened connectivity of fronto-parieto-hippocampal circuits [14–17], and enhanced cognitive performance [12, 18]. Yet, despite the favorable effects of physical activity and cardiorespiratory fitness on brain health and cognitive function, there remains significant individual variability in the extent to which any individual benefits from physical activity. For example, randomized controlled trials of physical activity indicate that a subset of individuals often show little cognitive or neural benefit even after spending 12 months in an intervention [19]. On the other hand, others in the intervention show little improvement in cardiorespiratory fitness, while still demonstrating significant improvements in cognitive and brain function [20]. These results suggest that there might be factors moderating the effects of physical activity. Moderating factors could act by either attenuating or augmenting the effects of physical activity on neurocognitive function. For example, it is possible that if greater physical activity is accompanied by an increase in cognitive stimulation that the favorable effects of physical activity on cognitive and brain function could be magnified. On the other hand, if increased physical activity is accompanied by a poor diet, then the benefits of activity might be significantly attenuated. For this reason, it is important for studies to reflect on the factors that are contributing to variation in the effectiveness of physical activity to influence neurocognitive health. Indeed, instead of simply considering individual differences as noise in the analysis they could be considered as (1) an important source for understanding the effectiveness of interventions, (2) a method for identifying potential mechanisms by which physical activity exerts its effects on the brain, and (3) a way to tailor physical-activity-based treatments to more successfully enhance cognitive function for the greatest number of people.

One of the challenges facing researchers in this field is that the list of possible moderating factors is virtually endless, making it difficult to identify which factors might be the most immediately relevant and the most important to study. However, there are several moderating factors that share characteristics with physical activity or have similar putative mechanisms or pathways underlying the effects that provide researchers with a theoretical platform to begin their investigation. Along these lines, pertinent moderators of the effects of physical activity on brain health include (1) genotypes, such as apolipoprotein E (APOE) [21], brain derived neurotrophic factor (BDNF) [22], and catechol-O-methyltransferase (COMT) [23] because these genes influence molecular pathways thought to be regulated by physical activity and (2) dietary variables, such as omega-3 fatty acids [24] that share molecular mechanisms and behavioral outcomes with physical activity. Although there are clearly other factors that are moderating the effects of physical activity on neural outcomes, we will focus this paper on these few moderators for which there is empirical support for their effects. Therefore, in this paper we first review current literature on physical activity and the aging brain (see Table 1 for select studies’ characteristics) in an effort to reveal the brain circuits influenced by physical activity. Secondly, we focus on several factors that might moderate the effects of physical activity on brain health and use this evidence to recommend future research directions with the hope of more comprehensively understanding the factors that influence cognitive and brain aging.

2. Physical Activity and Gray Matter (GM) Volume

There is increasing evidence that the brain remains plastic throughout the lifespan and that a greater amount of physical activity or higher fitness levels take advantage of this natural characteristic of the brain. For example, individuals reporting greater amounts of physical activity or who are more physically fit have greater GM volume than individuals reporting less activity [7] or are less physically fit [39–41]. The effect of greater amounts of physical activity on GM volume can be found throughout the brain; however, the prefrontal cortex [8, 41–43] and hippocampus [9, 19, 40, 44] appear to be especially sensitive to these effects. The prefrontal cortex is associated with executive functions, a group of goal-oriented tasks that involve working memory, verbal fluency, and multitasking. The hippocampus, on the other hand, is involved in memory consolidation, spatial learning, and other memory processes. What makes the prefrontal cortex and hippocampus of particular interest is that these regions are some of the earliest regions to atrophy in late adulthood [45–48].

A technique called voxel-based morphometry (VBM) is one way to measure GM volume using high-resolution brain images from magnetic resonance imaging (MRI). This technique uses an automated segmentation algorithm to demarcate gray matter, white matter, and cerebrospinal fluid. Then, on a point-by-point basis throughout the brain the volume or density of gray matter can be examined as a function of any variable of interest (e.g., fitness levels). Studies using VBM have shown widespread age-related atrophy in frontal brain regions [45, 49, 50]. For example, Good et al. [49] examined GM volume in 465 adults as a function of age using VBM and demonstrated significant GM volume loss in several frontal and parietal regions. These results, along with many others, confirm the age sensitive nature of frontal GM volume and highlight the frontal lobe as an area of interest in aging research.

Fortunately, physical activity appears to increase GM volume in the frontal cortex [8]. In a 6-month intervention, older adults were randomly assigned to either a moderate intensity aerobic walking group or to a stretching and toning control group. The walking group was monitored by exercise coordinators and exercised 3 days per week. The control group received similar amounts of social contact with the exercise coordinators, but partook in stretching exercises instead of walking. After the 6-month intervention, the aerobic walking group showed an increase in gray matter volume in the frontal cortex, along the medial wall near the...
<table>
<thead>
<tr>
<th>First author (citation no.)</th>
<th>Experimental method</th>
<th>Measure(s)</th>
<th>Population mean age (standard deviation)</th>
<th>N</th>
<th>Significant finding(s)</th>
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<tr>
<td><strong>APOE as variable of interest</strong></td>
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<tr>
<td>Honea et al. [25]</td>
<td>Cross sectional: APOE ε4 carrier status, dementia status × global connectivity, GM volume, cognitive performance, and fitness</td>
<td>APOE ε4 carrier status VO$_2$ peak, WMS III, WAIS, MMSE, Voxel-based morphometry, Diffusion tensor imaging</td>
<td>Older adults aged 73.4 (6.3)</td>
<td>117</td>
<td>Higher aerobic fitness levels were related to greater brain volume in the medial temporal lobe in early AD patients.</td>
</tr>
<tr>
<td></td>
<td>Nondemented (n = 56) Early-stage AD (n = 61)</td>
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<tr>
<td>Liang et al. [26]</td>
<td>Cross sectional: APOE ε4 carrier status × fitness, biomarker risk status</td>
<td>Walking, running, and jogging questionnaire, PIB, APOE ε4 carrier status</td>
<td>Healthy older adults aged 55–88</td>
<td>56</td>
<td>Physical activity was associated with reduced plaque deposition in APOE ε4 carriers.</td>
</tr>
<tr>
<td>Nichol et al. [27]</td>
<td>Control 1: nontransgenic mice Control 2: Tg2576 mice</td>
<td>IL-1β, TNA-α, Aβ</td>
<td>Tg2576 transgenic mice (n = 29) C57Bl6/SJL nontransgenic mice (n = 27)</td>
<td>56</td>
<td>IL-β and Aβ fibrils are significantly lower in transgenic mice with access to running wheel than transgenic control mice.</td>
</tr>
<tr>
<td></td>
<td>Experimental group 1: nontransgenic mice with 3 weeks access to running wheel Experimental group 2: Tg2576 mice with 3 weeks access to running wheel</td>
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<tr>
<td></td>
<td>Control 1: nontransgenic mice (n = 6) Control 2: Tg2576 mice (n = 6)</td>
<td>Morris water maze latency, Aβ mRNA expression CXCL1 and CXCL12 protein</td>
<td>Tg2576 transgenic mice C57Bl6/SJL nontransgenic mice</td>
<td>24</td>
<td>Transgenic mice with voluntary exercise performed significantly better on Morris water maze than control transgenic mice showed no increase in inflammatory markers and increased mRNA production of CXCL1.</td>
</tr>
<tr>
<td>Parachikova et al. [28]</td>
<td>Experimental group 1: nontransgenic mice with 3 weeks access to running wheel (n = 6) Experimental group 2: Tg2576 mice with 3 weeks access to running wheel (n = 6)</td>
<td>Minnesota leisure time activity questionnaire APOE ε4 carrier status</td>
<td>Adults aged &gt;65</td>
<td>3,375</td>
<td>There is a negative relationship between ε4 carrier status and performance on working memory tasks where ε4 carriers performed worse than noncarriers.</td>
</tr>
<tr>
<td>Podewils et al. [29]</td>
<td>Cross sectional: APOE ε4 carrier status × onset of dementia × physical activity</td>
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<td>Inactive group: self-report less than 1 hr/day physical activity Active group: more than 1 hr/day physical activity</td>
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Citation, experimental procedures, subject information, sample size, and main significant findings, are outlined for studies that have been highlighted as exemplary in text. Weschler Memory Scale III (WMSIII), Weschler Abbreviated Scale of Intelligence (WASI), California Verbal Learning Test II (CVLTII), and Pittsburgh Compound B (PIB).
anterior cingulate cortex (ACC) and increased white matter volume in the genu of the corpus callosum, whereas the control group showed typical reductions in volume in these same regions. The results from this study indicate that only 6 months of moderate intensity physical activity is sufficient for increasing volume in brain areas that usually shrink during this period of life.

