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Review

Exercise and the Aging Brain: Considerations for Sex Differences

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Abstract. Engaging in targeted exercise interventions is a promising, non-pharmacological strategy to mitigate the deleterious effects of aging and disease on brain health. However, despite its therapeutic potential, a large amount of variation exists in exercise efficacy in older adults aged 55 and older. In this review, we present the argument that biological sex may be an important moderator of the relationship between physical activity and cognition. Sex differences exist in dementia as well as in several associated risk factors, including genetics, cardiovascular factors, inflammation, hormones and social and psychological factors. Different exercise interventions, such as aerobic training and resistance training, influence cognition and brain health in older adults and these effects may be sex-dependent. The biological mechanisms underlying the beneficial effects of exercise on the brain may be different in males and females. Specifically, we examine sex differences in neuroplasticity, neurotrophic factors and physiological effects of exercise to highlight the possible mediators of sex differences in exercise efficacy on cognition. Future studies should address the potential sex difference in exercise efficacy if we are to develop effective, evidence-based exercise interventions to promote healthy brain aging for all individuals.

Keywords: Exercise, sex differences, brain, cognition, aging, dementia, Alzheimer's disease, neuroplasticity, neurotrophic factors, physical activity

INTRODUCTION

Worldwide, over 47 million people suffer from dementia and this number is expected to reach 74.7 million by the year 2030 and 131.5 million by 2050; the estimated total worldwide economic burden will be 2 trillion dollars by 2030 [1]. In the face of these staggering numbers, the societal value of identifying and developing effective intervention and prevention strategies is of utmost importance [2]. Effective pharmacological treatments of dementia remain elusive. Engaging in targeted exercise interventions is a promising, non-pharmacological strategy to mitigate the deleterious effects of aging and disease on brain health [3, 4]. However, despites its therapeutic potential, a large amount of variation exists in exercise efficacy [5–8]. To maximize effectiveness, it is vital to understand the sources of this variation and to identify factors that increase the likelihood of positive cognitive outcomes from exercise interventions. Given the greater prevalence of AD and faster rate of progression from mild cognitive impairment (MCI) to AD in females compared with males [9],

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there is a need to assess potential sex differences in treatment efficacy, including different exercise interventions. Unless otherwise specifically stated, this review focuses on older adults, aged 55 and older.

SEX DIFFERENCES IN DEMENTIA AND ASSOCIATED RISK FACTORS

Sex differences exist in dementia, although the relationships are complex and multifactorial. Females are disproportionally affected by AD, showing twofold greater risk at later ages [10], faster progression of brain atrophy (1–2.5% per year) [11, 12] and greater AD-related pathology [13–15] than men. Conversely, some studies find that males are at higher risk for MCI, a prodromal stage between normal age-appropriate cognitive changes and dementia [16], for both the amnestic and non-amnestic type [17–19]; although, not all studies find this male-advantage [20, 21]. Recently, it has been suggested that diagnosis of MCI may be delayed in females, which may be responsible for the possible increased risk for MCI seen in males. Specifically, females show greater verbal memory performance than males, despite similar levels of neurodegeneration [22, 23]. This finding suggests that females have cognitive reserve within this domain which delays manifestation of deficits until greater levels of pathology are present.

Sex differences in genetic risk factors

Sex differences also exist in risk factors for dementia. Apolipoprotein E ε4 (APOE4) is the greatest genetic risk factor for AD [24], and despite similar frequencies, females show greater detrimental effects. Female carriers of the ε4 allele have about a 1.5x higher risk for AD [25–28], more amyloid plaques and neurofibrillary tangles [29] and present with greater verbal memory declines over time [30] compared with male carriers. Further, APOE4 carriers show lower serum levels of BDNF, an association only seen in females with AD [31]. On the other hand, levels of cerebral microbleeds, a component of vascular cognitive impairment, are exacerbated (2-fold) in APOE4 males compared with females [32]. Further, recent work suggests the greater risk associated with carrying one copy of the ε4 allele in females may only be seen at younger ages, specifically between 65 and 75 years [26]. Thus the relationship between APOE4, sex and dementia is not straightforward.

