

Fitness, aging and neurocognitive function

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Abstract

In this manuscript we provide a brief review of the recent literature that has examined the relationship among fitness training, cognition and brain. We began with a discussion of the non-human animal literature that has examined the relationship among these factors. Next we discuss recent epidemiological studies of the relationship between physical activity and fitness and cognition and age-related disease such as Alzheimer's dementia. We then discuss the results of randomized clinical trials of fitness training on human cognition. Finally, we conclude with a review of the nascent literature that has begun to employ neuroimaging techniques to examine fitness training effects on human brain. In general, the results are promising and suggest that fitness may serve a neuroprotective function for aging humans.

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1. Introduction

The SPARK workshop focused on the relationship among obesity, diabetes, mood and cognition. Clearly, one important factor that relates to each of these constructs is physical activity and exercise. Lack of physical activity has been implicated in various health conditions including diabetes, cardiovascular disease, cancer, and osteoarthritis [14]. Increased physical activity reduces the risk associated with these diseases. Although less well-known, there is also an emerging body of literature that has found moderate to strong associations between physical activity and cognition, mood and human brain function, particularly in a group of individuals vulnerable to the loss of independence and cognitive decline, that is, older adults.

In the present paper we focus on the literature that has examined the relationship between physical activity and exercise on human cognition, brain structure and brain function. Specifically, we will examine the question of whether exercise can reduce age-related decline in cognition and decrease the risk for age-associated neurological disorders

such as Alzheimer's disease. Rather than providing a thorough historical overview of this rapidly expanding literature we will concentrate on the expansion in our knowledge of the relationship among exercise, cognition and brain that has taken place over the past decade or so. To this end we will review both prospective and retrospective epidemiological studies as well as randomized clinical trials of exercise effects on human cognition, brain structure and brain function.

However, before focusing on the human literature we believe that it is important to provide a context for these studies, which largely derives from experiments with non-human animals. The examination of exercise effects in animals represents an expansion of a research program that has focused on the influence of complex environments on the brains of rodents. Given that living in complex environments entails increased physical as well as cognitive challenges, researchers began to decompose the influence of different aspects of these environments on brain structure and function. For example, Black et al. [5] compared the influence of wheel running with motor skills training on the brain function of older rats. Interestingly, the wheel running group developed a higher density of capillaries in the cerebellum than the animals trained on motor skills or a group of inactive

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controls. On the other hand, the animals in the motor skill group showed a larger increase in synapses in the cerebellum than the other two groups. Other studies have shown similar effects of treadmill exercise on the vasculature in the motor cortex of middle aged monkeys [19].

Exercise training in aging animals has also been shown to increase levels of key neurochemicals that improve plasticity and neuronal survival, such as brain-derived neurotrophin factor (BDNF) and insulin-like growth factor 1 (IGF-1), serotonin, as well as reduced corticosteroid levels [4,6,12]. There have also been a number of recent demonstrations of enhanced learning and memory and neurogenesis with exercise training [21,22]. Finally, voluntary exercise has been found to decrease amyloid load in a transgenic mouse model of Alzheimer's disease [2]. Such data provide a promising context in which to examine the influence of fitness training on human cognition, brain structure and function.

2. Epidemiological studies of fitness effects on human cognition

A number of recent prospective studies with fairly large numbers of older participants have examined the relationship between measures of physical activity and cognition. For example, Yaffe et al. [23] reported a study of 5925 high functioning community dwelling women (>65 years of age), who were characterized in terms of the number of blocks that they walked per week. The central question was whether higher levels of activity, particularly the number of blocks walked per week, would serve a protective function for cognition 6–8 years in the future. Indeed, women with greater physical activity levels at baseline were less likely to experience cognitive decline, as assessed with the mini-mental status exam (MMSE) during 6–8 years of follow-up. This effect remained even after adjusting for age, education, health status, depression, stroke, diabetes, hypertension, smoking, and estrogen use. A similar study [3] with 349 participants 55 years of age and older at time one, also found that fitness level at baseline predicted higher levels of cognitive performance six years later. This study was noteworthy in that it used both measures of aerobic fitness and self-report measures of 22 different physical activities and also assessed a wider variety of cognitive processes. Indeed, higher levels of aerobic fitness at baseline, as measured via VO_2 peak, predicted better performance on a number of different measures of attention and executive function. Interestingly, the self report measures of physical activity obtained at baseline were not predictive of cognition six years later. These data suggest that either VO_2 peak is a more sensitive measure of activity level or perhaps that moderate aerobic exercise is required in order to reap cognitive benefits.