The hippocampus, on the other hand, is involved in spatial navigation and memory. Located in the medial temporal lobe, the hippocampus is also prone to age-related atrophy [40, 46]. Important for memory formation and recall, hippocampal decay may be responsible for many of the symptoms associated with AD [19, 51], but even normal aging is associated with reduced hippocampal volume [52]. Rodent models of AD have shown decreased learning and memory performance accompanied by significant atrophy or even absence of hippocampal tissue [53–55]. Fortunately, the hippocampus is highly sensitive to exercise. In a study by van Praag et al. [56], mice that had access to a running wheel showed a significant increase in hippocampal cell proliferation and survival of new cells when compared to nonrunning mice. These and many other studies [57–59] indicate that exercise affects both the morphology and physiology of the hippocampus, including neurogenesis in the dentate gyrus.

Participation in moderate intensity exercise also appears to affect the hippocampus in humans. In an intervention extending for 1 year, participants were randomly assigned to either a moderate intensity aerobic walking group or to a stretching and toning control group, similar to the 6-month study described above [19]. Over the year, the control group experienced normal age-related atrophy of the hippocampus. However, the walking group experienced a 2% increase in hippocampal volume over this same period. In addition, hippocampal atrophy rates within the control group were inversely related to preintervention fitness levels, indicating that higher fitness levels were protective against hippocampal atrophy. This study provides some key insights into the effects of exercise on the hippocampus: first, only moderate intensity physical activity for 1 year is sufficient for increasing the volume of the hippocampus during a time period of life when the hippocampus tends to decline in size and increasing the risk for dementia. Second, higher fitness levels could reduce the rate of hippocampal decay over a 1 year period. While this study was conducted using healthy adults, these results identify aerobic exercise as a potentially effective method for preventing and treating diseases, such as Alzheimer’s disease and dementia, that are associated with hippocampal atrophy.

Recent evidence has also linked the associations between higher fitness levels and greater GM volume with improvements in cognitive function. For example, Erickson et al. [40] found that higher cardiorespiratory fitness levels were associated with increased hippocampal volumes, which in turn mediated the relationship between fitness and spatial memory performance. A similar relationship was found between higher fitness levels, greater prefrontal cortex volume, and better performance on measures of executive control [41]. Thus, increased GM resulting from exercise and associated with higher fitness levels appears to have a significant association with improved cognitive function.

### 3. Genetic Moderators of Physical Activity on Brain Health

Many different factors may moderate the effect of physical activity on brain health. By including these variables as statistical interaction terms (i.e., physical activity × genotype), the effect of moderation on cognitive or neural outcomes can be quantified. In this way, genetic variants such as APOE, BDNF, and COMT may explain some of the individual differences in the extent to which physical activity augments brain health [60]. Effect sizes in these studies are often difficult to directly compare mainly because of the variation in samples, designs, and candidate genes studied. The genes in this paper have been chosen based on animal literature as well as some supporting human research.

#### 3.1. Apolipoprotein E (APOE)

The APOE gene has three different allele variations: ε2, ε3, and ε4. The majority of the population carries the ε3 allele, whereas the ε2 and ε4 alleles are less common [61]. The gene APOE creates the lipoprotein of the same name, abbreviated ApoE. ApoE is found throughout the body and is linked to cardiovascular functions such as the transport of fats and cholesterol from the blood stream to the liver for processing. There have been numerous studies linking the APOE gene to cognitive performance and risk for dementia [62, 63]. In particular, the APOE ε4 allele is considered a potent risk factor for AD [64]. The APOE ε4 variant also influences cognition in healthy adults without dementia. For example, Reinvang et al. [30] examined whether memory and executive functioning varied by APOE genotype in a group of healthy adults. APOE ε4 carriers performed more poorly on letter and digit span tasks as well as the Stroop color-word task than noncarriers.

β-amyloid (Aβ) plaques are also biomarkers and putative causes of AD and are closely linked to APOE genotype [65–68]. The ApoE protein produced by APOE ε4 can bind to Aβ more efficiently than the other allele variants, increasing the number of plaques, which are thought to lead to AD symptoms [65]. Rodent studies reveal APOE ε4 knockout mice have reduced Aβ deposition [66], further confirming APOE genotype as a risk factor for impaired clearance of Aβ and susceptibility for AD. While Aβ plaque deposition is a putative cause of AD, voluntary physical activity effectively reduces amyloid plaque deposits in rodents [27, 28, 69, 70]. Exercise may have this effect by promoting the expression of growth factors that are associated with reduced amyloid and changes in inflammatory pathways that alter Aβ plaque deposition. For example, a study by Parachikova et al. [28] used transgenic (Tg2576) mice as a model for AD where the particular mutation produces an abundance of amyloid precursor protein (APP), a protein that gets cleaved to produce amyloid. The results revealed a significant decrease in mRNA for inflammatory biomarkers in Tg2576 mice with 3 weeks access to a running wheel when compared to Tg2576 mice without access to running wheels. Nichol et al. [27] extended this to show that reduced mRNA for inflammatory
biomarkers coincided with decreased Aβ plaque deposition. Whether participation in physical activity moderates plaque deposition in humans has only recently been studied.

