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Invited Review

HIGHLIGHTED TOPIC | *Neural Changes Associated with Training*

Exercise, cognition, and the aging brain

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Kramer, Arthur F., Kirk I. Erickson, and Stanley J. Colcombe. Exercise, cognition, and the aging brain. *J Appl Physiol* 101: 1237–1242, 2006. First published June 15, 2006; doi:10.1152/japplphysiol.000500.2006.—We provide a brief review of the literature on exercise effects on brain and cognition. To this end, we focus on both prospective and retrospective human epidemiological studies that have examined the influence of exercise and physical activity on cognition and dementia. We then examine the relatively small set of human randomized clinical trials that have, for the most part, focused on exercise training effects on cognition. Next, we discuss animal research that has examined the molecular, cellular, and behavioral effects of exercise training. Finally, we conclude with a summary and brief discussion of important future directions of research on fitness cognition and brain.

physical activity; plasticity

MUCH AS BEEN WRITTEN OVER the ages about the benefits of exercise and physical activity. For example, Marcus Tullius Cicero stated, in ~65 BC, that "It is exercise alone that supports the spirits, and keeps the mind in vigor" (41). Somewhat more recently, in the mid-1760s, John Adams, the second president of the United States, suggested that "Exercise invigorates, and enlivens all the faculties of body and of mind . . . It spreads a gladness and satisfaction over our minds and qualifies us for every sort of business, and every sort of pleasure" (14). Clearly, however, not all opinions from politicians, philosophers, writers and others concerning exercise and physical activity have been positive. For example, Mark Twain, a literary giant of the 19th century, expressed his disdain for exercise in the statement "I take my only exercise acting as Pallbearer at the funerals of my friends who exercise regularly" (36). Similarly, Henry Ford, the early 20th century industrialist and automotive designer, stated that "Exercise is bunk. If you are healthy, you don't need it, and if you are sick, you shouldn't take it" (3).

In the present document, it is our goal to go beyond the varied opinions concerning the benefits and costs of exercise and physical activity to provide an up-to-date review of the scientific literature that has examined the influence of physical activity and exercise on cognitive and brain function. We will, for the most part, focus our review on the research conducted with older animals and humans, because this population has both much to gain from exercise and is of particular interest with regard to the notion of lifetime plasticity. Our review will cover what are often several disparate literatures. First, we will examine the prospective and retrospective epidemiological literature that has asked whether exercise and physical activity at one point in the life span are related to the level of cognition and age-related neurological disease, such as Alzheimer's dementia, later in life. Next, we will focus on longitudinal randomized clinical trial studies of exercise training effects on cognition and brain of older adults. We will then examine research conducted with nonhuman animals, which has begun to explicate the molecular and cellular mechanisms responsible for exercise effects on brain structure and function as well as learning and memory. Finally, we will suggest several future directions for the research on fitness effects on brain and cognition.

EPIDEMIOLOGICAL STUDIES OF EXERCISE AND PHYSICAL ACTIVITY EFFECTS ON COGNITION AND DEMENTIA

Over the past decade, there has been increasing focus on the influence of a number of lifestyle factors, including intellectual engagement, social interaction, nutrition, and physical activity, on the cognitive vitality of older adults. Some of these studies have examined changes in cognition within the normal range, whereas others have asked whether lifestyle factors reduce the risk or delay the onset of age-associated diseases such as Alzheimer's or vascular dementia. The time course of many of these studies is relatively short, ranging from 2 to 8 yr. However, a small minority of prospective or retrospective observational studies have examined much longer delays between initial assessment of lifestyle factors and cognition of older adults. With regard to assessing the effects of physical activity and exercise many of the epidemiological studies have employed self-report instruments of activity (e.g., delineating physical activities such as walking, fencing, gardening, swimming, bicycling, etc.).

