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Brain, Behavior, and Immunity 18 (2004) 214–220
BRAIN, BEHAVIOR, and IMMUNITY
www.elsevier.com/locate/ybrbi

Invited minireview

Cardiovascular fitness and neurocognitive function in older Adults: a brief review

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Received 28 October 2003; received in revised form 3 December 2003; accepted 11 December 2003

Abstract

We provide a brief review of the extant research on the influence of cardiovascular fitness training on brain and cognition. The review includes an examination of the non-human animal literature that has reported molecular, cellular, and behavioral consequences of fitness interventions. We relate this literature to human studies of the relationship between fitness and cognition, as well as the nascent literature on fitness influences on human brain structure and function with state-of-the art neuroimaging techniques. We also consider the important topic of participant adherence in clinical exercise trials. Finally, we suggest future directions for studies of cardiovascular fitness, aging, and neurocognitive function.

Keywords: Cardiovascular fitness; Aging; Cognitive function; Brain structure; Brain function; Behavioral interventions; Adherence

1. Introduction

There are currently 35 million adults aged 65 years and older in the US, a figure that is expected to double over the next several decades. Adults aged 85 years and older are the fastest growing segment of our population and this group is expected to grow from 4 million in 2000 to 19 million by 2050. Although mortality rates are decreasing and life expectancy is increasing (Federal Interagency Forum on Aging-Related Statistics, 2000), it is not well-established whether older adults are experiencing a better quality of life as they age. Indeed, quality of life can be considered a more important goal of health promotion than longevity. Quality of life is viewed by many as having multiple functional and well-being components (Stewart and King, 1991). One aspect of function that has been well-established as demonstrating age-related declines is cognitive function, typically characterized by decrements in a variety of processes including aspects of memory, attention, and perception. Declines in cognition have been identified as a major risk factor for nursing home entry (Federal Interagency Forum on Aging-Related Statistics, 2000) and age-associated diseases such as Alzheimer's Dementia (Wilson et al., 2002). Consequently, development of strategies to maintain or enhance cognitive function in later life is an important public health goal.

One behavioral modality that has been implicated in maintaining and enhancing multiple aspects of physical and psychological functioning across the lifespan is physical activity. As a modifiable risk factor, physical inactivity has been implicated in a variety of health conditions including cardiovascular disease, adult onset diabetes, cancer, disability, depression, and cognitive decline (Bouchard et al., 1994). In this paper, we examine the utility of physical activity and more specifically cardiovascular fitness training as a behavioral strategy for improving cognitive function in older adults through its effects on cardiovascular fitness (see Fig. 1). Reviewing the literature from both animal and human studies, we consider the extent to which fitness training might be an effective strategy for the maintenance of cognitive function and brain plasticity in late life. However, any such effects are predicated on keeping participants active over considerable periods of time. Unfortunately, sedentary behavior among older adults

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doi:10.1016/j.bbi.2003.12.007