Consistent with the rodent literature, several epidemiological studies have also reported that the association between greater amounts of physical activity and reduced risk of dementia might be dependent on APOE genotype. For example, Podewils et al. [29] examined 3,375 individuals in the United States, measuring physical activity levels with a modified Minnesota Leisure Time Activity Questionnaire. From this measure the authors categorized the activities into groups based on metabolic equivalents, creating a calculation of energy expenditure for each individual. Adults aged 65 and over who engaged in regular physical activity had a markedly reduced risk of developing AD after a 5-year follow-up than those who were sedentary. Interestingly, these results were enhanced in APOE ε4 noncarriers, such that ε4 carriers showed no significant changes in risk associated with increased participation in physical activity. Although one strength of this study is its large sample size, the self-reported nature of physical activity along with its observational design make it difficult to conclude the direction and strength of the association.

In contrast, several other studies have found that APOE ε4 carriers benefit more from exercise than do non-ε4 carriers. Schuit et al. [21] examined the relationship between levels of physical activity and cognitive decline in late adulthood as a function of the presence or absence of the ε4 allele in 347 elderly Dutch men. The infrequent exercising group, defined as those being physically active less than one hour per day, had a twofold increased risk of cognitive decline over the three-year period as measured by the Mini Mental State Exam, but this risk was mitigated in the more frequent exercising APOE ε4 carriers. Hence, this epidemiological study suggests that participation in regular exercise could offset genetic risk factors for dementia. Consistent with this finding, a study of nondemented middle-aged adults found that greater amounts of physical activity was associated with faster performance on a memory task and greater brain activation in APOE ε4 carriers compared to their more sedentary APOE ε4 peers [71]. Again, although provocative, the results from these studies need to be interpreted within the context that physical activity was assessed using self-reported measures, and these studies were observational in nature and not stemming from randomized controlled trials.

Evidence in AD patients shows a slightly different pattern than that described above. For instance, Honer et al. [25] examined whether the association between fitness and brain volume in 61 individuals with early-stage AD would be moderated by the APOE polymorphism. Consistent with previous findings of a cross-sectional study examining VO2 peak in dementia and early AD patients [10], higher aerobic fitness levels (VO2 peak) were related to greater brain volume in the medial temporal lobe in early AD patients, as measured using voxel-based morphometry. Surprisingly, APOE ε4 status did not moderate the relationship between fitness and brain volume in either the AD patients or in the 56 healthy control participants. Contrary to this finding, Smith et al. [15] examined the effect of physical activity and APOE ε4 on brain activity during memory processing in older (65–85) cognitively intact adults. They found that physical activity increased semantic memory-related brain activation in cognitively intact older adults who carry the APOE ε4 allele. However, the authors included only 17 subjects per group and assessed physical activity through the self-report Stanford Brief Activity Survey (SBAS), rather than an objective measure such as VO2 peak. Finally, in a study of amyloid deposition in older adults (55–88), greater amounts of self-reported physical activity were associated with reduced plaque deposition in APOE ε4 carriers [26]. Hence, despite some variability in the literature, there is a growing consensus that the harmful effects of the APOE ε4 allele are mitigated by greater amounts of physical activity. Yet, despite this preliminary conclusion, there is a need for more research to determine if APOE ε4 carriers who were randomly assigned to receive exercise could benefit more from an intervention than their non-ε4 counterparts. There is also a great need for larger sample sizes, as the costly nature of neuroimaging has limited the number of participants assessed in previous studies.

3.2. Brain-Derived Neurotrophic Factor (BDNF). BDNF is another gene that could be moderating the effectiveness of physical activity on brain health. Similar to APOE, BDNF refers to both the gene and its resulting protein. There is a valine to methionine substitution in the BDNF gene at codon 66 resulting in several natural occurring variants of this gene in the human population. The Val/Met and Met/Met genotypes have been associated with decreased cognitive performance [72–74] and GM volume [75, 76] compared to Val homozygotes. The Met allele is associated with a reduction in the regulated secretion and trafficking of BDNF from the cell, which is thought to impact the role of BDNF in cell proliferation and learning.

While present in all brain areas, BDNF is highly concentrated in the hippocampus and cortex [77], promoting cell proliferation and signaling through several pathways, most notably by binding to the receptor tyrosine kinase B (TrkB). BDNF binding to the TrkB receptor depolarizes glutamatergic cells and results in several intracellular signaling cascades that moderate mRNA transcription [78, 79]. Additionally, TrkB binding phosphorylates the NMDA receptors of the postsynaptic neuron, increasing cyclic-AMP production and promoting long-term potentiation (LTP) [80]. In the hippocampus, LTP is considered a cellular analog of learning and is closely coupled with behavioral indices of learning and memory [81]. Rodent models where BDNF-receptor binding has been blocked or in BDNF knockouts, animals show deficits in acquisition and retrieval on the Morris water maze [82]. Mu et al. [32] observed a decrease in spatial memory retention in rats treated with a BDNF blocking antibody, providing further evidence that BDNF is necessary for the facilitation of learning and memory. These studies suggest that BDNF binding is critical to several cognitive processes.

Interestingly for this discussion, BDNF levels also increase as a function of both immediate [83] and longer-term [33] exercise. In fact, increased BDNF expression is a
highly replicated effect in exercise studies [84]. For example, Stranahan et al. [33] examined amounts of voluntary wheel running in mice, finding that hippocampal BDNF levels increased with greater amounts of exercise, and in turn, higher levels of hippocampal BDNF was associated with greater dendritic spine density and hippocampal neurogenesis. Thus, increased BDNF signaling is considered one of the primary molecular pathways by which exercise improves neurocognitive function.

BDNF is also found outside of the central nervous system and can be measured in serum and plasma in humans. While it has been argued that serum levels are not a valid measure of cortical BDNF levels [85], rodent studies have found strong correlations between hippocampal and frontal BDNF levels and peripheral BDNF measures [86]. Human studies report that BDNF levels are a reliable biomarker for depression, where there is a strong negative relationship between peripheral BDNF levels and depression [87] and treatment of depression might result in an increase in serum BDNF [88]. Postmortem studies of individuals who have died from suicide also report that cortical levels of BDNF closely correspond to serum levels in individuals diagnosed with depression [89]. Other studies of serum or plasma BDNF find that levels are correlated with measures of brain integrity including hippocampal volume [31] and cognitive function [90]. Yet, despite these correlations, the translation from peripheral to cortical BDNF levels in humans is still unknown as is the significance of BDNF in the serum. Nonetheless, measuring BDNF in the serum allows for a minimally invasive proxy for examining a biomarker of brain health that is simply mirroring what is happening in the brain. From this perspective, given that animal studies have consistently reported increased BDNF levels after exercise, it has become a molecule of interest in human studies of physical activity and exercise. In fact, several studies have reported that acute bouts of physical activity are effective at increasing BDNF levels in serum [85]. In humans, Yarrow et al. [91] examined BDNF by sampling serum levels 0, 30, and 60 minutes into a physical activity session, where participants rode a stationary bike at a moderate pace, as well as 30 minutes after a brief cooldown. They demonstrated that BNDF levels were significantly elevated during and immediately after the physical activity session. Long-term exercise interventions, however, have not shown elevated levels of serum BDNF at follow-up [19] indicating some differences between the effects of acute and long-term exercise on BDNF pathways. The differences between acute versus long-term effects of exercise on BDNF levels remains a matter of speculation.