Sex differences in cardiovascular risk factors

Peripheral cardiovascular risk factors for dementia include hypertension, type 2 diabetes, obesity, atherosclerosis, and hypercholesterolemia. Cardiovascular risk profiles vary by sex and thus, their contributions to the development of dementias could also differ by sex [33]. Indeed, evidence does suggest the contribution of some cardiovascular risk factors may be greater in older females than older males [34, 35]. For example, the increased risk for vascular cognitive impairment from type 2 diabetes is 19% higher in older females than males [36]. In males, total cholesterol, a biomarker of cardiovascular health, is strongly associated with AD symptoms [37]. Further, a sex difference exists in vascular aging, a main risk factor for cardiovascular disease. Specifically, endothelial dysfunction, a key component of vascular aging, occurs gradually in males commencing approximately in midlife (approximately the third decade of life in this study), whereas in females, commencement is delayed and accelerates after the onset of menopause and loss of estrogens [38].

Sex differences in inflammation as a risk factor

Systemic and central (neuro) inflammation is a risk factor for AD and other dementias, and may be a stronger risk for aged females [37]. Aging is accompanied by a chronic, low-grade inflammatory phenotype evidenced by elevated serum levels of several pro-inflammatory cytokines including IL-6 and TNF-α and decreased levels of anti-inflammatory cytokines including IL-10 [39]. High levels of pro-inflammatory cytokines are related with cognitive impairment, MCI and AD [40]. Importantly, in humans the association between increased peripheral levels of pro-inflammatory cytokines and cognitive impairment is seen in older females but not older males [39, 41]. Within the brain, age-related induction of neuro-inflammatory genes differ between males and females, with females showing enhanced expression [42, 43]. Likewise, the aged female hippocampus presents with 25–40% more activated microglia, the brain's resident immune cells that secrete cytokines, and astrocytes compared to age-matched males [44]. Interestingly, accelerated or increased microglial development has been seen in AD brains compared to age-matched controls, and in mice, females show faster microglial maturation in the hippocampus than males [45], suggesting that microglia may be involved in the

sex differences seen in AD. Taken together, this suggests that sex differences may exist in the association among inflammation and dementia. However, whether inflammation is involved in the etiology or progression of dementia or both is currently under investigation [46].

Sex differences in hormones as a risk factor

Sex-specific risk factors for cognitive impairment also include loss of sex steroid hormones with age. In women, estrogens are rapidly lost with the onset of menopause which occurs on average at 51 years of age, whereas in men the loss of bioavailable testosterone is much more gradual with approximately 1-2% reduction per year beginning in the third decade of life [47, 48]. Menopause is associated with increased levels of AD biomarkers including hypometabolism, Aβ deposition, and decreased hippocampal volume [49] and surgical menopause that occurs prior to natural menopause is further associated with an increased risk of AD [50]. Use of hormone replacement therapy (HRT) may reduce this risk [51]. However, timing of HRT commencement in relation to estrogen loss is important as initiation of HRT years after menopause is associated with increased risk of dementia, whereas initiation closer to the onset of menopause may not be [52]. Furthermore, the type of estrogen taken is of considerable importance, as estrone and estradiol have different effects on cognitive performance [53–55].

Sex differences in social and psychological risk factors

Social and psychological risk factors for dementia may also differ by sex. For example, higher education and occupational attainment are protective factors in both females and men, as they are believed to increase cognitive reserve delaying the onset of cognitive deficits through engagement of compensatory mechanisms [56–59]. However, historically, females have had less opportunities to obtain higher education than men, thus low education may be a greater risk factor for females [60]. Women are most often the primary caregivers for people with dementia [61], a source of considerable psychological stress with physiological consequences. For example, premenopausal female caregivers (average age 38) show more rapid cellular aging, as indexed by telomere length [62]. Interestingly, although spousal caregivers of both sexes show significantly increased risk of developing dementia, the risk is 3x higher in male caregivers [63].

EFFECTS OF DIFFERENT EXERCISE INTERVENTIONS OF COGNITION AND BRAIN IN OLDER ADULTS

Broadly, there are two distinct forms of exercise: 1) aerobic training (AT; e.g., running, walking), aimed at improving cardiovascular health; 2) resistance training (RT; e.g., lifting weights), aimed at improving muscle strength. Although most research to date has focused on AT, both forms of exercise have beneficial effects on cognitive and brain plasticity in older adults [3, 64–67], although the underlying mechanisms may be different. Longitudinal cohort studies that rarely differentiate between types of exercise, show engaging in physical activity is associated with less cognitive decline over time in older adults [68–71]. Results from randomized controlled trials (RCTs) of targeted interventions provide stronger support for the relationship between exercise and cognitive functioning.