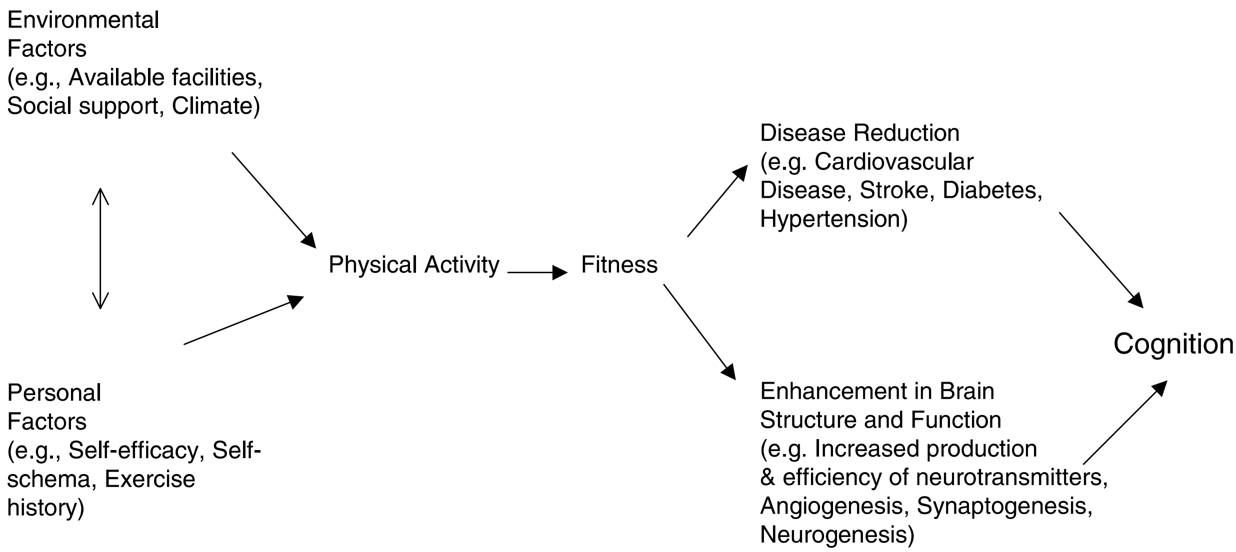

Fig. 1. Provides a schematic illustration of some of the important factors which both help to influence whether (and the extent to which) individuals participate in cardiovascular fitness training as well as the potential mechanisms of improved fitness and the influence of these mechanisms on cognition. The factors included in the illustration are derived from animal research, human epidemiological studies, and human randomized clinical trials. The factors, mechanisms, and links are speculative and provide a relatively high level summary of the current state of knowledge.

is highly prevalent. Even when older adults take up physical activity in community settings, the adherence rates have been reported to be little better than those reported for other segments of the population (Rhodes et al., 1999). Consequently, we discuss issues relative to adherence, in particular the social cognitive determinants of exercise behavior. Finally, we conclude with a brief section identifying areas of future endeavor in cardiovascular fitness and neurocognitive function.

2. Fitness training and cognition

Early studies of the relationship between fitness and cognition, which date back at least four decades, compared the cognitive performance of low and high fit older adults on an array of paper and pencil and computer-based tasks. In general, these studies found that higher fit individuals were able to perform more quickly and accurately on a wide variety of perceptual, cognitive, and motor tasks than low fit individuals (see Etnier et al., 1997, for review). However, whereas these early results were impressive with respect to the magnitude of fitness effects and relative consistency of results across studies, they were also inconclusive given the cross-sectional nature of the experimental designs. Although the fitness differences could indeed have been responsible for the differences in performance exhibited by the high and low fit individuals, so too could a multitude of other factors (e.g., socioeconomic status, education, lifestyle choices, general health, etc.) that may have covaried with the decision to attain and maintain high levels of fitness across many decades. Clearly, studies that entail fitness training interventions, with randomized distribution of study participants to aerobic training and control groups, were necessary to determine whether fitness training (and improvements in levels of aerobic fitness) per se, rather than the multitude of potential covarying factors, is responsible for the maintenance of perceptual, cognitive, and motor function during aging.

Indeed, a number of small randomized clinical trials have been performed to examine the influence of fitness training on the cognition of older adults (e.g., Blumenthal and Madden, 1988; Kramer et al., 1999). These studies enable one to isolate the effects of fitness training from other factors in terms of their influence on cognition. Unlike the relatively consistent pattern of results observed for cross-sectional studies of fitness and cognition, the longitudinal training studies have produced a more varied pattern of results with some studies reporting improvements in aspects of cognition with fitness training while other investigators failed to observe any such relationship between improvements in fitness and cognition. Interpretation of these somewhat ambiguous data is complicated by the variety of differences across the studies in the length, intensity, and type of fitness training regimens, the age, health, and pre- and post-training fitness levels of the study participants, the methods used for the assessment of cardiorespiratory fitness, and the tasks used to index perceptual, cognitive, and motor function improvements.

Another potential problem in interpreting the longitudinal literature on fitness and cognition is related to the fact that each of these studies enrolled a relatively small number of participants and often had substantial attrition rates and therefore likely had insufficient power to observe significant effects. To overcome this problem, Colcombe and Kramer (2002) conducted a meta-analysis to determine whether (a) fitness effects on cognition could be discerned when aggregating data across longitudinal studies and (b) whether these effects, if observed, are moderated by other variables such as age, length and intensity of fitness training, and the nature of the tasks used to assess cognition. Fitness intervention studies conducted from 1966 through 2001 were included in the analysis. Several interesting and potentially important results were obtained from the meta-analysis. First, a clear and significant effect of aerobic fitness training was found. Thus, when aggregating across studies fitness training does indeed have beneficial effects on the cognitive function of older humans. Second, fitness training had selective effects on cognitive function. Although fitness effects were observed across a wide variety of tasks and cognitive processes, the effects were largest for those tasks that involved executive control (i.e., planning, scheduling, working memory, interference control, and task coordination) processes. Such a conclusion supports our earlier findings indicating that increases in cardiovascular fitness significantly improved executive control tasks in older adults (Kramer et al., 1999). Executive control processes have been found to decline substantially as a function of aging (West, 1996), as have the brain regions that support them (Raz, 2000). Therefore, the results of the meta-analysis suggest that even processes which are quite susceptible to age-related changes appear to be amenable to physical activity intervention.