Other studies have also found that physical activity can have protective effects on the cognition of middle aged individuals. Richards et al. [20] found that self reported physical activity level at 36 years of age was predictive of higher levels

of verbal memory, in a sample of 1919 participants, from 43 to 53 years of age. Interestingly, spare time activities such as game playing, attending religious services or playing a musical instrument were not predictive of memory performance. Dik et al. [13] found that higher levels of activity early in life, from 15 to 25 years of age, were associated with faster information processing speed between 62 and 85 years of age.

Finally, Laurin et al. [17] reported that physical activity level at baseline was associated with lower risks of cognitive impairment, Alzheimer's disease, and dementia of any type five years after assessment. All participants in this study (4615 individuals) were high functioning 65+ year olds at the baseline assessment. Similarly, Abbot et al. [1] found a monotonic relationship between distance walked per day at the initial assessment and the probability of developing Alzheimer's disease up to eight years later in a group of 2257 71 to 93 year old men.

The results of the studies reported above suggest that modest levels of physical activity and exercise can have beneficial effects on several cognitive processes of middle aged and older individuals. Studies also suggest a reduced risk of Alzheimer's disease with physical activity. Although these studies are valuable in establishing a reliable association between exercise and cognition, conclusions must be tempered by the limits of prospective observational designs (e.g. self selection into exercise levels, limited cognitive and fitness assessments, etc.). In an effort to address these limitations we turn now to an examination of the relationship between fitness and human cognition and brain function in randomized clinical trials.

3. Fitness training effects on cognition and brain

Human fitness training studies conducted over the past several decades have produced a varied pattern of results. Some studies find a positive relationship between fitness training and cognition while other studies fail to observe such a relationship. There are a multitude of potential reasons for this mixed pattern of results including the use of different physical training and assessment protocols, different cognitive assessments, and generally small sample sizes. To increase the power to detect a relationship between aerobic fitness training and cognition and also to examine the influence of potential moderating factors we conducted a meta-analysis of physical activity intervention studies published between 1966 and 2001 with adults greater than 55 years of age [10]. Several interesting results were obtained in the meta-analysis. First, a clear and significant effect of aerobic exercise training was found. When aggregating across studies exercise training does indeed have positive effects on the cognitive function of older humans. Second, although exercise effects were observed across a wide variety of tasks and cognitive processes, the effects were largest for those tasks that involved executive control processes (i.e. planning,

scheduling, working memory, interference control, task coordination). Executive control processes have been found to decline substantially as a function of aging as have the brain regions that support them [18]. Therefore, the results of the meta-analysis suggest that even processes that are quite susceptible to aging appear to be amenable to intervention.

The meta-analysis also revealed that several other moderator variables influenced the relationship between exercise training and cognition. For example, aerobic exercise training programs combined with strength and flexibility training regimens had a greater positive effect on cognition than aerobic components alone. This effect may result from increases in insulin-like growth factor 1, which is known to increase in response to strength training. IGF-1 is a neuroprotective factor involved in neuronal growth and differentiation [6]. Exercise training programs also had a larger impact on cognition if the study samples included more than 50% females. This effect may be due, in part, to the positive influence of estrogen (in the present case estrogen replacement therapy) on both brain-derived neurotrophin factor and increased exercise participation [12]. Similar to aerobic exercise estrogen has been found to up-regulate BDNF. And both estrogen and BDNF are important for synaptogenesis and neurogenesis, especially in the hippocampus [4,15].