A study by Larson et al. (29) illustrates the general protocol followed in many recent studies. In this case, 1,740 men and women over the age of 65 yr without cognitive impairment were asked to report the number of times per week that they performed different physical activities (i.e., walking, hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, or weight training) for at least 15 min per time over the past year. A number of potential confounding factors, including

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self-reported health, a variety of medical conditions, lifestyle factors such as smoking and drinking, and demographic factors, were also recorded at the initial assessment. An assessment of genetic risk for Alzheimer's disease [one or more e4 alleles on the apolipoprotein E (apoe) gene] was also done at this time. After an average follow-up period of 6.2 yr, 158 individuals had developed Alzheimer's dementia. Alzheimer's disease is the most common type of dementia and negatively affects a variety of cognitive and neurological processes. After adjustment for the covariates obtained at the initial assessment the incidence rate for Alzheimer's disease was significantly higher for individuals who exercised fewer than three times per week (19.7 per 1,000 person yr) compared with those who exercised more than three times per week (13.0 per 1,000 person yr). These results were not influenced by a genetic predisposition for Alzheimer's disease (i.e., one or more e4 alleles on the apoe gene). However, the risk reduction for Alzheimer's disease was greater for those participants who initially had the poorest physical performance (e.g., on tests such as a 10-ft timed walk, which assesses the speed that a person can walk 10 ft, and is considered a proxy of physical fitness, balance test, etc.).

Other studies have reported similar effects of exercise on dementia. Podewils et al. (33) studied the relationship between physical activity and dementia in 3,375 men and women over the course of 5.4 yr. Physical activity in these individuals over the age of 65 yr was assessed via the Minnesota Leisure Time Questionnaire in which participants are asked about the frequency and duration of 15 types of physical activities over the past 2 wk. Like the Larson et al. (29) study, this study found an inverse relationship between Alzheimer's disease and the estimated energy expenditure and number of physical activities performed by the participants. However, unlike the Larson et al. study, the present study only found a significant relationship between physical activities and Alzheimer's disease for the e4 noncarriers, or those people with less of a genetic risk for developing Alzheimer's disease.

Studies have also found an inverse relationship between activity levels and cognitive decline within the normal range of functioning. For example, Yaffe et al. (48) found an inverse relationship between the number of blocks walked per week and energy expended and cognitive decline as assessed by performance on a general test of cognitive function, the Mini Mental State Examination, indicating that cognitive performance increased with increasing levels of reported activity. This study involved 5,925 women over 65 yr of age over the course of a 6- to 8-yr period (see also Ref. 45).

The studies described thus far have relied on subjective reports of activity and exercise. Although such a procedure is understandable when large populations of subjects are tested, a prospective study of physical activity by Barnes et al. (4) included both self-report and objective (i.e., peak oxygen consumption) measures of cardiorespiratory fitness in a 6-yr study of 349 individuals over the age of 55 yr. Interestingly, whereas a significant inverse relationship was observed for the objective fitness measures and cognitive decline, this was not the case for the self-report activity measures. Although the explanation for this dissociation cannot be unequivocally discerned in these data, it is conceivable that it is the aerobic nature of the physical activities, which are more reliably indexed by the objective than self-report measures, which are more strongly related to spared cognition than nonaerobic activities. This issue will be further addressed below.

A small set of observational studies have examined the relationship between physical activities and cognitive decline or dementia over much more extended time periods. Such studies have several advantages. First, they reduce the likelihood that subjects have undiagnosed dementias at initial assessment. Second, they enable the determination of whether levels of physical activity earlier in the lifespan have implications for cognition and dementia in later life.

Dik et al. (15) conducted a retrospective study in which they asked 1,241 62- to 85-yr-old men and women about their physical activities from 15 to 25 yr of age. Men, but not women, who were active at low or moderate levels when they were young displayed faster processing speed later in life. This relationship was significant after adjustments for a number of lifestyle and demographic characteristics. Interestingly, the most active men did not show cognitive benefits. The authors speculate that this could be due to the fact that high levels of activity for these men were work related and therefore less likely to be aerobic than leisure activities. The failure to find a significant relationship between physical activity and processing speed for women could have been the result of lower intensity activities pursued by women in this cohort.

An examination of the association between leisure time physical activity at midlife and dementia between the ages of 65 and 79 yr was conducted by Rovio et al. (39). Leisure time physical activity at midlife at least twice a week was associated with a reduced risk of dementia. Interestingly, the association between physical activity and dementia was stronger for apoe e4 carriers, that is, those people with the highest genetic risk for developing Alzheimer's disease.

