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Review article

Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans

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ABSTRACT

Exercise is a non-pharmacological strategy to mitigate the deleterious effects of aging on brain health. However, a large amount of variation exists in its efficacy. Sex of participants and exercise type are two possible factors contributing to this variation. To better understand this, we conducted a concurrent systematic review and meta-analysis of cognitively healthy older adults. Executive functions, episodic memory, visuospatial function, word fluency, processing speed and global cognitive function were examined for exercise- and sex-dependent effects. For executive functions, three types of exercise interventions – aerobic training, resistance training, and multimodal training (i.e., both aerobic and resistance training) – were associated with larger effect sizes in studies comprised of a higher percentage of women compared to studies with a lower percentage of women. This suggests that women's executive processes may benefit more from exercise than men. Regardless of sex, compared to control, all three exercise training approaches enhanced visuospatial function, but only multimodal training enhanced episodic memory. Overall, aerobic training led to greater benefits than resistance training in global cognitive function and executive functions, while multimodal combined training led to greater benefits than aerobic training for global cognitive function, episodic memory, and word fluency. Possible underlying mechanisms, including brain-derived neurotrophic factor and sex steroid hormones, are discussed.

1. Introduction

Exercise is an effective, economically attractive, non-pharmacological strategy to mitigate the deleterious effects of aging and disease on cognitive and brain health (Bherer et al., 2013; Davis et al., 2014, 2013, 2010). To maximize the utility of exercise as an intervention, it is imperative to provide personalized, evidence-based exercise recommendations. However, we currently lack the prerequisite knowledge regarding potential factors that mediate and moderate exercise efficacy. Specifically, a better understanding of what type of exercise regimen is most beneficial for cognitive performance, and for whom, is required to promote healthy cognitive aging.

Broadly, there are two distinct forms of exercise: (1) aerobic exercise training (AT; e.g., running, walking) and (2) resistance training (e.g., lifting weights). AT improves cardiovascular health and fitness and its effects on cognitive functioning and neuroplasticity have been widely studied in both humans and animals (Bherer et al., 2013; Barha et al., 2016; Cai and Abrahamson, 2016; Christie et al., 2008; Colcombe and Kramer, 2003; Cotman et al., 2007; Etnier et al., 2006; Heyn et al., 2004; Kelly et al., 2014; Knaepen et al., 2010; Szuhany et al., 2015; Trivino-Paredes et al., 2016; Voss et al., 1985, 2013). Observational studies generally show a positive relationship between higher aerobic fitness and cognitive performance (Etnier et al., 2006; Hamer and Chida, 2009; McAuley et al., 2004; Sofi et al., 2011). However, this association is less consistently seen in randomized controlled trials (RCTs) as considerable variation is found in the observed effect sizes. Hence, there is inconsistency in the findings of systematic reviews of RCTs of AT – with some concluding that AT has significant cognitive benefits (Bherer et al., 2013; Colcombe and Kramer, 2003; Heyn et al., 2004), while others remain inconclusive (Kelly et al., 2014; Smith et al., 2010; Young et al., 2015). In rodents, the beneficial effect of AT is more consistently seen in both young and aged adults, with greater cognitive performance compared to control animals, although not all studies find this effect (Cotman et al., 2007; Trivino-Paredes et al., 2016; Voss et al.,

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2013; Duzel et al., 2016). Although several factors have been proposed to help explain these equivocal findings, including differences in intervention length, intensity, and frequency (Colcombe and Kramer, 2003), as well as sample populations (Smith et al., 2010), we focus on a potential sex difference in responsivity to AT.

In a meta-analysis of 18 RCTs, Colcombe and Kramer (2003) first suggested that women may show greater cognitive benefits from AT than men. Specifically, they found a larger effect size for the positive effect of AT in studies with more than 50% female participants compared to studies with less than 50% female participants (Hedges $g = 0.604$ vs. 0.150). Although no study to date has directly examined the interaction between sex and AT group, a RCT conducted in older adults with MCI by Baker et al. (2010) showed that 6 months of AT statistically improved performance on three tests of executive function in women compared to control; whereas, AT only improved performance on one test in men compared to control. Furthermore, another RCT conducted in older adults with MCI found that increased adherence to a 1-year AT intervention was associated with improved executive functions and memory in women and improved memory in men (van Uffelen et al., 2008). Together, these studies suggest that AT may elicit greater cognitive benefits in females than in males.

Resistance training aims to improve muscle strength, power, and mass. Although there has been far greater focus on AT, evidence from RCTs suggests that RT also enhances cognitive function in healthy older adults (Bherer et al., 2013; Barha et al., 2016; Kelly et al., 2014; Voss et al., 1985; Constans et al., 2016). For example, twice weekly RT improved selective attention, associative memory and enhanced functional brain plasticity with cortical regions associated with executive function in older women with subjective memory complaints (Nagamatsu et al., 2012; Liu-Ambrose et al., 2012). In older cognitively healthy women, twice weekly and once weekly RT improved selective attention and reduced whole-brain volume, with the improvement in selective attention persisting for one year after intervention termination (Davis et al., 2010; Liu-Ambrose et al., 2010). RT also improves spatial learning and memory in both elderly humans (Cassilhas et al., 2007) and young adult rodents (Cassilhas et al., 2012).