The meta-analysis also revealed that a number of other moderator variables influenced the relationship between fitness training and cognition. For example, fitness training programs that were combined with strength and flexibility training regimens had a greater positive effect on cognition than fitness training programs that included only aerobic components. Fitness training programs also had a larger impact on cognition if the study samples included more than 50% females. Finally, exercise effects on cognition were found to be largest for exercise training interventions that exceeded thirty minutes per session. In sum, the results of the Colcombe and Kramer meta-analysis provide support for the veracity of the fitness-cognitive function relationship, as well as identifying important moderating influences on this relationship. We now consider the functional significance of these moderating effects by critically reviewing the non-human animal research that has attempted to explicate the mechanisms that underlie fitness effects on performance and cognition at the molecular and cellular level.

3. Animal research on fitness, brain structure, brain function, and performance

The animal research on fitness effects on brain function and structure can be traced to a long-term interest of neuroscientists in brain plasticity. Much of the early research on brain plasticity examined the influence of enriched versus impoverished environments with rats and mice but was restricted to the study of young animals, largely because brain plasticity was believed to exist only in young organisms. However, later research discovered that morphological changes in brain structure could also be obtained with older animals, albeit to a lesser extent than with young organisms. The changes engendered by enriched environments include increased dendritic branching, capillary development, the development of new neurons presumably from adult stem cells, enhanced learning and memory, as well as a cascade of molecular and neurochemical changes (Rosenzweig and Bennett, 1996).

Studies have also focused on the influence of fitness interventions on brain structure and function. For example, Black et al. (1990) contrasted the effects of fitness training with motor skill learning. Groups of rats had either free access to activity wheels, were encouraged to utilize an activity wheel, or learned non-aerobic motor skills (e.g., traversing rope bridges, climbing over and under obstacles, etc). The groups with access to the activity wheel (either forced or voluntary) were found to have a higher density of capillaries in the cerebellum than the animals trained on motor skills or the inactive control animals. Interestingly, the animals in the motor skill group showed a larger number of synapses in the cerebellum than the other three groups. Thus, these two different forms of training, aerobic and motor skill, had differential effects on the vasculature and synaptic connectivity of the brain. Subsequent studies have shown that fitness training can also enhance vascularization of other regions of the brain, such as the motor cortex, in primates as well as rats. It has been suggested that increases in vascularization serves an important function in providing a greater reserve capacity to respond in situations requiring increased oxygen (Swain et al., 2003).

Other studies have shown additional benefits for physical activity. For example, physical activity has been found to increase cell proliferation, cell survival, and neurogenesis in the hippocampus, to improve hippocampus-dependent spatial learning, and to enhance long-term potentiation or synaptic plasticity (van Praag et al., 1999). Physical activity has also been found to increase levels of nerve growth factors, such as brain-derived neurotrophic factor (BDNF), which serves to enhance synaptic efficiency, by supporting the survival and growth of a number of neuronal subtypes. These effects, in turn, support plasticity through enhanced learning and memory.

The findings derived from the study of fitness training on brain function and structure in animal models provides a conceptual framework for better understanding the cognitive function-cardiovascular fitness relationship in humans and the factors that may moderate this relationship. For example, meta-analytic findings (Colcombe and Kramer, 2002) suggest that aerobic training interventions that also included a strength training protocol may provide greater overall benefits on cognitive performance than those that only have an aerobic training component. One possibility is that the additional strength gained in the anaerobic training simply provides greater physical resources to facilitate the aerobic training component. Or, one might argue that weight training might induce an increase in cognitive activity in participants, which itself may increase cognitive function. However, strength training is known to increase levels of insulin-like growth factor 1 (IGF-1) (Borst et al., 2002), which in turn is known to have positive effects on neuronal growth, survival, differentiation, and performance, perhaps by acting as an upstream moderator of BDNF mRNA transcription (Mackay et al., 2003; Cottman and Berchtold, 2002). Therefore, increased levels of IGF-1 may help to accentuate the effects of aerobic training in older individuals by modulating exercise-induced levels of BDNF. Although somewhat speculative, the corroboration between human cognitive studies and data from animal models suggests that the assessment of strength training history, or combined strength and cardiovascular training on brain morphology and/or cortical function in humans may be warranted. We now turn to studies that have attempted to empirically link animal research that has focused on fitness effects on brain structure and function and human research that has examined the link between fitness and cognition.