BDNF clearly remains one of the primary molecular pathways by which exercise is thought to influence cognitive function. In line with this hypothesis, hippocampal volume is correlated with serum BDNF levels in older adults [31], and exercise-induced increases in hippocampal volume are associated with increased BDNF serum levels [19]. Although there is not a one-to-one association between BDNF protein and the BDNF polymorphism, the link between the Met allele and reduced secretion and trafficking of the protein suggests that physical activity could play an important moderating role. Unfortunately, to date, there have not been published investigations of whether physical activity moderates the effect of the BDNF polymorphism on neurocognitive function. This will be an important avenue for future research.

3.3. Catechol-O-methyltransferase (COMT). COMT is a gene that produces an enzyme of the same name and has been hypothesized to influence cognitive function and brain health. The COMT enzyme works by breaking down the neurotransmitters dopamine, epinephrine, and norepinephrine. COMT is located mainly in the frontal cortex and is necessary for the regulation of the aforementioned neurotransmitters but is predominantly associated with dopamine [92]. Dopamine is concentrated in the prefrontal cortex, where it plays a role in executive control [93, 94]. The COMT enzyme is altered by its genotype where a valine (Val) to methionine (Met) amino acid substitution at the 158/108 locus of the peptide sequence affects the thermostability of the enzyme. The COMT gene therefore has three variants, Val/Val, Val/Met, and Met/Met, where Val carriers show increased enzyme activity, which in turn reduces dopamine levels at a faster rate in the synapse [92]. Wishart et al. [35] found that Val homozygotes displayed decreased performance on executive tasks. Additionally, de Frias et al. [34] revealed reduced cognitive performance and greater cognitive decline after a 5-year follow-up in older adult Val/Val individuals. There have now been numerous studies documenting the association between the COMT gene and cognitive performance; yet several recent reviews and meta-analyses have questioned the robustness and consistency of the effect across populations and tasks [95]. Such variation suggests that there might be factors that are moderating the effect of the COMT gene and influencing the direction and consistency of the effect.

One such moderator might be participation in physical activity. Physical activity influences dopaminergic circuitry in both the prefrontal cortex and basal ganglia in animal models [96–99] suggesting that its effects on cognitive function might be partially mediated by its effects on dopamine. Unfortunately, few studies have examined whether the COMT gene moderates the effect of physical activity on neurocognitive function. In one study, Stroth et al. [23] examined whether variants of the COMT gene would be moderated by participation in a 17-week physical activity intervention in a sample of 75 adults. At the end of the intervention, Val carriers who were in the running group displayed disproportionately faster response times on a working memory paradigm when compared to Met homozygotes, indicating that the benefits associated with physical activity on working memory function were dependent on the COMT genotype. This effect could be happening through the effects of physical activity on the gene itself, through physical activity effects on dopamine, or on dopamine receptors. In other words, the pathways by which this effect occurs remain a matter of speculation.

The evidence outlined above marks the COMT gene as a possible moderator of the effects of physical activity on cognitive function, but more studies are needed to
replicate this effect and expand it to larger sample sizes and other populations. However, there is a striking resemblance between the moderating effects of physical activity on APOE and COMT genotypes. In each instance there is speculation or evidence that participation in physical activity might mitigate the effect of the gene on cognitive function.

4. Dietary Moderators of Physical Activity on Brain Health

Omega-3 fatty acids provide many beneficial effects to the body [100] and brain [101], and the pathways by which omega-3 fatty acids work on the body are similar to the pathways thought to be regulated by physical activity. Hence, several human and animal studies have speculated about the additive or multiplicative benefits that might arise from combining omega-3 administration or supplementation with greater amounts of physical activity [102].

There are two distinct types of omega-3 fatty acids: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA is primarily located in the cortex and is linked to a variety of cognitive functions such as attention and memory. EPA, however, is found all over the body and is known for its anti-inflammatory effects on the cardiovascular system. Higher DHA levels in the serum and self-reported dietary intake of DHA have been associated with better performance measures on executive function [103, 104]; however many of these studies have been either cross sectional in nature or consisting of rather small sample sizes. On a molecular level, DHA is critical to cell membrane structure, fluidity, and ion permeability and is synthesized in small amounts in humans [105, 106]. As a result, humans are required to consume most of their necessary DHA to maintain appropriate levels.

DHA has also been linked to dopaminergic pathways via the D2 dopamine receptor [107–109]. Rodents consuming a DHA deficient diet show significantly fewer D2 receptors in the striatum, mimicking similar pathology to rodent models of depression [110]. Rodent models of Parkinson’s disease, where dopaminergic cells and receptors are significantly reduced, demonstrate that DHA supplementation is associated with a greater number of dopaminergic cells in the substantia nigra when compared to mice consuming a DHA deficient diet [111]. DHA is also under investigation as a potential nonpharmaceutical treatment for schizophrenia because of its effect on maintenance and preservation of normal dopaminergic function [112].

While both EPA and DHA are currently being explored as nonpharmaceutical treatments for schizophrenia, Parkinson’s disease, and other psychiatric and neurological conditions, other research is examining its links to cognitive function in middle-aged and geriatric populations. Muldoon et al. [36] tested the association between DHA serum levels and measures of cognitive function in midlife adults. They recruited 280 volunteers between 35 and 54 years of age, free of major neuropsychiatric disorders, who were not taking fish oil supplements. Individuals with higher DHA levels performed better on tasks of nonverbal reasoning and mental flexibility, working memory, and vocabulary. They concluded that DHA is related to cognitive health throughout the lifespan and may influence the prevalence of neuropsychiatric and impaired cognitive function in late life. However, this study was cross sectional, as are many others on DHA, so the directionality of the effects remains questionable.

In fact, some evidence suggests DHA might play an important role in dementia and age-related cognitive decline [113]. Individuals with self-reported diets high in omega-3 fatty acids decline at a slower rate on the MMSE as compared to omega-3 deficient individuals [38]. Several reviews of the literature and epidemiological studies over the past 10–12 years have revealed differing results, however, when conducting randomized trials of DHA supplementation or longitudinal studies following individuals with variation in fatty acid intake [114]. There is some evidence that greater intake of DHA might help to prevent or delay AD by preventing tangles and Aß plaques [37, 115]. Although some research has hypothesized that DHA may be effective at reducing Aß plaques, no consistent evidence for the treatment of AD has been found in association with DHA supplementation. Jicha and Markesbery [116] outline both epidemiological and clinical studies and conclude that there is evidence that DHA supplementation may act in cellular preservation but cannot be considered a reliable treatment for AD.

