Personalising exercise recommendations for brain health: considerations and future directions

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ABSTRACT

The societal value of strategies that delay the onset and progression of dementia cannot be overstated. Physical activity—unstructured and structured—is a promising, cost-effective strategy for the promotion of brain health. However, a large degree of variation exists in its efficacy. Therefore, to increase its utility as 'medication' for healthy cognitive ageing, it is imperative to identify key moderators and mediators of the positive effects of targeted exercise training on brain health. In this commentary, we focus on the type of targeted exercise training, the determinants of individual variation, including biological sex and genotypic factors, and the mechanisms by which exercise exerts its influence on the brain. We argue that a better understanding of these factors will allow for evidence-based, personalised, tailored exercise recommendations that go beyond the one-size-fits-all approach to successfully combat dementia.

INTRODUCTION

Accumulating evidence across several disciplines support the notion that leisure time physical activity and targeted exercise training are promising strategies for the promotion of brain health across the adult lifespan. Human and animal studies show that physical activity augments cognitive function, brain structure and brain function. Prospective epidemiological data indicate that engaging in higher levels of physical activity is associated with reduced risk of dementia.[1–3] Specifically, a meta-analysis of 16 prospective epidemiological studies found that higher levels of physical activity at baseline reduced the risk of developing dementia from all causes by 28% and of developing Alzheimer's disease (AD) by 45%.[4] A meta-analysis of 15 studies among individuals without dementia found that high levels of physical activity reduced risk of cognitive decline by 38% (HR 0.62, 95% CI 0.54 to 0.70), while low to moderate levels reduced risk by 35% (HR 0.65, 95% CI 0.57 to 0.75).[5] Results from randomised controlled trials (RCTs) further corroborate the link between structured physical activity and brain health, as they consistently show that engaging in targeted exercise training programmes promote cognitive performance in older adults.[6–12] Moreover, neuroimaging studies show changes in brain structure and connectivity in relation to exercise training, indicating enhanced functional brain plasticity.[13–17] Supporting evidence is provided by rodent studies that show the benefits of voluntary wheel running on cognitive performance, as well as underlying neural circuitry and neuroplasticity markers in key brain regions involved in learning and memory, including the hippocampus and prefrontal cortex (for review, see[18–21]). However, despite this promising body of literature, a large degree of variation still exists in exercise efficacy for improving cognitive function in humans, as several meta-analyses of RCTs have found modest to minimal or no effects of engaging in targeted exercise training (effect size estimates ranging from −0.26 to 0.38).[22–24]

To maximise its utility and effectiveness, it is imperative to use evidence-based recommendations to personalise targeted exercise recommendations. However, we currently lack the prerequisite knowledge regarding potential factors that moderate exercise efficacy. A better understanding of *what type* of exercise regime is most beneficial for cognitive performance and for *whom*, and *how* each type of exercise exerts its influence on the brain will lead to tailored strategies that go beyond the one-size-fits-all approach, allowing exercise to be prescribed as medication for healthy cognitive ageing. The purpose of this commentary is to outline and describe potential factors that moderate or mediate the positive relationship between targeted exercise training and brain health that require focused and extensive consideration in future human and animal studies. Specifically, we will describe the type of targeted exercise training (the what), potential moderators, including biological sex and genotypic factors (the who), and the mechanisms by which targeted exercise training exerts its influence on the brain (the how).

THE WHAT: TYPE OF EXERCISE

The relationship between exercise and cognition may be dependent on the *type* of exercise being employed.[18 25 26] Broadly speaking, there exist two distinct types of exercise: (1) aerobic training (AT; eg, running, walking); and (2) resistance training (RT; eg, weight lifting). Although the vast majority of research has focused exclusively on AT, AT and RT have been found to enhance cognitive and brain outcomes in older adults.[6 27–30] AT and RT have both common and divergent physiological effects. Both types of exercise reduce cardiometabolic risk factors; however, AT specifically improves cardiovascular fitness (ie, maximum oxygen uptake) and cardiovascular health, whereas RT improves muscle mass and strength.