Meta-analyses of RCTs in older adults show that engaging in targeted AT programs promotes cognitive performance [5, 8, 67, 72, 73], although others have found modest to minimal or no effects [6, 74–76]. The beneficial effect of AT on cognitive functioning has been seen across different clinical and non-clinical populations, including MCI, vascular dementia and cognitively healthy older adults [77–80]. Studies suggest executive functions are the cognitive domain that most benefits from AT [5, 81]. Moreover, AT interventions can lead to changes in brain structure, activation, and connectivity, indicating enhanced functional brain plasticity [for example see 79, 82, 83–87], and recent work suggest that brains that are organized with greater connections within modules and less connections between modules are more likely to show AT-dependent gains in executive functions [88].

Although much less studied, RT in older adults is also beneficial for cognitive functioning [8, 67, 75]. In one of the first large-scale RCTs of RT, Liu-Ambrose and colleagues showed that engaging in progressive RT at 2 doses, once or twice per week, for 12 months improved the executive functions of selective attention and conflict resolution in older women [89], effects that were maintained for an additional 12 months post-training [90]. Previous to this RCT, evi-

dence from 2 smaller trials in men only indicated that RT was beneficial for cognition [91, 92]. Associative memory performance is also enhanced with 6 months of RT in older women [93]. The cognitive-gains from RT are further reflected in hemodynamic effects within the brain. Specifically, RT in older women led to functional changes within regions involved in executive functions – the anterior portion of the left middle temporal gyrus and the left anterior insula extending into the lateral orbital frontal cortex [94]; and associative memory – right lingual, occipital-fusiform, and right frontal pole [93]. Furthermore, twice-weekly RT reduced volume of white matter lesions [95] and reduced cortical white matter atrophy [90].

Despite common cognitive outcomes, AT and RT exert their benefits through distinct physiology and are possibly subserved by both divergent and common mechanistic pathways. For example, AT increases cardiovascular fitness as measured by maximum oxygen uptake while RT increases muscle mass and strength [96]. Work in young adult male rats suggests that while both AT and RT improved spatial learning and memory, AT preferentially increased brain-derived neurotrophic factor (BDNF) while RT preferentially increased a different neurotrophic factor, insulin-like growth factor-1 (IGF-1) [97]. On the other hand, both types of training reduce cardiometabolic risk factors for neurodegeneration [89, 98–103] and associated systemic inflammation [64, 96, 104, 105] to different degrees. Studies are required to compare and contrast these two forms of exercise as well as examine their combined influence on cognition and brain function.

POSSIBLE SEX DIFFERENCES IN EXERCISE EFFICACY

Possible sex differences in exercise efficacy: Meta-analytic findings

Older females greater than 65 years of age are more sedentary and engage in less physical activity than age-matched males [106, 107] and being sedentary may have greater negative impact on processing speed in older age in females then males [108]. Thus increasing physical activity levels in females may have a greater impact on cognition. Colcombe and Kramer [5] first suggested that females greater than 55 years of age may show greater cognitive benefits from AT. This was recently confirmed in a meta-analysis of RCTs showing that sex moderates the effect of exercise on cognitive function [8]. Specifically, AT was associated with a larger effect size in studies that utilized a higher percentage of females (over 71%) than studies with lower percentage of females for executive functions (effect sizes: 2.83 vs. 1.46) [8]. A similar female-advantage was found for rodent studies that utilized forced AT (effect size for female studies: 1.24; effect size for male studies: 0.53) but not voluntary AT for hippocampus-dependent learning and memory [109]. Further, human studies of RT as well as multimodal training (e.g., combined AT and RT) also show the female-advantage for executive functions [8].