In summary, the studies reviewed above suggest a significant, and sometimes substantial, relationship between physical activity and later cognitive function and dementia. Indeed, there is some evidence that this relationship can span several decades. However, it is important to note that other studies (46, 47) have failed to find such relationships. Clearly, there are many reasons why inconsistent associations might be observed across studies, including the collection of self-report activity data; the failure to distinguish between aerobic and nonaerobic activities; the failure to assess duration, intensity, and frequency of activities; the difficulty of eliminating participants with subclinical signs of dementia; and power. The moderating influence of genetic factors on fitness effects on cognition, mostly with regard to apoe, is also intriguing but at present these results are inconsistent. Clearly, additional studies will be necessary that address these issues and likely also incorporate additional genetic markers that target genes related to particular neurotransmitter system functions and those with neurotrophic effects.

HUMAN CLINICAL TRIALS: COGNITION AND BRAIN

The studies reviewed above suggest that physical activity can have a neuroprotective effect on later life cognition. However, given the observational nature of these studies, causation cannot be established. Fortunately, there have been an increasing number of randomized intervention studies that have examined the relationship between fitness training and cognition and dementia. Similar to the observational studies, a

mixed pattern of results have been observed in the interventions with some studies finding significant improvements in cognition and delayed dementia, whereas other studies fail to observe an effect of fitness training on cognition. The potential reasons for these mixed results remain to be fully elucidated. However, two recent meta-analyses of the literature on fitness training provide some interesting clues.

Colcombe and Kramer (11) surveyed the literature, from 1966 through 2001, that examined fitness training effects on the cognitive function of nondemented older adults. Studies were included in the meta-analysis if they entailed a randomized design of an aerobic fitness training group along with a control group. The central question examined in the analysis was whether, across the 18 intervention studies in the analysis, fitness training had a positive influence on cognition. The answer was affirmative. A moderate effect size (0.48) for fitness training was obtained in the analysis. Additional analyses examined whether there were significant moderators of the relationship between fitness and cognition. Several significant moderators were revealed. First, although fitness training broadly influenced a variety of cognitive processes, the largest positive effects were observed for executive control processes. Executive control processes include components of cognition such as planning, scheduling, working memory, inhibitory processes, and multitasking. Interestingly, these are many of the processes that show substantial age-related decline (13). Second, effects of fitness training were larger when programs of aerobic training were combined with strength and flexibility training. Combinations of different treatment protocols may engender both more varied brain changes (e.g., Ref. 7) and serve to further reduce age-associated cardiovascular and muscular skeletal disorders. Third, and perhaps most interestingly, studies that included more women showed larger fitness training benefits than studies with fewer women. The potential explanations for these moderators will be explored below.

Heyn and colleagues (25) conducted a meta-analysis to examine whether exercise is beneficial for people with dementia and related cognitive impairments. The outcome variables were broader in this study then they were in the study of Colcombe and Kramer (11) encompassing exercise effects on a variety of physiological, behavioral, and cognitive end points. Twelve intervention studies that targeted cognition were examined. These studies ranged in duration from 2 to 28 wk and included a variety of different low-intensity exercises, including walking, strength, and resistance training. A moderate effect size of 0.57, very similar to that observed by Colcombe and Kramer for nondemented older adults, was obtained. Unfortunately, however, the authors did not examine potential moderators of the relationship between exercise and cognition.

The intervention studies discussed thus far have focused on cognitive outcomes as indexed by paper and pencil or computer-based test. However, given the increasingly well documented decrease in brain function and structure with age (24, 35), studies are beginning to address whether fitness training can positively influence the human brain. One of the earliest studies of the relationship between physical activity on cognition and the brain was a 4-yr prospective longitudinal study (38) of ninety 62–70 yr olds. Across the 4-yr period individuals who continued to work and retirees who exercised showed sustained levels of cerebral blood flow and superior performance on a general measure of cognition compared with the group of inactive retirees.