4. Beyond cognition and fitness: human studies of the relationship between fitness and brain structure and function

The studies reviewed above suggest that fitness effects can be observed in both brain structure and function. However, thus far the study of fitness effects on cognitive function and brain structure has been largely confined to humans and animals, respectively. A recent study from our research group (Colcombe et al., 2003) attempted to bridge this gap by examining the relationship between the density of cortical grey and white matter and aerobic fitness in a sample of adults ranging from 55 to 79 years of age. To do so, high resolution magnetic resonance imaging (MRI) scans were analyzed using a Voxel-Based Morphometric (VBM) approach. In VBM analyses, high-resolution brain scans are segmented into grey and white matter maps, spatially warped into a common coordinate system, and examined for systematic changes in tissue density as a function of some other variable of interest (e.g., age, cardiovascular fitness, etc.). This technique allows examination of the entire brain in a point-by-point fashion, revealing spatially precise estimates of systematic variation in brain tissues. VBM provides a substantial advantage over other techniques, such as global estimates of grey and white matter volume, in that it allows researchers to localize the effects of a given variable to a specific region of the brain.

Our findings indicated that cardiovascular fitness levels significantly moderated the trajectory of age-related tissue loss. Older adults with greater levels of aerobic fitness demonstrated significantly less grey matter loss in the frontal, temporal, and parietal lobes, and significantly less tissue loss in the anterior and posterior white matter tracts. It is noteworthy that these findings remained statistically significant even after correcting for the potential moderating effects of socioeconomic status, tobacco, caffeine, alcohol consumption, and hypertension. Further analyses of these data have enabled us to examine the relationship between hormone replacement therapy (HRT), aging, and fitness. Consistent with the observations in the animal literature (Berchtold et al., 2001) we found a trend for increased cortical density in females who exercised, with the greatest effect for post-menopausal females who were currently undergoing hormone replacement therapy (HRT). One explanation for this effect is that estrogen replacement is known to increase mRNA transcription of BDNF in ovarectomized animals (Berchtold et al., 2001). As such, estrogen replacement may boost BDNF levels in a synergistic fashion with exercise, leading to an accentuation of the benefits of cardiovascular fitness in post-menopausal females. Indeed, the brain regions that benefited from the interaction of HRT and fitness were the same as those that demonstrated a beneficial influence of fitness differences in the sample of older male and female participants in the Colcombe et al. (2003) study.

These latter effects are interesting, particularly given that a high proportion of females were reported to show greater benefits of cardiovascular fitness training in the Colcombe and Kramer (2002) meta-analysis. Although somewhat speculative, the effects of HRT on cortical density suggest the possibility that a subset of females undergoing estrogen replacement therapy in these studies may have been responsible for driving the apparent gender effect in the Colcombe and Kramer meta-analysis. Recent meta-analyses of the effects of estrogen replacement on demented and non-demented post-menopausal females has shown that estrogen replacement can have a positive impact on cognitive function (Maki et al., 2001; Zek and Trivedi, 2002) whereas other studies (e.g., Shumaker et al., 2003) have shown that combined estrogen and progestin therapy may have a negative impact on cognitive function Further studies will be necessary to examine the complex relationship between HRT, fitness and cognition in older women (LeBlanc et al., 2001).

The cortical density findings reported by Colcombe et al. (2003) are consistent with the findings from the behavioral literature that show fitness has its greatest impact on executive functions, which are subserved in large part by the frontal and parietal regions of cortex (see Kramer et al., 1999). The corroboration of the behavioral changes that result from improvements in fitness and the regional differences in brain morphology seen as a function of participants' current fitness status suggest that improvements in behavioral functioning resulting from aerobic training protocols are manifest at a relatively low biological level. Specifically, aerobic fitness can help to maintain the structural integrity of both the local cortical processing units (grey matter) and the pathways by which these processing units coordinate themselves to accomplish complex computations (white matter tracts). This supposition is further bolstered by recent findings from our laboratories that suggest both high levels of cardiovascular fitness and improvements in fitness brought about by aerobic training can impact cortical recruitment in aging individuals. We turn now to a brief report of these data.

