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Effects of physical activity on cognition, well-being, and brain: Human interventions

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Abstract This article provides a review of the human intervention literature that has examined the influence of fitness training on cognition, well-being, brain structure, and brain function. Meta-analyses of this literature, which are reviewed here, suggest robust effects of fitness training on cognition and well-being. Although there are currently few human intervention studies that have examined fitness effects on human brain function and structure, the studies that have been conducted report promising results.

Keywords: Aging; Fitness training; Brain function and structure; Cortical plasticity

1. Introduction

During the past several years, there has been growing scientific and public interest in the effects of physical activity on cognitive maintenance and brain health. This interest has been driven in large part by epidemiologic studies reported during the past decade, in which physical fitness has emerged as one of the critical lifestyle factors associated with perseverance of cognitive function in older adults. In addition, a growing body of data from laboratory and animal studies has begun to reveal the potential cellular and molecular mechanisms by which physical activity might influence brain structure and function, with concomitant benefits to cognitive processes.

The confluence of epidemiologic and animal data supporting beneficial brain effects of physical activity (reviewed elsewhere in this supplement), combined with the prospect of a looming public health crisis as a result of an aging population at greater risk for cognitive decline and dementia, has fueled interest in developing fitness-based public health interventions that might interrupt, prevent, or at least delay cognitive decline. Toward that end, a small number of randomized, controlled human clinical studies have examined the effects of various fitness training regimens on cognitive skills and, more recently, on brain structure and patterns of neural activity. The results of these studies have been mixed, with some showing a significant effect of fitness training on cognition and the delay of dementia and others finding no effect. There are a number of reasons why this might be the case. For one, researchers have used a number of different fitness training regimens, which have varied in program duration, session length and intensity, and type of activity (eg, aerobic vs nonaerobic). Methodologies, study subjects, and cognitive tasks used to assess fitness effects have also varied among the studies, making it difficult to generalize results. Critically, sample sizes in many studies have been very small, and thus they lack the power to make strong conclusions about cause and effect. Meta-analytic studies have combined data from smaller trials to increase the statistical power of the evidence and, at the same time, have shed light on potential moderators of the fitness effect and provided directions for additional research. Despite the many questions that remain, the emerging view from this growing literature supports a neuroprotective effect of fitness training for aging humans.

Here we focus on three meta-analyses that have examined physical activity training studies dating back to the 1960s. We also review the results of a recent study designed to examine interactions between physical fitness and hormone replacement therapy, which is one variable that might help explain mixed results in epidemiologic and intervention studies.

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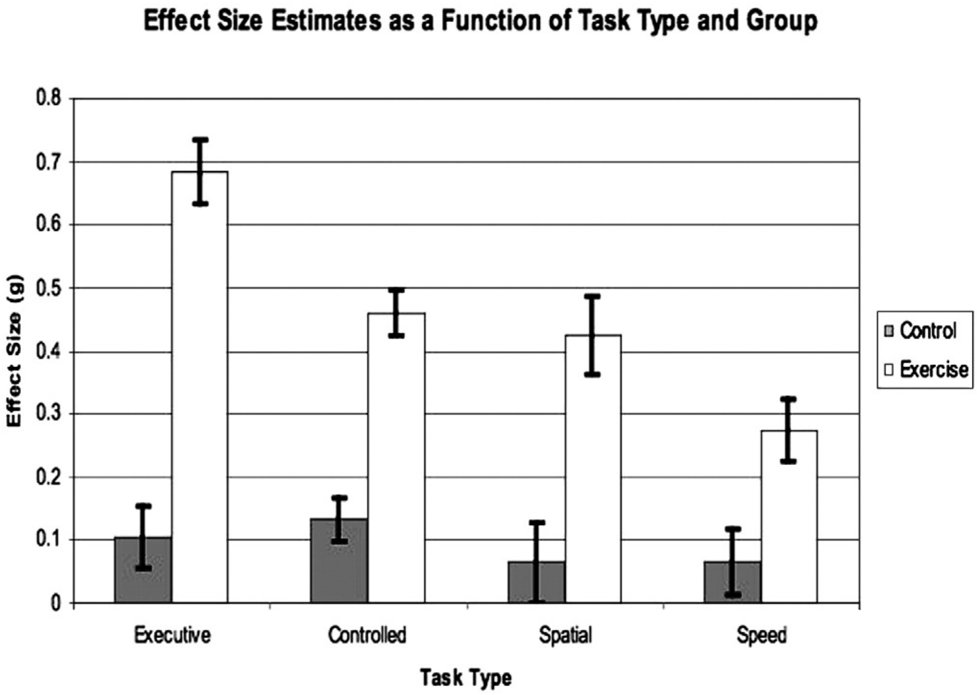