In a more recent study, Colcombe and colleagues (10) randomly assigned older adults to participate in either a walking group or a stretching and toning control group for a 6-mo period. The walking group were continuously monitored by a trained exercise coordinator and walked three times a week for 45-min periods. The control group received the same contact with an exercise coordinator, but instead of participating in a walking regimen, this group partook in nonaerobic stretching exercises three times a week for 45-min periods. All participants performed a focused attention task during an event-related functional magnetic resonance imaging protocol. This task requires participants to focus on a single, central object while ignoring irrelevant distractor objects that flank the target item. Older adults who participated in the walking protocol were better able to ignore the misleading flanking items, but the control older adults were not. Importantly, aerobically trained older adults, but not controls, showed increased activity in the frontal and parietal regions of the brain, which are thought to be involved in efficient attentional control and performance on this task, and reduced activity in the dorsal region of the anterior cingulate cortex, a region thought to be sensitive to behavioral conflict or to the need for increased cognitive control.

Kramer and colleagues (28) used a semiautomated image segmentation technique on high-resolution magnetic resonance imaging data to assess longitudinal changes in the brain structure of older adults who were randomly assigned to participate in either a 6-mo aerobic training program or a nonaerobic control group. This technique provides a means to estimate tissue atrophy on a point-by-point fashion throughout the brain with reasonably high spatial resolution. This allows for regionally specific conclusions about the variables of interest on changes in brain matter. Kramer and colleagues found that older adults who participated in the aerobic training group showed a significant increase in gray matter volume in regions of the frontal and superior temporal lobe, compared with controls. These results suggest that even relatively short exercise interventions can begin to restore some of the losses in brain volume associated with normal aging. However, it should be noted that the limitations of the semiautomated segmentation technique do not allow one to infer precisely what mechanism results in these changes (e.g., increase in cell body size, increased dendritic connections, increased capillary bed volume, increased glial size or number, etc.).

As described earlier, Colcombe and Kramer (11) reported in their meta-analysis that studies with more women showed greater effects of exercise on cognition than studies with fewer women. The loss of estrogen and the presence of hormone replacement therapy (HRT) in postmenopausal women were speculated as contributing to this effect. Indeed, at least one animal study has reported that the benefits of exercise in female rodents are dependent on the presence of estrogen and that the combination of aerobic exercise and estrogen replacement are greater than either exercise or estrogen replacement by themselves (5). Erickson et al. (16) examined the relationship between HRT and objective fitness levels (oxygen consumption) on brain volume and executive control in human postmenopausal women. There were a few interesting findings to note of in this study. First, all women, regardless of HRT status, showed cognitive and brain volume

benefits of being more physically fit. Second, short-term HRT use (within 10 yr) was beneficial on brain volume and executive control, whereas long-term HRT use (longer than 16 yr) 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. This interesting finding not only indicates that multiple lifestyle factors can have interactive effects on brain and cognition in old age but also may explain the finding that studies with more female participants show larger effects of exercise.

In summary, the human intervention studies discussed in this section tentatively suggest a causal relationship between fitness training and improved cognition, more efficient brain function, and spared brain volume in older humans. However, clearly additional intervention studies will be needed to further examine the relationship between different fitness training protocols (as well as different intensities and durations of fitness training), aspects of cognition, and measures of brain structure and function.

EXERCISE EFFECTS ON THE BRAIN: MOLECULAR AND CELLULAR BIOLOGY

As reviewed above, human studies have provided intriguing evidence for positive effects of exercise on neurocognitive function in older adults. Evaluating the effects of exercise in animal populations has the benefits of reducing some of the inherent confounding variables that are often present in human studies while also providing a translational and cross-species approach to exercise-induced neurocognitive plasticity. The animal studies reviewed in this section have used voluntary-wheel running protocols to examine *1*) whether aerobic exercise improves behavioral performance on learning and memory paradigms in young and old animals; *2*) whether neural activity and long-term potentiation (LTP), a cellular model of memory, are enhanced with exercise; *3*) whether molecular factors associated with brain plasticity are upregulated during exercise in young and old animals; and *4*) whether exercise promotes the growth of new neurons and vasculature in aged animals. The results from these studies provide important evidence for the use of animal models in evaluating the effects of exercise on human populations.

The majority of animal studies examining the influence of exercise on neuronal systems have focused on the hippocampus, a structure located in the medial temporal lobe. This structure shows dramatic alterations in cell number in persons with Alzheimer's disease and has also been associated with some forms of amnesia. In rodents, the hippocampus has been frequently associated with spatial learning and memory tasks such as the Morris water maze (described below). The hippocampus also has several subfields that play distinct roles in the formation of new memories and may be disproportionately affected with exercise. These subfields include the dentate gyrus, CA1, and CA3, among others.