In a recent series of studies (Colcombe et al., in press), we investigated the relationship between fitness and cortical function using an event-related functional magnetic resonance imaging (fMRI) technique. Specifically, we asked older adults to perform a modified version of the flanker paradigm, while we assessed regional blood flow using a T2* echo-planar imaging scanning protocol. Participants were asked to identify the orientation of a central arrow cue ('<' or '>') by depressing a left or right button. These central cues were flanked on either side by two arrow cues that pointed in the same direction (e.g., '<<<<<') or a different direction (e.g., '>><>>'). In order to make a correct response in the presence of inconsistent flanking cues, participants were required to inhibit or filter the information provided by the inconsistent cues in favor of the central cue.

In study 1, participants completed the fMRI portion of the study, and then their current levels of aerobic fitness were assessed. In study 2, subjects participated in a 6-month randomized controlled trial comparing effects of an aerobic training condition and a non-aerobic control condition. Participants in study 2 completed the fMRI portions of the study prior and subsequent to the training intervention. If, in fact, aerobic fitness positively influences cortical functioning, we would expect that the recruitment of areas involved in selective attention would show increased activity associated with greater baseline levels of aerobic fitness (study 1) and cardiovascular fitness change brought about by aerobic training (study 2). Additionally, the increased performance of these regions should lead to reductions in interference from the inconsistent flanking items and reduction in activity in regions of cortex sensitive to the behavioral conflict engendered by the inconsistent flanking cues.

The results of the studies were consistent with the predictions above. In study 1, older adults with higher levels of fitness showed significantly less behavioral conflict than their lower fitness counterparts, as measured by the relative amount of time taken to respond to the central cue in the presence of the inconsistent flanking items, compared to congruent stimuli. Similarly, aerobically trained individuals in study 2 showed significantly less behavioral interference after the 6-month training protocol, whereas control participants showed no such benefit. Additionally, high fit participants in study 1 showed greater activity in attentionally relevant regions of the cortex of the frontal and parietal lobes than low fit participants, and less activity in the dorsal anterior cingulate cortex, a region of cortex sensitive to behavioral conflict. Also, aerobically trained individuals in study 2 showed an increase in the recruitment of attentional circuitry and a reduction in activity in the dorsal anterior cingulate after the 6-month training protocol, compared to control participants. Moreover, these regions spatially overlapped with those identified in study 1.

Taken together, the observed effects of cardiovascular fitness on brain structure and function are encouraging and suggest that maintaining higher levels of aerobic fitness may protect the brain against the normal effects of aging as well as cumulative effects of age-associated health problems. Additionally, it appears that even relatively short aerobic training interventions may begin to repair or restore the aged brain as well as enhance performance on a variety of cognitive tasks. However, the exact mechanisms that underlie these improvements are not clearly established in humans. It is possible that the same effects resulting from aerobic exercise seen in other animal models, such as increased neuronal number, interconnections, etc. underlie both the differences in volume and cortical recruitment seen in the studies reviewed in this paper.

5. Behavioral issues relevant to fitness effects on brain structure and function

Employing cardiovascular fitness training as a behavioral intervention to maintain and enhance brain structure and function is an exciting avenue of research with the potential for a considerable public health yield. However, it is important to remember that such effects are a function of a *behavioral* intervention and therefore all benefits are predicated on successfully adhering to exercise regimens. Unfortunately, sedentary behavior among adults represents more normative behavior than an exception to the norm with approximately 66% of adults aged 65 and older not engaging in any regular physical activity (Administration on Aging, 2002). Even when older adults take up physical activity in community settings, the adherence rates have been reported to be little better than those reported for other segments of the population (Ecclestone et al., 1998).

Our research group, in realizing the importance of adherence to successful outcomes at the cognitive and neuroanatomical levels, has adopted a social cognitive perspective to better understanding and facilitaing adherence to fitness training interventions. Self-efficacy expectations play a pivotal role in social cognitive theory (Bandura, 1986) and have been the most consistently identified correlate of physical activity adherence. However, until recently, no empirical examinations have considered what factors influence these beliefs regarding behavioral capabilities. In the context of a 6-month randomized controlled trial, we were able to demonstrate that participants who exercised more frequently, had a more positive affective experience, and enjoyed greater social support during the intervention were more efficacious with respect to maintaining physical activity beyond program termination (McAuley et al., 2003a). In turn, in a long-term follow-up study (McAuley et al., 2003b), self-efficacy was a significant independent predictor of physical activity at 6 months and 18 months beyond completion of the exercise intervention. Such findings have implications for how exercise interventions are structured to facilitate adherence and for identifying strategies to maximize maintenance of physical activity over time. Moreover, we believe that our research relative to cardiovascular fitness and brain structure and function and the psychosocial factors underlying adherence to physical activity regimens in older adults illustrate the importance of a multidisciplinary approach to the understanding of aging, physical activity, and optimal functioning.