Possible sex differences in exercise efficacy: RCT findings

Direct support for the supposition that older females show greater cognitive benefits from exercise than males is provided by a recent secondary analysis of a RCT of 6 months, 3 times per week progressive AT in participants with mild subcortical ischemic vascular cognitive impairment. Specifically, a significant interaction was found between treatment group (AT or control) and biological sex, with AT significantly improving the executive function of set-shifting in females (36% improvement in performance from baseline) but not males (31% decline in performance from baseline), an effect that was retained 6 months after trial termination [110]. Additional support for a possible sex difference in AT efficacy is found in two RCTs that stratified analyses by sex. In participants with MCI, Baker et al., [77] found AT increased performance compared to controls on 3 cognitive tests in females but only on 1 test in males. Additionally, increased adherence to a 12 month AT program was associated with improved attention and memory in older females with MCI and with only memory in older males [111]. Although no RCT has examined sex differences in brain outcomes, in a cross-sectional study Varma et al., [112] found that greater amounts of objectively measured walking activity over one week were significantly associated with larger hippocampal volumes among older females but not among males and, in another study, they found greater enhancements in the volume of the subiculum, which is part of the posterior hippocampus in females only [113]. Together these findings indicate that engaging in AT leads to greater beneficial effects on cognition in females than males.

HOW CAN SEX MODERATE EXERCISE EFFICACY?

Despite the many studies investigating the impact of exercise on cognitive and brain function in humans, comparatively little is known about the biological mechanisms underlying these effects, and whether these vary by sex is yet to be examined. Our current understanding of how exercise promotes cognitive and brain function largely stems from animal studies and is mainly restricted to AT as there is a dearth of mechanistic evidence for RT. Cotman [64] proposed an integrative model by which AT enhances cognition, brain function, and neuroplasticity through induction of neurotrophic factor cascades (i.e., BDNF, IGF-1, vascular endothelial growth factor (VEGF)). In support of this model, rodent studies indicate that central BDNF levels mediate the beneficial effects of AT on the brain [4, 65, 66, 114, 115]. In humans, although AT-induced increases in peripheral levels of BDNF are generally seen, some studies do fail to find this effect [116–119] and biological sex may be an important moderating factor [116]. BDNF supports neuronal survival and growth, synaptic plasticity, is involved in cellular mechanisms required for learning and memory, and sex differences exist in some of its functions [120–124]. Furthermore, AT benefits cognition through enhancements in neuroplasticity, including hippocampal neurogenesis; processes which also show sex differences. Physiological responses to exercise may also underlie the beneficial effects on the brain, and these may also help explain the sex difference in AT efficacy on cognition.

Sex differences in neuroplasticity

Rodent studies show that running benefits cognition through alterations in neuroplastic processes in key brain regions involved in learning and memory, including the hippocampus and prefrontal cortex (PFC) [for review see 4, 65, 66, 125]. Neuroplasticity, the ability of the adult brain to change, remodel and reorganize in response to the environment, includes changes in dendritic branching, synaptogenesis, angiogenesis, and neurogenesis. Many of these forms of neuroplasticity show sex differences and are altered by exposure to sex hormones, such as estradiol and testosterone [55, 126, 127]. Although a complete review of this topic is beyond the scope of this manuscript, we include a few examples to provide evidence that sex differences in exercise efficacy may be related to sex differences in neuroplasticity.

Sex differences exist in neuroplastic mechanisms at the structural, cellular, and molecular levels. Dendritic spine density on neurons in the CA1 region of the hippocampus respond to estradiol in female but not male rodents [128, 129], whereas spine density responds to testosterone in both females and males [129, 130]. Further, chronic stress causes retraction of apical dendrites of CA3 neurons of the hippocampus [131] and shrinkage of certain dendrites in the medial PFC [132] in males but not female rats. Adult hippocampal neurogenesis, the production of new neurons in the dentate gyrus in adulthood, is involved in learning and memory. Although female and male rodents do not seem to differ in overall basal levels of hippocampal neurogenesis, sex differences do emerge in response to stimulation including hormones and behavior [55, 127, 133]. For example, adult male rats show increases in hippocampal neurogenesis in response to spatial water maze training, a task with a male-advantage in performance, but females do not [134]. On the other hand, compared to males, females show greater increases in hippocampal neurogenesis after training on a task with a female-advantage in performance [135]. Further, exposure to stress in adolescence leads to sex-specific effects on hippocampal neurogenesis in adulthood, with female rats showing decreased and male rats showing increased levels of new neurons [136]. Another example of sex differences in neuroplasticity is seen in the response to chronic estradiol treatment of hippocampal neurogenesis, which was seen only in female rats and not male rats [137]. Sex differences extend to the molecular level, as signalling pathways subserving synaptic plasticity also differ between the sexes, including the calcium/calmodulin kinase kinase (CaMKK) pathway [for review see 126].