Physical activity, however, may provide an avenue by which the effects of DHA on cellular integrity and cognitive function may be enhanced [102, 106]. Chytrova et al. [24] revealed an additive effect of physical activity and DHA supplementation in a rodent model of synaptic plasticity and membrane structure in the dentate gyrus of the hippocampus. Mice in the DHA condition showed increased levels of membrane-bound synaptic proteins when compared to mice in the regular diet condition; however those mice receiving both DHA supplementation and physical activity showed greater levels of synaptic proteins than their counterparts not receiving physical activity. These results suggest that physical activity potentiated the effects of DHA supplementation on membrane proteins associated with synaptic plasticity. Unfortunately, studies in humans have not yet determined whether the effects of DHA on cognitive function are moderated by participation in physical activity. Given the molecular and cellular associations described above, it would be reasonable to hypothesize that such an interaction might be present.

5. Conclusion

Physical activity is effective at enhancing cognitive and brain function; however, many genetic and behavioral factors may be attenuating or augmenting the effect of physical activity. Genes such as APOE, BDNF, and COMT share molecular pathways with exercise and therefore might have the potential to moderate the effect of physical activity on cognitive function and neuronal health. For example, DHA reduces Aß plaque build-up, similar to APOE, functions in
the cell membrane, targets the synapse, similar to BDNF, and has strong ties to the dopaminergic pathway similar to COMT. Physical activity also affects all of these pathways, further weaving these independent variables together as part of a much larger story.

Unfortunately, many studies only assess one or two variables at a time in relation to cognitive function or physical activity. Therefore, the influence of genes or dietary variables on the effect of physical activity remains largely speculative. In fact, in this paper we highlight the evidence that there might be interactions between these variables, but to date, few studies have formally assessed these associations. Future studies with larger sample sizes and more comprehensive assessments of these variables are needed to move this field forward. Individual variability in prior studies highlights the need to more closely examine the potential moderators described here.

In addition, the way in which each of the genetic variables moderates the effect of physical activity is largely unknown. While there is evidence for physical activity to increase mRNA transcription of BDNF and COMT, the exact promoters targeted, and the way in which they are activated has not been identified. Animal models could provide insight to the pathways involved in the moderating effect of certain genotypes on physical activity and are a critical starting point for understanding these potential moderators of physical activity on neuronal changes, brain health, and cognitive function.

It will be important for new studies to take into consideration the individual variability contributed by dietary variables such as omega-3 levels and genes. These variables are clearly a source of “noise” within the data and could contribute to explaining the effects, or lack thereof, of physical activity on cognitive function. As we stated earlier, it will be important for future research to consider these variables as potential moderators instead of just “noise.”

In sum, prior reviews and meta-analyses have focused on the protective and enhancing effects of exercise on neurocognitive function [12]. In this paper we have taken a different approach and have described several potential moderating factors that could be contributing to variation in the effectiveness of physical activity to enhance cognition. Although there is a long list of potential moderators, we have chosen here to focus on three different genes and a single dietary factor. This of course does not preclude other potentially important moderators such as intellectual engagement, other genes, other dietary factors, age, sex, or the combination of different types of physical activities (e.g., resistance training paired with aerobic training). We argue that it will be important for future research to consider these variables when designing studies, analyzing data, and interpreting the results from physical activity studies.

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References


Effects of Gait and Cognitive Task Difficulty on Cognitive-Motor Interference in Aging

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Although gait-related dual-task interference in aging is well established, the effect of gait and cognitive task difficulty on dual-task interference is poorly understood. The purpose of this study was to examine the effect of gait and cognitive task difficulty on cognitive-motor interference in aging. Fifteen older adults (72.1 years, SD 5.2) and 20 young adults (21.7 years, SD 1.6) performed three walking tasks of varying difficulty (self-selected speed, fast speed, and fast speed with obstacle crossing) under single- and dual-task conditions. The cognitive tasks were the auditory Stroop task and the clock task. There was a significant Group × Gait Task × Cognitive Task interaction for the dual-task effect on gait speed. After adjusting for education, there were no significant effects of gait or cognitive task difficulty on the dual-task effects on cognitive task performance. The results of this study provide evidence that gait task difficulty influences dual-task effects on gait speed, especially in older adults. Moreover, the effects of gait task difficulty on dual-task interference appear to be influenced by the difficulty of the cognitive task. Education is an important factor influencing cognitive-motor interference effects on cognition, but not gait.

1. Introduction

Functional community ambulation requires an ability to perform cognitive tasks while walking and an ability to adapt to extrinsic environmental factors that increase the complexity of mobility, such as obstacle avoidance (e.g., curbs) and time-critical tasks (e.g., crossing the street within the time constraints imposed by traffic signals) [1]. A reduced capacity for dual-task walking may limit community mobility. Research has shown that healthy older adults experience significant decrements in gait speed when cognitive tasks are performed while walking [2], a phenomenon referred to as dual-task interference or cognitive-motor interference.

A limitation of the existing research on dual-task interference in aging is that it has focused predominantly on dual-task performance during unobstructed walking at preferred gait speed. Therefore, the effect of dual-task interference on gait and cognitive performance during more attention-demanding gait tasks remains largely unknown. Furthermore, because slowing down during unobstructed walking in the gait laboratory is inconsequential for successful completion of the motor task, individuals may place more importance on performing the cognitive task [3]. Indeed, healthy young and older adults appear to place greater priority on the secondary (nongait) task in many dual-task situations [4, 5]. It seems reasonable to assume that when gait task complexity increases and there is a greater potential threat to stability, individuals would place more importance on completing the gait task safely. The current study explores how gait task difficulty affects cognitive-motor interference.

Bock et al. [4] examined the dual-task costs of performing cognitive and gait tasks of varying difficulty in both young and older adults. The authors concluded that in dual-task conditions, older adults were at greater risk for falls than young adults. However, the effect of task difficulty on dual-task interference was not explicitly analyzed and remains unclear. Numerous studies have examined dual-task effects on gait during obstacle avoidance in older adults [6–15], but none have directly compared the dual-task effects during obstacle negotiation to those during unobstructed walking.
Kelly et al. [16] recently examined the effects of walking task difficulty (usual walking versus narrow-based walking) on dual-task performance in young adults. They found that walking task difficulty affected walking performance but not cognitive performance. Because this study included only dual-task conditions with specific instructions to focus primarily on either the cognitive task or the gait task, it is not known what effect task difficulty has on a person’s default prioritization; that is, the way in which the person chooses to allocate his attention in the absence of explicit instruction. Moreover, the study included only young adults, so age-related differences in the effects of task difficulty on dual-task interference are not currently known.