Behavioral studies in rodents have reported performance benefits of wheel running on hippocampus-related spatial learning tasks. For example, in the Morris water maze, animals are placed in an opaque pool of water in which a platform is submerged just beneath the surface. The platform remains in the same position on all trials, but the animal is placed into the pool at variable locations, and must learn the location of the submerged platform by using extramaze cues. In this paradigm, Fordyce and Wehner (21) reported that, in young animals, physical activity produced a 2- to 12-fold increase in learning performance, or a reduction in the time needed to find the platform, but swim speeds remained the same for both exercising and sedentary animals (see also Refs. 23, 37).

Fewer studies have examined the effects of exercise on Morris water maze performance in aged (usually ~25–30 mo of age for rats and ~19–20 mo of age for mice) or adult rodents. However, recently, both Albeck et al. (2) and van Praag et al. (44), using the Morris water maze, reported that aged rodents that exercised showed faster acquisition and greater retention for the hidden platform than age-matched controls. In van Praag et al., aged mice (19 mo old) had unlimited access to a running wheel for 45 days and did not differ in overall running distance from that of 3-mo-old runners. In addition, van Praag et al. demonstrated that aged runners not only showed enhanced acquisition on the Morris water maze but also showed, with bromodeoxyuridine labeling of newborn cells, that they had more newborn neurons in the dentate gyrus than age-matched sedentary controls. Other studies have also reported exercise-induced neuron proliferation in the dentate gyrus of young and aged animals (26, 43). Although the growth of new neurons may not necessarily translate into improved cognition, van Praag et al. (44) suggest that exercise in aged animals can enhance both cognition and neuron proliferation.

Exercise also has effects on the neuronal structure and responsiveness that underlie cognition and behavior in both young and adult animals. For example, enhanced LTP in exercising adult Sprague-Dawley rats has been related to increased mRNA expression of a particular receptor subunit (NR2B of the *N*-methyl-D-aspartate receptor) in the dentate gyrus that may be related to enhanced learning due to exercise (19). Farmer et al. (19) also reported that brain-derived neurotrophic factor (BDNF) mRNA levels were elevated in the dentate gyrus of running animals, but not in other areas of the hippocampus, and that this elevation may be related to enhanced neurogenesis and learning in exercising animals. Others have also posited a role for BDNF in neurogenesis and the induction of LTP in learning and memory observed in animals that exercise (e.g., Ref. 12).

It has been well established that exercise increases BDNF levels in the hippocampus (12, 30) and that aged brains are also responsive to exercise-induced BDNF expression in the hippocampus (22), although the time course and duration of the BDNF expression may differ between aged and young animals (1). Garza et al. (22) using in situ hybridization methods reported that, in young animals (3 mo old), exercise-elevated BDNF mRNA levels were found in CA3, CA4, and dentrate gyrus regions, whereas in old animals (22 mo old), elevated BDNF mRNA levels were found mostly in CA1 and CA2 regions suggesting a possible change in the physiology and regional specificity of BDNF expression in the hippocampus across the lifespan. Given the activity dependence of BDNF and the importance of BDNF in LTP, Pang and Lu (31) have suggested that reduced expression of BDNF and cleavage proteins such as tissue plasminogen activator as well as the expression of neurotrophic receptors such as the tyrosine kinase receptor B may underlie age-related deficits in LTP, learning and memory, and hippocampal function. Further re-

search is needed to delineate the relationship between BDNF and age-related cognitive and neuronal loss as well as the role of exercise in moderating age-related changes in BDNF.

Some neurotransmitter systems are also affected by exercise. For example, Poulton and Muir (34) reported that treadmill running resulted in an attenuation of dopamine depletion in the striatum of hemi-parkinsonian rats, suggesting that exercise may be a potential intervention to reduce onset rate or incidence of Parkinson's disease (40). In addition, serotonin (8) and acetylcholine (20) levels are also increased throughout the brain in exercising rats, and medial septal GABAergic neurons have been suggested to play a key role in exercise-induced benefits on cognition (6). Importantly, BDNF has been shown to regulate neurotransmitters, including dopaminergic and cholinergic systems (27), and may be playing an important role in the exercise-induced effects on neurotransmitters.