Fig. 1. Effect sizes for the four different theoretical hypotheses concerning the nature of the process-based specificity of fitness training. Reproduced from Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Printed with permission from Psychol Sci 2003;14:125–30. Copyright 2003 Blackwell Publishing.

2. Meta-analyses

Since 2003, three groups have published meta-analyses of human clinical studies examining the relationship among physical fitness, cognition, and brain health: Colcombe and Kramer [1], Heyn et al [2], and Netz et al [3].

In a meta-analysis published in 2003, Colcombe and Kramer [1] identified 18 controlled clinical trials focused on fitness training and cognitive outcomes. The studies, conducted between 1966 and 2001, enrolled high-functioning adults between the ages of 55 and 80 years; sample sizes ranged from 16 to 124. The primary interest was whether there was a main effect for aerobic fitness training on cognition, and what factors might moderate such an effect.

Heyn et al [2] focused on studies that examined effects of fitness training on people 65 years and older who had cognitive impairments or dementia (the original trials often did not distinguish between Alzheimer's-type dementias and vascular dementia). The authors looked at outcomes broader than cognition, encompassing overall fitness performance, body mass index, and a number of other physiologic and behavioral end points in addition to cognition. Thirty studies conducted between 1970 and 2003 were surveyed, with sample sizes from 14 to 180. Of these, 12 targeted cognition; moderators of the exercise-cognition effect were, unfortunately, not analyzed.

In the third meta-analysis, Netz et al [3] analyzed 36 studies focused on the effects of physical activity on well-being, 22 of which included control groups. A number of other positive and negative end points were also examined, and data were broken out by age, sample size, and exercise dose, including duration (number of weeks of exercise), frequency (number of sessions per week), and length (minutes per exercise session for treatment groups). The majority of the intervention programs were of relatively short duration; only one study continued beyond a year. As with studies in the previous meta-analyses, sample sizes of the original studies were small, with a mean sample of 38 participants.

The central question posed by each of these meta-analyses was whether there was a significant, robust main effect of fitness training on cognition or well-being in human intervention trials. The answer is yes. The analyses by Colcombe and Kramer [1] and Heyn et al [2] found remarkably similar effect sizes of 0.60 and 0.57, respectively, for the relationship between fitness training and cognition (only one small study overlapped both analyses). The meta-analysis by Netz et al [3] reported an overall effect size of 0.24 for psychological well-being.

Notably, fitness training appears to have both broad and specific effects on cognition. This is in contrast to the reported effects of cognitive training on cognition, which tend to be very task-specific with a narrow generalizability to related tasks [4]. As seen in Fig. 1, when we broke down the data from our meta-analysis according to the nature of the cognitive processes being measured, we found significant effect sizes across a number of cognitive domains. Compared with controls, participants who exercised (aerobic exercise was the most prevalent type in this sample) had significantly greater improvements in speeded versus unspeeded tasks, in spatial processing tasks, in controlled versus automatic processes, and in measures of executive function. The biggest effects were seen in executive control tasks, encompassing skills such as planning, scheduling, working memory, multitasking, and being able to focus even in the face of distractions.