Current evidence suggests that different types of exercise may promote cognitive function via both similar and divergent neurobiological pathways (Cassilhas et al., 2012). Both AT and RT reduce peripheral cardiometabolic risk factors for neurodegeneration and systemic inflammation (Cornelissen and Fagard, 2005; Dishman et al., 2006; Mattusch et al., 2000; Strasser et al., 2010). Furthermore, rodent models of AT and RT indicate that both influence hippocampal neurogenesis, though the effects are dependent on several factors including length of training, component of neurogenesis being measured (i.e., cell proliferation, cell survival or cell death), and use of noxious stimuli to motivate rodents to engage in training (Trivino-Paredes et al., 2016; Voss et al., 2013; Strickland and Smith, 2016). In humans, although evidence suggests both AT and RT impact the brain, they do so in similar and different ways. Both appear to impact functional cortical activation (Nagamatsu et al., 2012). Divergent mechanisms include increased hippocampal volume with AT (ten Brinke et al., 2015; Erickson et al., 2011, 2009), and increased cortical thickness in the posterior cingulate as well as reduced white matter lesion progression with RT (Bolandzadeh et al., 2015; Suo et al., 2016).

Despite common cognitive outcomes, work in young adult male rats indicates that the neurotrophic and molecular signaling pathways subserving the beneficial effects of AT and RT differ. AT induces brain derived neurotrophic factor (BDNF), insulin growth factor 1 (IGF-1) and calcium/calmodulin-dependent kinase II, while RT impacts IGF-1 and AKT (Cassilhas et al., 2012). Thus, the type of training regimen may also moderate the relationship between exercise and cognitive health. Importantly, the possible sex difference seen in AT efficacy has yet to be addressed in either RT or combined AT and RT exercise training (multimodal) interventions.

Therefore, we conducted a systematic review and meta-analysis of the literature to evaluate the effect of exercise interventions on domain-specific cognitive functioning in cognitively healthy middle-aged and aged human females and males. Our objectives were to determine whether: (1) the cognitive enhancing effects of AT are greater in females than in males in humans; (2) a sex difference exists in the efficacy for other types of (i.e., non-AT) exercise interventions (RT and combined AT and RT training referred to as multimodal in this review (MT)); and (3) AT exerts a more beneficial influence on cognitive functioning compared to RT and multimodal training (MT). To address how exercise may influence cognitive health, we have also provided a preliminary evaluation of the role of BDNF where possible in the systematic review and meta-analysis.

2. Methods

2.1. Literature search

A search of the human peer-reviewed literature was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) statement (Liberati et al., 2009). We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and PsychInfo databases to identify all RCTs studying the effects of exercise on cognition. We limited our search to middle-aged and older human RCTs. Language, publication date or publication status restrictions were not imposed. Medical Subject Heading Terms and keywords related to exercise (e.g., 'aerobic exercises', 'exercises', 'resistance training', 'physical activity', 'strength training'), cognition (e.g., 'executive function', 'spatial learning', 'spatial navigation', 'memory', 'neuropsychological tests', 'cognit*'), and aging (e.g., 'aging', 'aged', 'elderly', 'middle age') were searched in combination with each other. The final search was conducted in October 2016. The complete electronic search strategy for MEDLINE is presented in Fig. 1A.

2.2. Study selection

Initially, we examined all retrieved study citations and removed duplicates. Study eligibility based on an initial title and abstract screen was determined independently by two reviewers (CKB, RSF). Studies that potentially met the inclusion criteria were further evaluated by reviewing full-texts. A third reviewer (JCD) resolved disagreements.

2.2.1. Inclusion criteria

Studies were selected if they met the following criteria: (1) RCTs. (2) Participants were middle-aged and older adults (45 years and older) without any neurodegenerative disorders or clinical disorders (e.g., Metabolic syndrome, stroke, depression, diabetes). (3) Intervention was aerobic exercise, resistance training, or combined of any style (e.g., walking, running, swimming, free weights, resistance bands) that was at least two months in duration and occurred at least once a week. Yoga, Tai Chi and meditation only studies were excluded. (4) Cognitive performance in the following cognitive domains – memory, executive functioning, verbal fluency, visuospatial ability, processing speed.

2.2.2. Exclusion criteria

Studies were excluded if participants were from a clinical population. Studies were also excluded if they only assessed global cognitive functioning (e.g., MMSE, MoCA). Studies that did not report sufficient data and for whom we were unable to contact the authors were excluded from the meta-analysis, but were retained for the systematic review.

2.3. Data extraction

One reviewer (CKB) used a custom form developed by CKB and JCD to extract data. The following categories were extracted: (1) participant