The purpose of this study was to determine the effect of gait and cognitive task difficulty on dual-task interference in healthy young adults and older adults. We specifically compare obstructed and unobstructed gait because of the relevance to community ambulation. We hypothesized that as the difficulty of the gait task increased, attention to gait would increase, resulting in smaller dual-task effects relative to simple walking (unobstructed at self-selected speed). We focus on gait speed as the measure of gait performance in dual-task conditions, since meta-analysis results show that cognitive-motor interference effects across a range of cognitive tasks are prominent in gait speed [2]. Furthermore, because research has shown that dual-task effects on gait vary according to the type of cognitive task [17], we explore our hypothesis in two different cognitive-motor dual-task combinations.

2. Methods

2.1. Participants. Twenty young adults (mean age 21.7 years, range 20–27) and 15 older adults (mean age 72.1 years, range 66–84) were recruited through advertisements at Northeastern University and local senior centers. To be included, participants had to be 18–30 years or older than 65 years, be able to walk independently in the community for at least 50 meters, have intact cognition according to the Mini-Mental State Exam (score > 23), and have normal or corrected-to-normal hearing and vision. Participants were excluded if they had a history of neurological disorders, any orthopedic conditions affecting gait, reported more than 2 falls in the past year, had an acute hospital stay within the last 3 months, or had a lower extremity amputation. Participants who met the selection criteria signed an informed consent form. The study was approved by the Institutional Review Board at Northeastern University.

Demographic information was collected for each participant, including age, gender, and education. Cognitive abilities of the participants were characterized using the Mini-Mental State Exam [18], Digit Substitution Test [19], Stroop Color-Word Interference Test [20], Comprehensive Trail Making Tests [21], and the Activities-specific Balance Confidence (ABC) Scale [22]. Functional mobility was assessed using the Timed Up and Go test (TUG) [23].

2.2. Procedures. Each participant performed three gait tasks and two different cognitive tasks in isolation (single-task conditions) and each gait task in combination with each of the cognitive tasks (dual-task conditions). The cognitive tasks were the auditory Stroop [24] and the “clock task” [25]. In the auditory Stroop task, participants heard the words “high” and “low” spoken in either a high pitch (360 Hz) or a low pitch (180 Hz). The participants were instructed to indicate the pitch of the word they heard (ignoring the actual word presented) by responding verbally “high” or “low” as accurately and as quickly as possible. In the clock task, the participants heard a time (e.g., one-twenty-five) and were required to determine whether the two hands of the clock at the given time were in the same half (left/right) or opposite halves. If the hands were the same half, participants were asked to respond “yes”; if the hands were in opposite halves, the participants were asked to respond “no.” There were no clock-task stimuli in which one of the hands was exactly on the twelve or six (e.g., one-thirty). For each task, the participants completed at least two practice blocks of 30 trials while sitting. Single-task performance in each cognitive task was recorded in sitting and was always performed immediately before the dual-task conditions. Both the Stroop and clock tasks were produced using DirectRT (Empirisoft, New York, NY, USA). The stimuli were delivered through wireless headphones and participant responses were recorded through a wireless microphone (Logitech, Newark, CA). For both cognitive tasks, we measured reaction time (in milliseconds) and accuracy (percent of correct responses). Our assumption was that the clock task was more difficult because it required greater cognitive processing.

The three gait tasks were walking at self-selected speed (SS), walking at fastest comfortable speed (FC), and walking at fastest comfortable speed while stepping over an obstacle (OB). The three gait tasks were chosen to provide differing levels of task difficulty. A critical assumption was that walking at fastest comfortable speed was more attention-demanding than walking at preferred (self-selected) speed, and that walking fast and stepping over an obstacle further increased the demands of the task. All gait tasks involved participants walking across a 6.1-meter Platinum GAITRite walkway, which contains pressure activated sensors. The associated software computes spatio-temporal parameters of gait. The participants started and finished each pass 2 meters beyond the end of the walkway so that only steady state gait data were captured. Participants completed 6 passes of the walkway for each condition and the average of the 6 passes was used for analysis. In the OB condition, a 15 cm high hurdle was placed at the 4.5 m mark of the GAITRite walkway. The order of the three gait tasks was randomized, but was performed in the same order for the single-task and the two dual-task (Stroop, clock) blocks. Block order (single, Stroop, clock) was also randomized across participants.

2.3. Measures of Dual-Task Interference. To analyze the effect of task difficulty on dual-task interference, we calculated the dual-task effect (DTE) on both gait speed and cognitive task performance (reaction time and accuracy). Dual-task effects
on gait speed (DTEg) and clock and Stroop-task accuracy (DTEacc) were calculated as follows [16]:

\[
DTE = \frac{\text{dual task} - \text{single task}}{\text{single task}} \times 100\%.
\]

Whereas a decrease in gait speed and accuracy represent performance decrement, an increase in reaction time (i.e., slower response) represents performance decline, therefore DTE on reaction time (DTErt) was calculated as follows [16]:

\[
DTE = -\frac{\text{dual task} - \text{single task}}{\text{single task}} \times 100\%.
\]

Thus, for each variable, negative values for DTE indicate that performance deteriorated under dual-task conditions (i.e., dual-task cost), and positive values represent an improvement in the dual-task condition relative to single-task performance (i.e., dual-task benefit).

2.4. Statistical Analysis. The young and older adults were compared on profile measures using independent t-tests. To verify whether the clock task required greater cognitive processing than the Stroop task, we conducted paired t-tests on mean reaction times for the two tasks in the single-task (sitting) condition for each group. To determine whether participants increased their SS gait speed as instructed in the FC and OB conditions, we analyzed changes in gait speed across conditions with a 3 Gait Task (SS, FC, OB) × 3 Cognitive Task (single, Stroop, clock) ANOVA for each group. Tukey’s post hoc tests were used as needed.

To analyze the effects of gait and cognitive task difficulty on dual-task interference, we applied a 3 Gait Task (SS, FC, OB) × 2 Cognitive Task (Stroop, clock) × 2 Group (young, older) repeated measures ANCOVA with education (years) as covariate to each dependent variable (DTEg, DTErt, DTEacc). Significant three-way interactions were followed up with two-way analyses and post hoc tests as needed. The partial eta squared (ηp²) is presented as a measure of effect size for each repeated measures ANCOVA. By convention, 0.01 indicates a small effect size, 0.06 is moderate, and 0.14 represents a large effect [26]. Due to technical issues three older adults and one young adult were missing gait data from one or more of the gait tasks. Listwise deletion meant that these subjects were excluded from the analyses for gait variables, resulting in minor variations in degrees of freedom. All analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

The young and older adults did not differ in global cognition assessed using the MMSE, but there were significant differences in specific cognitive domains, including executive function, inhibition of habitual response, and speed of processing (Table 1). The older adults also had significantly lower balance self-efficacy and took longer to complete the TUG. However, the differences between the groups on the cognitive and mobility measures were not considered clinically meaningful, since the older adults performed within normal limits for their age [21, 27, 28]. On average, the young adults had more years of education than the older adults (Table 1).