3. Moderators of fitness-cognition equation

A close examination of how various factors impact the size of the fitness-cognition effect not only can provide important clues to understanding what type of training is most beneficial and who might benefit most but also can indicate directions for further research and strategies for improving intervention protocols. Two of the studies [1,3] examined various factors that moderate the fitness-cognition equation.

Several points are noteworthy regarding the impact of various moderators:

- In the analysis by Colcombe and Kramer [1], there was a larger effect for training regimens that combined aerobics with strength and flexibility training versus cardiovascular training alone.
- In terms of program duration, both short-term (1 to 3 months) and long-term (6+ months) programs showed the greatest effect (0.522 and 0.674, respectively). Oddly, programs of medium duration (4 to 6 months) had a much less effect on cognition. This is difficult to explain but might be a reflection of the small sample sizes or of the heterogeneity of cognitive effects and the specific tests used in the various studies.
- Exercise sessions of moderate duration, defined as 31 to 45 minutes per session, showed the greatest cognitive benefit (effect size of 0.614), which were trailed by longer-duration sessions (effect size of 0.466). Exercising for less than 30 minutes per session had a smaller impact on cognitive measures.
- How gender moderates the fitness effect is still not entirely clear, in part because many of the older trials did not include women, and those that did include women did not distinguish between exercise training effects for men versus women. We divided the studies according to whether there were mostly female or mostly male participants and determined that those studies with more than 50% female subjects had a significantly larger effect size on average. Men also exhibited significant improvements in cognitive tasks after an exercise regimen, but the benefits were significantly less than those seen in women. There are a number of possible explanations for this gender gap, including the influence of hormone therapy, as discussed later.
- "Old-olds," defined here as ages 71 to 75 years, tended to exhibit the largest benefits from exercise, which might reflect the fact that this group might have the most to gain from an exercise training intervention.
- In the analysis by Netz et al [3], which focused on well-being rather than cognitive processes per se, improvements in physical fitness status (whether defined by cardiovascular, strength, or flexibility parameters) or in functional capacity were associated with greater benefits for well-being. Formerly sedentary participants gained more benefits than those who had some prior level of regular exercise.
- Aerobic exercise had the largest effect on well-being, and moderate-intensity exercise was the most beneficial, adding to the growing literature suggesting that exercising harder does not always provide benefits above moderate workouts.

4. Human intervention studies

Very few human intervention trials have examined fitness training effects on the brain. One of the first, reported by Rogers et al [5] in 1990, assessed the impact of retirement versus continuing to work on cognition and cerebral blood flow in a prospective, 4-year study involving 90 retirees aged 62 to 70 years. Those who either continued to work or exercised routinely had better cognitive performance and tended to maintain fairly steady levels of cerebral blood flow during the course of the study period, compared with inactive retirees.

More recently, a few laboratories have measured event-related brain potentials (ERPs) to better understand how physical activity influences the neuroelectric profile of older adults. Previous work has suggested that regular aerobic exercise produces dynamic changes in ERP patterns of older adults, such that older exercisers more closely resemble the patterns found in younger people performing the same task. In particular, changes in both the amplitude and latency of the P3 component of ERPs among older adults who exercise suggest that physical activity might alter the allocation of attentional resources and might speed cognitive processing. Hillman et al [6–8] have found that exercise participation increases P3 amplitude and decreases P3 latency, which might play roles in the maintenance of cognitive performance. These data support earlier work by Dustman et al [9].

In the most recent report by Hillman et al [8], the authors used a task-switching paradigm that has been used to study selective aspects of executive control. By comparing three different conditions—repeated task trials in task-homogenous blocks, switch trials in task-heterogeneous blocks, and non-switch trials or repeated task trials in task-heterogeneous blocks—it was possible to distinguish among certain aspects of executive control processes and identify the interactions among them. A cross-sectional analysis of the 66 participants, who were divided into four groups according to age and levels of activity, found that physical activity positively influences task performance for both younger and older subjects, as evidenced by faster reaction times. Physically active individuals also demonstrated larger P3 amplitudes and faster P3 latencies than sedentary participants, reflecting a beneficial effect of fitness on both perceptual/central processing and response-related processing.