Circulating levels and brain uptake levels of insulin-like growth factor I (IGF-I) are also increased with exercise (9, 42). Carro et al. (9) reported that exercise increased the expression of c-Fos, a neuronal marker of activity, throughout numerous regions of the brain, but when the uptake of IGF-I was blocked, the exercise-induced increase of c-Fos was also blocked. However, systemic injection of IGF-I in sedentary animals resulted in similar c-Fos and BDNF expression as that of exercising animals, indicating an important mediating role of IGF-I on exercise-induced neural benefits. In addition, Trejo et al. (42) reported that blocking the entrance of IGF-I into the brain resulted in prevention of exercise-induced neuron proliferation in the dentate gyrus, suggesting that IGF-I also plays an essential role in neurogenesis. This evidence indicates that IGF-I plays an important role in the influence of exercise on cognition, BDNF levels, and neurogenesis. However, very little research has been conducted so far that studies the relationship between IGF-I on the effects of exercise on the brains of older animals.

In summary, exercise increases cognitive performance in both young and aged animals and increases mRNA and protein levels of BDNF, which may be contributing to exercise-induced neurogenesis in the dentate gyrus. Neurotransmitter systems are also affected by exercise and reveals exercise as a potentially important intervention in treating, off-setting, or preventing some pathological disease states. In addition, IGF-I may be mediating the effects of exercise on BDNF, neurogenesis, and cognitive performance. Animal studies provide information on the effects of exercise that is difficult to obtain in human intervention studies. The sum of these animal studies overlap with results from human studies and suggest that exercise is an effective enhancer of neurocognitive functioning in both young and old animals.

FUTURE DIRECTIONS

The animal and human studies that we have reviewed above suggest that physical activity and aerobic exercise training can serve to moderate undesirable age-related changes in cognition, brain function, and brain structure. Importantly, these data add substantially to the growing literature that suggests that cognitive and brain plasticity is maintained, albeit to a lesser extent than for younger organisms, well into old age. Such results have important implications both for our understanding of aging as well as in terms of their public health implications.

There are, however, many unanswered questions with regard to the relationship between physical activity, aging, cognition, and brain. For example, we do not yet know how much and what types of physical activity training produce the most rapid and robust effects on cognition and brain. Nor do we know how long exercise effects last after cessation of training or how much exercise is needed to reinstate previously observed benefits. We are also ignorant about the extent to which the same or different biological mechanisms subserve exercise training and other interventions, such as cognitive training, social interventions, and nutritional programs, which have shown promise in reducing age-related declines in cognition and brain function. Indeed, to our knowledge there have been only two published studies that have contrasted the separate and joint effects of cognitive and fitness training on performance-based metrics of selective aspects of cognition, and these studies have come to opposite conclusions with regard to whether the effects of these two training modes are additive or interactive (17, 18).

There is also little knowledge about the moderating influences of specific genotypes on the magnitude of cognitive and brain effects of interventions such as aerobic exercise training. Given the rapidly developing knowledge of the relationship of allelic variation of genes with single-nucleotide polymorphisms, that is, a substitution of a single amino acid in the DNA sequence that alters the configuration of the resulting protein, to neurotransmitter systems and neurotrophins, and in turn, the influence of this variation on specific aspects of cognition, the marriage of molecular genetics with intervention-based research is another fertile area for future research (32). As discussed above, several observational studies have examined whether the presence of an e4 allele on the apoe gene, a gene implicated in cognitive deficits and Alzheimer's dementia, moderates the effects of fitness training on cognition. However, the findings are inconsistent, likely as a result of uncontrolled variables, subjective rather than objective measures of exercise and cardiorespiratory fitness, and in some cases small sample sizes. Clearly, additional studies are needed to examine the moderating effect of allelic differences on the apoe gene as well as other genes that influence neuroprotective molecules such as BDNF and neurotransmitter systems influenced by exercise.

In summary, the research reviewed in this paper highlights the positive effects that exercise has on the aging brain in clinical populations, nonpathological populations, and nonhuman animals. Although more intervention research is needed to further address questions related to the benefits of exercise, it appears to be the case that the benefits of physical exercise or physical activities promotes brain and cognitive vitality well into older adulthood.

GRANTS

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