The mean reaction time while sitting (single-task) for the clock task (young adults \(M = 1403\) ms, SD = 271; older adults \(M = 1889\) ms, SD = 433) was significantly longer than that for the Stroop task (young adults \(M = 805\) ms, SD = 109; older adults \(M = 956\) ms, SD = 216) for both young adults, \(t(19) = -10.5, P < .001, d = 2.9\), and older adults, \(t(14) = -9.5, P < .001, d = 2.7\). Thus, consistent with our assumption, the clock task required greater cognitive processing than the Stroop task. In both tasks, mean reaction time of older adults was slower than young adults.

3.1. Task Difficulty and Dual-Task Interference on Gait Speed

The mean gait speeds for young and older adults in each condition and each gait task are shown in Table 2.

### Table 1: Characteristics (mean, SD) of sample.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young adults ((n = 20))</th>
<th>Older adults ((n = 15))</th>
<th>(P^\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21.7 (1.6)</td>
<td>72.1 (5.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Female gender (number, %)</td>
<td>18 (90%)</td>
<td>12 (80%)</td>
<td>.418</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.3 (0.7)</td>
<td>12.4 (2.0)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MMSE(^a) (max. 30)</td>
<td>28.6 (1.1)</td>
<td>27.5 (2.2)</td>
<td>.080</td>
</tr>
<tr>
<td>Activities-specific balance confidence scale (max. 100)</td>
<td>95.8 (4.9)</td>
<td>85.9 (10.9)</td>
<td>.004</td>
</tr>
<tr>
<td>Digit symbol copy (time in seconds to complete)</td>
<td>57.4 (6.9)</td>
<td>84.1 (21.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Digit symbol substitution (number correct in 90 seconds)</td>
<td>74.2 (9.1)</td>
<td>46.1 (13.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Stroop color-word interference(^b)</td>
<td>24.1 (7.5)</td>
<td>35.8 (13.0)</td>
<td>.005</td>
</tr>
<tr>
<td>Comprehensive trail-making test interference(^c) (seconds)</td>
<td>13.8 (9.7)</td>
<td>35.1 (24.8)</td>
<td>.006</td>
</tr>
<tr>
<td>TUG (seconds)</td>
<td>7.4 (0.7)</td>
<td>9.6 (2.4)</td>
<td>.003</td>
</tr>
</tbody>
</table>

\(^\dagger\) t-test for independent samples.

Abbreviations: MMSE: Mini Mental State Examination; TUG: Timed Up and Go test; \(P\) value is for t-test comparing young and older adults.

\(^a\) MMSE measures global cognitive function; Digit symbol modalities test measures speed of processing and attention; Stroop and Trail Making Tests measure executive function; TUG measures balance during functional performance.

\(^b\) Stroop interference score calculated as difference in number correct between baseline condition and interference condition.

\(^c\) Trail-making test interference score calculated as difference in time (seconds) between time to complete Trail 5 and Trail 1.
Table 2: Mean (SD) gait speeds (m/s) for each condition and each gait task. Values are only from the subjects with gait speed data for all conditions.

<table>
<thead>
<tr>
<th>Gait task</th>
<th>Young adults (n = 19)</th>
<th>Older adults (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-task</td>
<td>Dual-stroop</td>
</tr>
<tr>
<td>SS</td>
<td>1.50 (0.17)</td>
<td>1.49 (0.16)</td>
</tr>
<tr>
<td>FC</td>
<td>1.97&lt;sup&gt;b&lt;/sup&gt; (0.21)</td>
<td>1.90 (0.17)</td>
</tr>
<tr>
<td>OB</td>
<td>1.96&lt;sup&gt;c&lt;/sup&gt; (0.21)</td>
<td>1.88&lt;sup&gt;bc&lt;/sup&gt; (0.19)</td>
</tr>
<tr>
<td>Mean</td>
<td><strong>1.81</strong> (0.17)</td>
<td><strong>1.76</strong>&lt;sup&gt;a&lt;/sup&gt; (0.15)</td>
</tr>
</tbody>
</table>

SS: walking at self-selected speed, FC: walking at fastest comfortable speed, OB: walking at fastest comfortable speed with obstacle crossing.

<sup>a</sup>Significant differences between single-task and dual-task (none of the differences between the two dual-tasks were significant), P ≤ .05 (Tukey’s HSD).

<sup>b</sup>Significant differences between self-selected and fast, P ≤ .05 (Tukey’s HSD).

<sup>c</sup>Significant differences between self-selected and fast obstacle, P ≤ .05 (Tukey’s HSD).

<sup>d</sup>Significant differences between fast and fast obstacle, P ≤ .05 (Tukey’s HSD).

<sup>∗</sup>Significant difference between older adults and young adults, P < .001.
Participants significantly increased their walking speed when instructed to walk at their fastest comfortable speed. Among young adults, there were no significant differences in average gait speed between FC and OB for single-task or dual-task walking (Table 2). However, for older adults, average gait speed in OB was significantly slower than FC (Table 2). Table 2 also illustrates that there were significant declines in gait speed during the Stroop and clock tasks relative to single-task walking in both groups during the obstacle condition. Both groups had a significant reduction in FC walking speed for the clock task but not the Stroop task. In the SS condition, the older adults reduced their gait speed during Stroop but not clock task. Young adults had no significant change in gait speed in either dual-task in SS.

These findings are corroborated by the significant Gait Task × Cognitive Task × Group interaction effect on DTEg, $F(2, 56) = 3.17, P = .050, \eta_p^2 = .10$. Although the statistical significance was marginal, the effect size was large. Follow up two-way ANCOVAs revealed that the three-way interaction occurred because the Cognitive Task × Group interaction was significant for the FC gait task ($P < .001; \eta_p^2 = .39$), but not for SS ($P = .794; \eta_p^2 < .01$) or OB ($P = .376; \eta_p^2 = .03$) (Figure 1). Specifically, in FC, the dual-task cost (negative DTE) on gait speed for the older adults during the clock task was significantly greater than that of young adults, and was also greater than DTEg during the Stroop task for either group (Figure 1). In SS and OB, there was no effect of cognitive task on DTEg for either group, although Figure 1 shows a tendency for a larger dual-task cost in the clock task in OB among older adults.

### 3.2. Task Difficulty and Dual-Task Interference on Cognition

Young adults had mean accuracy of 99% (SD 0.01) in the Stroop task and 97.2% (SD 0.1) in the clock task. Older adults, on average, were significantly less accurate than young adults ($P < .001$), with lower mean accuracy in the clock task ($M = 83.6\%$, $SD = 0.2$) than the Stroop task ($M = 93.1\%$, $SD = 0.1$) ($P = .045$). Mean values for DTErt and DTEacc for each gait task and cognitive task are presented in Table 3. After adjusting for education, there were no significant main effects or interaction effects in the Gait Task × Cognitive Task × Group ANCOVA on DTErt or DTEacc. As illustrated by the wide confidence intervals in Table 3, there was large variability in the dual-task effects on both reaction time and accuracy for the Stroop and clock tasks.