Magnetic resonance imaging (MRI) and functional MRI (fMRI) are increasingly being applied to examine the relationship between physical activity and brain networks or structure. We have used a high-resolution, 3 Tesla MR scanner to measure fitness effects on brain networks while participants perform a number of different cognitive tests. In one recent study [10], we randomly assigned 38 older adults (ages 62 to 77 years) to either an exercise or control group. The exercise group trained in aerobic exercise an average of 1 hour a day, three times a week during the 6-month intervention period, while the control group participated in group toning and stretching exercises for the same duration and frequency. One of the cognitive tests used in this study was the Sternberg task, which is a well-accepted measure of short-term memory that shows clear aging effects [11]. In this task, participants are provided a set of items to remember, words, letters, or images, and then are asked at a later time to identify which of the items they had previously encountered. Set sizes can be manipulated to increase or decrease the number of items subjects must remember. At the end of the intervention period, the exercise group as a whole had improved their performance on the Sternberg task by about 22%, whereas the control group improved by only 5%.

We also recorded fMRI activity in response to the presentation of the stimulus set and to the probe items that subjects compared with the items held in memory. We saw increases in both left ventrolateral and dorsolateral prefrontal cortex in the aerobic exercise group as compared with the toning and stretching control group after the 6-month intervention. Left dorsolateral cortex activation is thought to be associated with encoding information into working memory. Notably, we found all the differences in fMRI scans in brain regions related to encoding of information and none in areas associated with information retrieval. This could reflect more efficient attentional processes or more efficient rehearsal strategies.

In a previous study of the effects of fitness on attentional control processes, Colcombe et al [12] randomized 29 high-functioning, community-dwelling older adults into two groups, an aerobic group and a control group. The aerobic intervention was designed to improve cardiorespiratory fitness through a walking regimen, which began at 10 to 15 minutes per session and gradually increased to 40 to 45 minutes per session by about 3 months into the 6-month intervention period. Controls participated in supervised toning and stretching classes following the same schedule and format as the aerobic group.

The authors had subjects perform an Ericksen flanker task [13], a measure of attentional control in which subjects press a button to indicate the direction of a center arrow presented within a line of arrows. Functional MRI activity was recorded in a 3 Tesla MRI system during the task performance. Like the Sternberg task, this task has been fairly well-studied in terms of the cognitive processes it uses and the underlying brain circuits that support performance. Previous work has found an age-related increase in response time and errors when the center arrow is inconsistent with those on either side of it (interference effect). At the end of the 6-month intervention, walkers had improved performance on the task (as measured by the percent decrease in the interference effect) by 16%, whereas stretching and toning control subjects increased by 6%. The walkers also increased Vo_2 levels, a measure of cardiorespiratory fitness, by 10% versus 2% among controls. These very modest performance effects are likely a reflection of the relatively mild intensity of the training program with the older adult participants.

The fMRI data, shown in Fig. 2, indicate increased activation in aerobic exercisers over controls in the medial frontal gyrus and superior parietal lobe, two areas previously associated with selective attention and resolution of conflicting response cues [14]. Among the many functions subscribed to the medial frontal gyrus is the maintenance of goals, which is likely to be important for focusing attention and for remembering what needs to be done in the task. The superior parietal lobe has been shown to be important for focusing attention on different locations in visual space, which would also be useful in this task. Notably, we did not find increased activity in favor of the aerobic exercisers in all areas; the toning and stretching control group actually had an increase in activity over time in the anterior cingulate cortex. The anterior cingulate cortex has been linked with many different cognitive functions; perhaps most relevant here is its apparent involvement in distinguishing among confusing or disparate stimuli and resolving conflict [13,15,16]. These data suggest that the hemodynamic response is not brain-wide but is specific to the task being performed, and that better performance in the aerobic exercisers versus controls is associated with the activation of different brain networks.