Despite the large and ever expanding animal literature that has examined the influence of fitness training on brain structure and function, few human studies have addressed this relationship. In one such study [7] a technique called voxel based morphometry (VBM) was used to examine both age-related differences and age \times fitness interactions on the cortical volume assessed via MRI. In a cross-sectional examination of 55 older adults they found, consistent with previous studies, age-related volume losses in grey and white matter tended to be greatest in the frontal, prefrontal and temporal regions [18]. Moreover, older adults who were more aerobically fit also tended to lose less tissue in the frontal, parietal and temporal cortices as a function of age. Subsequent analyses, factoring out other potential moderating factors such as hypertension, caffeine, tobacco, and alcohol consumption, confirmed that none of these other variables moderated the effect of aerobic fitness. A follow-up study [9] examined the influence of a six month aerobic fitness training program on the brain structure of older healthy but sedentary adults. MRIs were obtained from thirty subjects in an aerobic exercise training group (i.e. walking) and from another thirty control subjects in a stretching and toning control group. Increases in the volume of anterior white matter and several gray matter regions (i.e. anterior cingulate, middle frontal gyrus, and superior temporal lobe) were observed in the aerobic but not in the non-aerobic control group. Although little is known about the relationship between cortical volume changes as indexed by VBM and cellular changes as indexed via histological examination, the non-human animal literature reviewed above suggests that the changes observed are likely the result of some combination of changes in synaptic interconnections, axonal integrity and capillary bed growth.

In addition to structural changes in the human brain, other fitness training studies have observed changes in the neural networks that underlie specific cognitive processes. Colcombe et al. [8] examined the influence of a six month program of aerobic exercise training as compared to a control group of older adults trained in stretching and toning on brain function and cognition. Participants in the randomized intervention performed a flanker task, in which they were asked to identify the orientation of a central arrow presented among an array of distracting stimuli, while brain function was recorded using event-related fMRI. On 50% of the trials, the orientation of the distracting stimuli were congruent with the central cue while on the other 50% the distracting stimuli were incongruent with the central cue. On incongruent trials, participants were required to suppress the information provided by the flanking stimuli in order to make a correct response. This paradigm has previously been found to be sensitive to age-related decrements in attentional control as well as to increments in aerobic fitness [16].

After six months of aerobic exercise training the older adults showed improved performance, particularly in terms of reducing their response times to the incongruent trials while the participants in the non-aerobic stretching and toning group did not. Furthermore, the older aerobically trained participants showed increased activation in the superior parietal cortex and middle frontal gyrus, brain regions responsible for assisting in the focus of spatial attention and maintaining task goals in working memory, respectively. On the other hand, individuals in the non-aerobic group showed increased activation in the anterior cingulate cortex, a brain region that assists in resolving response conflicts. One interpretation of this pattern of results is that higher levels of aerobic fitness lead to more efficient prefrontal control of extrastriate and parietal regions of cortex that are responsible for the selective processing of stimulus attributes.

A more recent study [11] found that a six month aerobic exercise intervention with older adults resulted in both faster and more accurate performance in a Sternberg memory search task and a change in the pattern of fMRI activation in prefrontal cortex which mimicked that observed for younger adults. These changes were not observed for older adults in a stretching and toning control group. Thus, these results suggest that exercise participation leading to improved aerobic fitness may provide a remediative effect to the functional integrity of the older adult brain and cognition.

4. Conclusions and future directions

The human behavioral and brain data discussed above suggest that fitness training holds great promise as a neuroprotective intervention during the course of the adult lifespan. The human data also are compatible with non-human animal studies of fitness training effects on performance, brain function, and brain structure.

However, there clearly are important questions that remain to be answered. For example, it is still unclear as to the dose response relationship among mode, duration and intensity of exercise training and changes in cognition and brain. Given the potential interaction among these factors, as well as the moderating effects of age, large randomized intervention trials may be necessary to examine these relationships. Second, the observation in the Colcombe and Kramer [10] meta-analysis that studies with greater than 50% women participants showed larger benefits of exercise on cognition is intriguing. Indeed, recent reports of a synergistic relationship between estrogen and exercise on BDNF [4,12] suggest that a randomized clinical trial that manipulates both fitness training and hormone replacement therapy with a group of menopausal women might be prudent. Third, although it has become clear that older adults can benefit from cognitive training and dietary interventions little is known about the similarities of mechanisms which underlie these factors or how they may jointly influence cognition, brain function and structure over the adult lifespan. Clearly, although the study of the relationship between fitness, cognition and brain has yielded interesting and potentially important results, much remains to be learned concerning the factors and mechanisms of successful aging. We look forward to reading and contributing to this literature in the future.

Conflict of interest

None of the authors have any conflict of interest to report. The study was conducted consistent with ethical principles.

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