The specific neurobiological mechanisms that support the positive effects of AT and RT on the brain are far from fully understood and largely stem from rodent studies restricted to AT. Cotman *et al*[31] introduced an integrative model in which AT induces inter-related mechanisms, including

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neurotrophic factor cascades (ie, brain-derived neurotrophic factor, BDNF; insulin-like growth factor 1, IGF-1; vascular endothelial growth factor), a central mechanism mediating exercise-dependent benefits in cognitive performance, synaptic plasticity and neurogenesis. In mouse and rat studies, increases in central BDNF levels mediate the cognitive-enhancing and neuroplasticity-enhancing effects of AT (ie, voluntary wheel running).[15 18–20] In humans, the evidence supporting the role of BDNF in the relationship between AT and cognition is equivocal, with some studies finding increased levels and other studies finding no change in systemic BDNF following long-term AT.[32] Several factors have been proposed to help explain the discrepancies in study results, including timing of BDNF measurement in relation to the last AT bout, exercise frequency (single vs repeated sessions), matrix in which BDNF is measured (serum vs plasma), age and sex of participants (see below). Furthermore, two forms of BDNF exist as pro-BDNF is the precursor molecule and it is converted to mature BDNF. These two forms of BDNF have opposing effects on neuronal morphology and physiology, as pro-BDNF is neurotoxic and mature BDNF is neuroprotective.[33] Studies likely differ in the assays and the specific form of BDNF measured as ELISA and multiplexing kits can differ widely on the specific form of BDNF measured.[34]

Despite a dearth of mechanistic evidence, the neurobiological mechanisms underlying the cognitive-enhancing effects of RT may be different from those of AT. A study conducted in male adult rats demonstrated that divergent mechanistic pathways underlie AT and RT, despite common cognitive and neuroplastic outcomes.[35] Specifically, while AT and RT improved hippocampus-dependent spatial reference learning and memory in adult male rats and increased the neuroplasticity markers synapsin 1 and synaptophysin in the hippocampus, AT preferentially increased BDNF, while RT preferentially increased IGF-1 in the hippocampus.[35] Furthermore, the increase in new neurons in the dentate gyrus of the hippocampus (hippocampal neurogenesis) that is seen in response to AT may not occur after RT in adult male rats.[36] In line with these results, in humans, AT significantly increased hippocampal volume, whereas RT failed to do so in older women with probable mild cognitive impairment (MCI).[29] Conversely, in the same population, RT significantly changed functional regional blood flow of the brain during associate memory performance, while AT had no effect.[30] Taken together, the literature suggests that AT and RT may promote brain function via divergent and common biological pathways. Thus, the type of exercise is an important factor to consider when prescribing exercise regimes to individuals. Importantly, type of exercise may further interact with other factors, such as sex and genotype, to moderate the magnitude of benefit on cognitive and brain outcomes.

THE WHO AND THE HOW: BIOLOGICAL SEX, BDNF, GENOTYPE AND THEIR INTERACTION

Biological sex

Women are disproportionally affected by AD, showing a greater risk and prevalence of the disease compared with men,[37] as well as faster rate of cognitive and functional decline after diagnosis.[38] Moreover, there is a faster rate of progression from MCI, an intermediate stage between normal cognitive changes associated with ageing and dementia, to AD in women compared with men.[39] In support of this, women with MCI also show more rapid decline in brain volume compared with men.[40] Importantly, some studies find a higher prevalence of non-amnestic MCI in men,[41 42] which is associated with non-AD dementias such as vascular cognitive impairment. Thus, the issue of a sex difference in dementia is complex and is likely dependent on many factors, including the type of dementia under consideration, as the greater risk of developing AD in women may not extend to other dementias.[37 43] Regardless of the direction of effect, the sex difference in AD and other dementias leads to the intriguing suggestion that treatment efficacy may also vary by sex.

Preliminary evidence suggests that the size of the ameliorative effects of physical activity on cognitive ageing may depend on biological sex. This was first suggested in a meta-analysis of 18 RCTs by Colcombe and Kramer[9] who found that the effect of exercise with an aerobic component on cognition was statistically larger in samples that consisted of more than 50% women (effect size: 0.604) compared with samples of more than 50% men (effect size: 0.150). Evidence from subsequent studies supports the notion that AT elicits greater cognitive benefits in women than in men. Importantly, only a limited number of studies have stratified their analyses by sex. As reviewed by Hogervorst *et al*,[44] three observational prospective studies found that the association between physical activity and reduction in the risk for dementia was greater in women. Furthermore, in the Canadian Study of Health and Aging prospective cohort study, self-reported moderate–high exercise was associated with reduced risk of cognitive impairment and dementia of any type in aged women but not men.[45 46] Although using data from the same cohort, Fallah *et al*[47] failed to find this association employing a four-parameter truncated Poisson distribution. In a cohort of elderly Chinese participants, a lack of exercise at baseline was associated with a statistically significant twofold increase in the risk of cognitive impairment over a 36-month period in women only.[48] Contrary to the above findings, in a cross-sectional analysis of self-reported level of physical activity, Lindwall *et al*[49] found that engaging in light exercise was associated with better executive functions and global cognition compared with never exercising in men, but this same relationship was not seen in women. The authors, however, note that the discrepancy in their results was likely due to the fact that the women who never exercised in their study scored higher on the cognitive tasks compared with the men who never exercised, indicating that there was more room for improvement in the men with increasing level of exercise.