In addition to changes in neural networks, animal studies have provided evidence for a fitness effect on brain structure (reviewed elsewhere in this supplement), but human data for such effects have been sparse as a result of the obvious limitations of conducting histologic examinations of human brain tissue. We have used a semiautomated image segmentation technique on high-resolution MR data (voxel-based morphometry) to compare longitudinal changes in brain structure in older adults randomized to either a 6-month

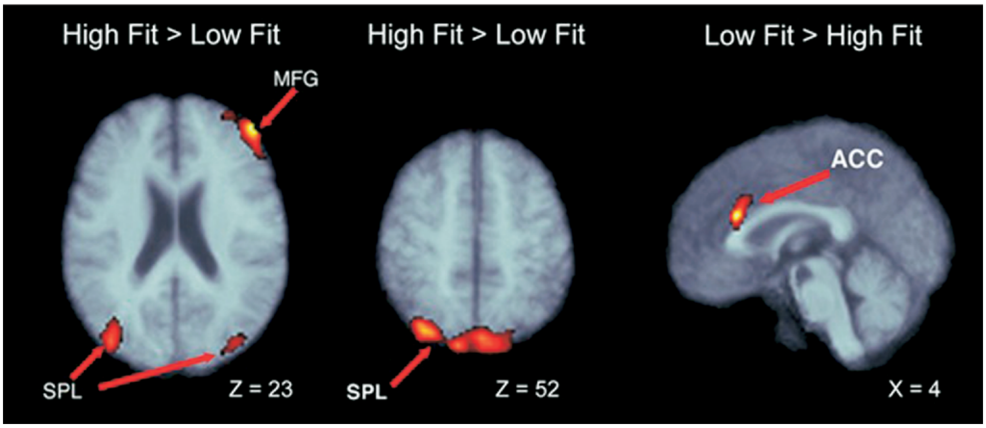

Fig. 2. Patterns of fMRI activation after intervention (compared with before intervention) for subjects in the aerobic (walking) and nonaerobic (toning and stretching groups). Reproduced from Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. Printed with permission from Proc Natl Acad Sci U S A 2004;101:3316–21. Copyright 2004 National Academy of Sciences, U.S.A.

aerobic training regimen or a nonaerobic (toning and stretching) control group. A number of laboratories have used this technique to estimate tissue atrophy regionally in the brain, and it continues to be optimized for research applications. Detailed methodology for this technique has been previously published [17–19]. Voxel-based morphometry allows isolation of structural tissue changes on a point-by-point fashion with fairly high spatial resolution, providing a means to approximate the distribution of any three-dimensional voxel of tissue to cerebral spinal fluid, white matter, or gray matter.

Consistent with a previous cross-sectional study by Colcombe et al [20] that examined brain differences between high-fit and low-fit older adults, we found increased gray matter volume in the anterior cingulate cortex, supplementary motor area, and medial frontal gyrus and increased volume in anterior white matter for the aerobic group but not for the nonaerobic control group during the period of the 6-month intervention.

Although voxel-based morphometry can reliably identify areas of increased or decreased volume, it cannot reveal precisely what mechanisms underlie such changes, of which there are a number of possibilities (eg, angiogenesis, synaptogenesis, increases in size or number of neurons or glia). Determining the underlying mechanisms requires that histologic data in non-human animals be used along with high-resolution MRI data to determine the relationship between brain volume changes as a function of exercise and changes in underlying processes like those discussed above.

Although there is clearly a need for additional studies, the human intervention trials that have been reported to date suggest some tentative conclusions. First, fitness training appears to have a beneficial influence on the neural networks that support several aspects of cognition, including attentional control and short-term memory. Second, fitness training appears to have a positive influence on brain structure, primarily in prefrontal, temporal, and parietal regions, and on anterior white matter. Last (and most tentatively, because of the unknowns in the data), there are interesting differences between men and women, and even among women, in fitness effects, as well as in brain structure, cognitive performance, and lifestyle choices that moderate the fitness-cognition equation.