Sex differences in BDNF

BDNF is vital for neuronal health, survival and plasticity and, importantly, sex differences exist in its functioning [120–124]. The promoter region of the BDNF gene contains an estradiol-response-like element [138] and BDNF protein levels fluctuate across the estrus (in rodents) and menstrual (in humans) cycles with increases in estradiol associated with greater BDNF expression [139]. Within the mossy fiber pathway of the hippocampus BDNF expression is sex-dependent, with estradiol upregulating and testosterone suppressing BDNF levels [140]. Interest-

ingly, BDNF levels decline with age and functionally, this decline is related to impaired cognitive function in older females but not males [141]. Further evidence of sex differences in BDNF function are seen in studies of the BDNF Val66Met polymorphism; the Met allele is related to reduced activity-dependent secretion of the mature form of BDNF from neurons [142]. There are sex differences in the effects of the Met allele on hippocampal blood flow, age-related cognitive and brain volume decline and on AD risk [143–146]. Further, in the BDNF Val66Met mouse model, estradiol interacts with the Met allele to influence hippocampal memory and hippocampal BDNF expression across the estrous cycle [147]. Although not directly examined yet, there is some suggestion that sex differences exist in the AT-induced increase in circulating BDNF. In a meta-analysis of 9 studies, AT effects on BDNF levels were greater in studies utilizing female rodents compared to studies with male rodents (effect size for female studies: 2.59; effect size for male studies: 0.46) [109]. Furthermore, in humans, 6 months of AT increased circulating BDNF levels to a greater extent in females than males [110]. Therefore, sex differences in BDNF functioning may extend to AT-induction of BDNF.

Sex differences in the physiological adaptations to exercise

Sex differences exist in several key systems involved in exercise – including the respiratory system, musculoskeletal system, and cardiovascular system – as well as in the physiological responses of these systems to exercise training. Inherent functional and anatomical differences exist between the sexes in lung size and volume, airway diameter, diffusion surface, and maximal expiratory flow rates that affect exercise capacity across the lifespan, with females at a disadvantage [148, 149]. Age-dependent declines in aerobic capacity as measured by maximal oxygen uptake (V02 max) are greater in males than females in later life (60 years and older) [150, 151]. Premenopausal females and age-matched males differ in whole-body fuel use with females utilizing more lipids and males utilizing more carbohydrates and protein, which is related to sex differences in expression of genes associated with fat and carbohydrate metabolism and the sex hormone estradiol [152]. Muscle mass, strength and quality decline with age [153], and strength exercises help maintain and improve these indices in older adults [154]; however, the degree of benefit may differ by sex with males showing greater effects [155], although this is not consistently found [156]. Interestingly, supplementation with fish-oil in conjunction with RT was more effective in improving muscle quality in older females than males [157]. Age-associated changes in the cardiovascular system differ between the sexes [158] and influence exercise capacity. For example, decreases in maximal cardiac power output and reserve and maximal oxygen uptake seen in older males are preserved in older females [150, 159]. Conversely, studies report greater beneficial effect of exercise on some hemodynamic responses in older males than females, including lower blood pressure [160] and increased leg blood flow [161] in response to AT. Interestingly, these differences between males and females in the physiological responses to exercise may be related to sex differences in effective dose of exercise [for review see 161] and future studies are required to examine this. Further, engaging in chronic exercise attenuates age-associated endothelial dysfunction in older males [162, 163]. However, in older females the beneficial effects of exercise on endothelial function are diminished [162, 163] and may be dependent on the presence of estrogens [164].

FUTURE STUDIES AND CONCLUDING REMARKS

Engaging in physical activity is a promising, non-pharmacological strategy to mitigate the deleterious effects of aging and disease on cognitive and brain health. However, to maximize the utility of exercise, interventions should be targeted and tailored to specific populations and move beyond the 'one-size-fits-all' approach. Specifically, we argue that biological sex may be an important factor that moderates the relationship between exercise and cognition. A large gap exists in the current knowledge as few studies of exercise and brain health have directly examined this potential sex difference. It is also currently not known whether the proposed mechanisms underlying exercise effects on the brain differ between the two sexes. Thus future studies of RT and AT as well as alternative forms of exercise such as yoga, should address the potential sex difference in exercise efficacy if we are to develop effective, evidence-based exercise interventions to promote healthy brain aging for all individuals.

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