To date, RCTs that specifically examine the potential moderating effect of biological sex are rare. Engaging in a 12-month moderate intensity walking programme designed to improve aerobic fitness resulted in improved attention and memory in older women with MCI with increasing number of exercise sessions attended, whereas in men, only memory was improved.[50] Baker *et al*[12] found that 6 months of high-intensity AT had sex-dependent effects on cognition compared with stretching control programme, such that women showed improvements in multiple tests of executive functions and men only showed improvements in one test. More recent evidence from human neuroimaging studies show that a greater amount of low-intensity walking objectively measured is associated with statistically larger hippocampal volume among older women, but not among older men.[51] In rodents, AT results in beneficial functional and hippocampal adaptations in males and females.[19 21] However, few studies have *directly* compared men and women to address the question of potential sex differences in the magnitude of exercise efficacy. In adolescent rats, AT results in statistically enhanced hippocampal long-term potentiation, a cellular model of learning and memory, in males but not in females.[52] Furthermore, in a triple-transgenic mouse model of AD (3×Tg-AD), AT enhanced hippocampal-dependent reference

learning and memory to a greater extent in young adult female mice compared with male mice.[53] Together, these results suggest that there may be sex differences in the hippocampal response to exercise.

Biological sex and BDNF

The apparent sex difference in the exercise-induced cognitive response may be related to several factors, including differential regulation of BDNF. To date, the majority of studies have used only men or only women, not directly comparing the sexes. However, 5 months of voluntary wheel running in male and female mice led to statistically greater BDNF mRNA expression and higher mature BDNF protein levels in the hippocampus of males compared with sedentary controls, but the same was not seen in females.[52] However, it is important to note that many studies find that wheel running increases BDNF levels in the female rodent hippocampus,[54] but this increase may not be to the same extent as found in males. A possible sex difference in the ability of AT to induce BDNF may also be seen in humans. A meta-analysis of 29 studies, the vast majority of which utilised AT programmes of differing lengths, found that biological sex moderated the effect of exercise on BDNF levels, as they found a statistically significant negative correlation between effect size and percentage of women in studies ($r(33)=-0.38$).[32] This sex-specific effect on BDNF may also extend to other forms of exercise, including RT. A recent study conducted in healthy older men and women indicated that engaging in 12 weeks (3×/week) of a moderate level of RT with a high number of repetitions led to statistically significant increase in circulating levels of total BDNF in serum assayed 24–48 hours after the last training session in men only.[55]

This seemingly contradicting finding that AT may increase cognition in women but may not increase BDNF may be related to several factors, such as timing of BDNF assessment after last exercise session, intensity of AT and the presence or absence of gonadal steroid hormones. The ability of exercise to increase BDNF in women may be dependent on gonadal steroid hormones, in particular oestradiol. Oestradiol, a neuroprotective hormone,[56] regulates BDNF expression in several ways. For example, exogenous administration as well as high endogenous levels of oestradiol induces BDNF in specific brain regions, including the hippocampus.[57] Oestradiol may increase BDNF levels via an oestrogen response-like element within the promoter region of the BDNF gene.[58] Importantly, it has previously been shown that the exercise effect on BDNF upregulation is reduced in ovariectomised female rats, which have a complete absence of gonadally derived oestradiol.[59] In humans, menopause results in the dramatic reduction, but not the complete absence, of circulating levels of several steroid hormones, including oestradiol. Although no study has directly compared the ability of exercise to induce BDNF levels in premenopausal versus postmenopausal women, examining the effect sizes of studies included in a meta-analysis by Szuhany *et al*[32] that looked at BDNF levels after regular programmed exercise indicates that larger effect sizes are found in studies with younger, premenopausal women (effect size range: 0.59–0.81) compared with older, postmenopausal women (effect size range: −0.17 to 0.19). Although BDNF levels were not assessed, indeed, short-term treatment with oestrogens (type not specified) enhanced the beneficial effects of higher aerobic fitness (assessed by VO_2 peak) on executive functions and prefrontal cortical grey matter volume in postmenopausal women.[60] Thus, these findings collectively suggest that exercise confers beneficial effects on cognition through different mechanisms or pathways in men compared with women and that women with greater levels of oestradiol may potentially benefit more from exercise.