4.1. Hormone replacement therapy–fitness interactions

As discussed briefly above, the meta-analysis by Colcombe and Kramer [1] of studies exploring the influence of fitness training on cognition revealed some intriguing gender differences that warrant further exploration. In particular, those studies that included more than 50% women showed larger cognitive benefits from fitness training than studies that enrolled mostly men. One potential explanation for this observation is the possibility of an interactive effect of fitness with estrogen in the female subjects. Hormone replacement therapy (HRT) has been shown to reduce age-related cognitive decline [21] and delay dementia [22], and two imaging studies have suggested that HRT reduces age-related declines in gray and white matter in cortical regions [18,23]. Yet other research in rodents [24], monkeys [25], and humans [26,27] confounds these positive results, suggesting that extended hormone therapy has both benefits and costs to the brain. Moreover, the largest prospective clinical trial to date, the Women's Health Initiative, has found an increased risk for dementia with estrogen treatment [28]. These seemingly inconsistent results raise the question as to whether and how an individual's level of physical fitness, as one variable among many potential lifestyle moderators, impacts the cognitive effects of HRT.

To investigate this possible interaction between fitness levels and HRT on cognitive function, Erickson et al [29] analyzed HRT use, cardiorespiratory fitness (Vo_2 max), and executive function (as determined by Wisconsin Card Sorting Test) among 54 healthy postmenopausal women aged

58 to 80 years and then used voxel-based morphometry to determine regional brain differences in gray and white matter. All women, regardless of HRT status, exhibited cognitive and brain volume benefits (ie, more volume in a variety of prefrontal and temporal regions) of being more physically fit. Second, short-term HRT use (10 years or less) had beneficial effects on brain volume and executive control, whereas long-term HRT use (longer than 16 years) negatively affected both cognition and brain volume. However, Erickson et al found that being more physically fit reliably offset negative effects of long-term HRT use and augmented the short-term benefits of HRT use.

These results present a possible explanation for the meta-analysis finding that studies with more female subjects show larger exercise effects and also reinforce the concept that many different lifestyle factors interact to influence cognition.

5. Summary

In summary, results of three meta-analyses on fitness training effects on cognition and a small number of randomized human intervention trials that have examined fitness training effects on human brain structure and function provide evidence for a neuroprotective effect of physical activity for older adults. Many factors influence the strength of the fitness effect, as McAuley et al [30] have summarized. Environmental and personal factors clearly play important roles, ranging from one's physical environment and how conducive it is to engaging in physical activity (eg, the nature of one's work, accessibility to venues for physical activity) as well as one's personal lifestyle choices (eg, dietary choices, hormonal therapy, education, levels of intellectual activity). The duration, intensity, and type of the physical activity are also critical; the studies reviewed show a clear benefit for aerobic-type exercise over nonaerobic forms, and moderate-intensity exercise (an average of about 1 hour a day, at least three times a week) appears to show greater cognitive and brain effects. These factors all contribute to one's overall level of physical fitness, which in turn influences disease susceptibility (eg, cardiovascular disease, type 2 diabetes) and seems to impact brain structure and function. In turn, disease reduction and enhancement of neural networks and structures presumably impact cognition both generally and in specific cognitive domains, including executive function.

There is clearly a need for further research to better define the impact of moderating factors and to solidify the fitness effects suggested by research to date. The interaction between fitness dose and cognitive maintenance and/or dementia delay/prevention is one area in which more work is needed to better define when, how much, and what type or types of physical activity should be recommended as a means of promoting cognitive health with age. We also need to better understand whether fitness effects on selective aspects of cognition, brain structure, and function translate into changes outside the lab; is there a related enhancement in activities of daily living, for example, or in one's ability to continue to work? If so, to what degree is there? A broader question is how best to combine the multitude of lifestyle factors that appear to have a positive effect on cognition and brain to maximize healthy aging and, if possible, reduce comorbidities. Finally, a more long-term question is whether healthy aging interventions might be custom-tailored on the basis of the genomic profiles of individuals.

Acknowledgments

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