Education was significantly related to DTEacc in the OB condition ($r = .38, P = .026$); lower levels of education were weakly associated with larger dual-task costs in accuracy on the clock task during obstacle crossing. Before adjusting for education, the three-way interaction on DTEacc was significant due to a Gait Task × Cognitive Task interaction for older adults but not young adults: dual-task cost on accuracy was significantly greater in the clock task during OB than in any other task among older adults; the effect was not significant after adjusting for education.

### 4. Discussion

The purpose of this study was to determine the effect of gait and cognitive task difficulty on dual-task interference in aging. An important finding was that young adults were able to maintain fast walking speed in the obstructed condition with or without a simultaneous cognitive task, whereas older adults could not maintain fast walking speed in the obstructed condition even when no additional cognitive task was required. However, fast-obstacle walking speeds for older adults were still significantly faster than self-selected gait speed during single-task and Stroop task, but not in the clock task. In other words, although older adults reduced their gait speed in the fast-obstructed condition relative to fast-unobstructed walking, they were still able to walk faster than their preferred speed, except when they had to perform the clock task while stepping over the obstacle. This suggests that
among older adults the attentional demands of performing a
difficult cognitive task interfere with the attention processing
requirements of negotiating an obstacle. Indeed, obstacle
negotiation requires attention to spatial characteristics of gait
in order to adjust strides and avoid hitting the obstacle. It is
likely that the older adults slowed down as an adaptive safety
strategy to avoid making motor errors when stepping over
the obstacle, and that this effect was exaggerated when the
added cognitive task demanded greater attentional resources.

Consistent with previous research [17], older adults
demonstrated a significant dual-task decline in gait speed
during the Stroop task whereas young adults did not. Young
adults, however, experienced a significant dual-task decline in
gait speed during the Stroop task in the fast-obstacle
condition. This finding suggests that in more attention-
demanding gait tasks such as obstacle avoidance, a relatively
simple cognitive task can impact gait speed, even in healthy
young adults. Whereas the Stroop task affected walking
speed in the fast-obstructed condition but not the fast-
unobstructed condition, the clock task significantly reduced
speed in both fast-obstructed and fast-unobstructed
walking conditions. Thus, more difficult cognitive tasks may
amplify dual-task interference in gait speed in easier gait
tasks. The three-way interaction on DTEg corroborates the
findings for gait speed and provides evidence for differential
effects of gait and cognitive task difficulty on cognitive-motor
interference during walking between young and older adults.

We hypothesized that increasing the attentional demands of gait
would reduce the dual-task costs on gait speed due to
increased allocation of attentional resources required for the
gait task. In contrast to our hypothesis, there was a tendency
for dual-task effects on gait speed to increase with increasing
gait task difficulty, although this was only significant for
the older adults in the clock task in the FC condition (see
Figure 1). It is possible that because we did not instruct the
participants where to prioritize their attention during the
dual-task conditions, they chose to slow down to optimize
safety and/or to maintain performance on the cognitive
task. The large variability in the dual-task effects however,
especially for cognitive task performance, implies that par-
ticipants used a range of strategies to perform the dual-
tasks. Future research should concentrate on identifying
whether personal characteristics influence how individuals
spontaneously allocate their attention during gait-related
dual-task situations and whether particular subgroups of
older adults are vulnerable to the effects of task difficulty.

An important finding from this study was the effect that
controlling for education had on the dual-task interference
effects on cognition. Analysis of the unadjusted means
showed that the dual-task cost on accuracy in the clock task
was significantly greater during obstacle avoidance than in
any of the other gait conditions, but only for older adults.
However, after controlling for between-group differences in
education, the Cognitive Task by Gait Task interaction
for older adults was no longer significant. The lack of
significant interaction effects for cognitive variables after
controlling for education suggests that education may play an
important role in counteracting dual-task costs on cognitive
task performance, especially accuracy. It may be that more
education leads to fewer errors in cognitive processing during
dual-task walking, regardless of the difficulty of the gait
or cognitive task. That is, greater education may increase
cognitive reserve and thereby reduce susceptibility to dual-
task interference. The idea that education contributes to
cognitive reserve, and that increased cognitive reserve can
limit clinical expression of cognitive changes is supported by
strong evidence from the field of dementia research [29, 30].

Although we tried to simulate the challenges of real-
world walking demands by adding elements of speed and
obstacle negotiation to our gait tasks, a limitation of
this study is that the research was still conducted in a
quiet research laboratory. Thus, it remains unknown how
real-world environmental factors (e.g., noise, distraction)
affect dual-task interference. Furthermore, we assumed a
hierarchical increase in gait task difficulty between walking
at self-selected speed, walking at fastest comfortable speed,
and walking fast while stepping over an obstacle. However,
we did not ask the participants of their perceptions of
the tasks. Finally, the findings from this study may be
limited in their generalizability due to the small sample
size and the predominance of women in the sample. Thus,
the findings should be viewed as preliminary; investigations
involving larger, more representative samples are needed
to examine the interactions between age group, gait task
difficulty, and cognitive task difficulty on cognitive-motor
interference. In the future, manipulating the timing of
the onset of the stimulus in the obstacle negotiation path
may provide more insight into the interactions between

| Table 3: Adjusted means (95% confidence intervals) for dual-task effects on reaction time (DTErt) and accuracy (DTEacc) for each cognitive
task as a function of gait task. Positive values indicate a dual-task benefit relative to single-task; negative values indicate a dual-task cost relative to single-task performance. None of the main effects or interactions in the ANCOVA were significant for DTErt or DTEacc. |

<table>
<thead>
<tr>
<th></th>
<th>STROOP</th>
<th>CLOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Self-selected</td>
<td>Fast comfortable</td>
</tr>
<tr>
<td><strong>Young</strong></td>
<td>−7.6 (−14.8, −0.4)</td>
<td>−0.5 (−8.1, 7.2)</td>
</tr>
<tr>
<td><strong>Older</strong></td>
<td>−3.7 (−12.4, 5.0)</td>
<td>−5.2 (−14.5, 4.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DTEacc (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fast comfort</td>
<td>Fast obstacle</td>
</tr>
<tr>
<td><strong>Young</strong></td>
<td>4.7 (−3.0, 12.5)</td>
<td>18.4 (11.2, 25.7)</td>
</tr>
<tr>
<td><strong>Older</strong></td>
<td>14.5 (5.1, 23.9)</td>
<td>14.7 (5.9, 23.5)</td>
</tr>
</tbody>
</table>
attentional processing associated with obstacle avoidance and the attention processing of an additional cognitive task.

5. Conclusions

In conclusion, the results of this study suggest that obstacle negotiation at fast walking speed, such as when stepping up a curb to avoid traffic, is highly attention-demanding for older adults and significantly compromises the ability to maintain walking speed. This study provides evidence that gait task difficulty influences dual-task effects on gait speed, especially in older adults. Moreover, the effects of gait task difficulty on dual-task interference appear to be influenced by the difficulty of the cognitive task. Education and/or cognitive reserve may be an important factor influencing cognitive-motor interference, especially in terms of performance of the cognitive task.

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