Biological sex and genotype

Biological sex may also interact with different genes identified as potential risk factors for dementia and AD to explain variability seen in exercise efficacy.[18 20] The ε4 allele of the apolipoprotein ε (*APOE*) gene confers increased risk for accelerated cognitive decline and late-onset AD.[61] Carriers of the *APOE* ε4 allele are at increased risk to develop AD, as well as to develop AD at an earlier age.[61 62] Importantly, the deleterious effects of the *APOE* ε4 allele are more pronounced in women than in men in terms of risk for AD, AD-related pathology and cognitive decline (for review, see ref. 38). Several studies indicate that greater levels of physical activity have more profound beneficial effects on cognition and AD risk in *APOE* ε4 allele carriers than non-carriers in women specifically[63] and in both sexes.[64 65] However, other studies have not found this relationship between physical activity and the *APOE* ε4 allele.[66 67] Given the greater effect of this allele in women, it is possible that discrepancies in results between studies may be related to biological sex of participants. Future studies should endeavour to examine whether the *APOE* ε4 allele moderates the relationship between different forms of exercise and cognitive function.

The variation seen in exercise efficacy related to biological sex may also be related to the presence of a functional single-nucleotide polymorphism within the prodomain region of the human BDNF gene resulting in an amino acid substitution of valine (Val) to methionine (Met) at position 66, termed the Val66Met substitution. The Met allele alters intracellular trafficking of the precursor form of BDNF, reducing the activity-dependent secretion of the mature form of BDNF.[68] Carriers of the Met allele have reduced memory and smaller hippocampal volumes compared with Val/Val carriers in men and women.[68–71] Findings from the few studies that have investigated the moderating influence of the BDNF polymorphism on the effects of AT are equivocal. Self-reported higher levels of physical activity improved the Met-associated reduction in working memory in middle-aged men and women.[72] As well, in older male and female Val/Val carriers, higher levels of self-reported physical activity were statistically associated with increased volume of the hippocampus,[73] decreased dementia risk[74] and better episodic memory.[75] Engagement in a multimodal exercise programme also increased serum BDNF in male and female Val/Val carriers only.[76] Importantly, none of these studies examined biological sex in their analyses. However, there are important sex differences in the effects of the Met allele on hippocampal blood flow, age-related cognitive and brain volume decline and on AD risk, with female Met carriers showing the greatest decrements.[77–81] These findings suggest that biological sex may interact with the BDNF polymorphism to moderate exercise efficacy. Thus, it is imperative to directly examine the role of biological sex in the relationship between exercise and the BDNF polymorphism.

FUTURE DIRECTIONS

Worldwide, it is estimated that by the year 2030, 75.6 million people will have dementia and this number will triple to 135.5 million by the year 2050.[82] In Canada, it has been estimated that if exercise reduced dementia by 1/100th of 1%, this would lead to savings of $3.3M.[83 84] Thus, it is crucial to maximise the beneficial effects of exercise for brain health and dementia prevention by developing personalised, targeted exercise recommendations and guidelines. To achieve this, it is critical to

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identify key moderators and the underlying mechanisms of different types of exercise regimes. In this commentary, we have argued that to increase the utility and efficacy of '*exercise as medicine*', the priority of future studies should be to determine what type of exercise elicits the greatest benefits for cognition and brain function and for whom using sufficiently powered RCTs. Specifically, we discussed the importance of biological sex and possible interactions with the *APOE* ε4 allele and the BDNF Val66Met polymorphism in exercise efficacy. A major hindrance to directly and closely examining these factors and their interactions is the insufficient sample sizes in previous studies, particularly in RCTs. Large samples are especially important in genetic analyses in which the distribution of the variant allele may be low, prohibiting our ability to examine interactions with sex. Thus, it is crucial to pool resources and maximise existing cohort studies to obtain large enough sample sizes to test the interaction between biological sex and genotypic variation. Ultimately, identifying biological and genetic moderators of exercise efficacy will allow for more efficient and targeted deployment of current interventions and will also spur the development of alternative tailored interventions for individuals for whom current strategies are ineffective to promote healthy cognitive ageing.

What are the findings?

- Type of targeted exercise training may interact with biological sex to mediate their effects on the brain health.
- A sex difference may exist in exercise efficacy, with women benefiting more than men in cognitive outcomes.
- APOE4 and brain-derived neurotrophic factor Val66Met polymorphism may interact with biological sex to moderate the benefits of targeted exercise training on the brain.
- Future research should focus on understanding factors that moderate and mediate the positive effects of exercise on cognition to increase the utility of targeted exercise training in combating dementia.

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