6. Future research directions

The research that we have reviewed above has suggested that cardiovascular fitness training can have a variety of beneficial effects on cognition, brain, and psychosocial function of older adults. However, the literature also points to a number of gaps in our knowledge. For example, the Colcombe and Kramer (2002) meta-analysis suggests that women benefit more than men with respect to the cognitive benefits of fitness training and that combined aerobic and strength training interventions have a larger impact on cognitive function. However, the mechanisms that underlie such effects, as well as their robustness across heterogeneous populations that differ in age, lifestyle factors, culture, and race remain to be explored. Despite the fact that there is a growing body of animal literature on the impact of improved fitness on brain structure and function, there is at present little such information on humans. However, given the recent and continued growth of a number of neuroimaging technologies (e.g., fMRI, PET, and optical imaging) this is an area that will likely show rapid growth in the near future. Finally, it will be important to address the multiple routes by which fitness influences human cognition—whether through the reduction of cardiovascular disease, diabetes, hypertension, and stroke and/or increased cortical plasticity through changes in brain structure and function.

Acknowledgments

The preparation of this report and the research that we described from our laboratories was supported by the Institute for the Study of Aging and the National Institute on Aging (AG18008; AG 12113). Authorship of this manuscript is considered joint and reprints can be requested from any of the authors at: emcauley@uiuc.edu; a-kramer@s.psych.uiuc.edu; scolcomb@s.psych.uiuc.edu.

References

Administration on Aging. Fitness facts for older adults. 2002. Available from URL: www.aoa.dhhs.gov/aoa/eldractn/fitfact.html.

Bandura, A., 1986. Social Foundations of Thought and Action: A Social Cognitive Theory. Prentice-Hall, Englewood Cliffs, NJ.

Berchtold, N.C., Kesslak, J.P., Pike, C.J., Aldard, P.A., Cotman, C.W., 2001. Estrogen and exercise interact to regulate brain derived neurotrophin factor mRNA transcription and protein expression in the rat hippocampus. Eur. J. Neurosci. 14, 1992–2002.

Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A., Greenough, W.T., 1990. Learning causes synaptogensis, whereas motor activity causes angiogensis in cerebellar cortex of adult rats. Proc. Natl. Acad. Sci. USA 87, 5568–5572.

Blumenthal, J.A., Madden, D.J., 1988. Effects of aerobic exercise training, age, and physical fitness on memory-search performance. Psychol. Aging. 3, 280–285.

Borst, S.E., Vincent, K.R., Lowenthal, D.T., Braith, R.W., 2002. Effects of resistance training on insulin-like growth factor and its binding proteins in men and women aged 60 to 85. J. Amer. Geriat. Soc. 50, 884–888.

Bouchard, C., Shepherd, R.J., Stephens, T. (Eds.), 1994. Physical Activity, Fitness, and Health: International Proceedings and Consensus Statement. Human Kinetics, Champaign, Il.

Colcombe, S.J., Kramer, A.F., Erickson, K.I., Scalf, P., McAuley, E., Cohen, N.J., Webb, A.J., Jerome, G.J., Marquez, D.X., Elavsky, E., in press. Cardiovascular fitness, cortical plasticity, and aging. Proc. Natl. Acad. Sci. USA.

Colcombe, S.J., Kramer, A.F., 2002. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol. Sci. 14, 125–130.

Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J., McAuley, E., Kramer, A.F., 2003. Aerobic fitness reduces brain tissue loss in aging humans. J. Gerontol:Bio. Med. Sci. 53, 176–180.

Cottman, C.W., Berchtold, N.C., 2002. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 25, 292–298.

Ecclestone, N.A., Myers, A.M., Paterson, D.H., 1998. Tracking older participants of twelve physical activity classes over a three-year period. J. Aging Phys. Activ. 6, 70–82.

Etnier, J.R., Salazar, W., Landers, D.M., Petruzzello, S.J., Han, M., Nowell, P., 1997. The influence of physical fitness and exercise upon cognitive functioning: a meta-analysis. J. Sport Exerc. Psychol. 19, 249–277.

Federal Interagency Forum on Aging-Related Statistics, 2000. Older Americans 2000: Key Indicators of Well-Being. US Government Printing Office, Washington, DC.

Kramer, A.F., Hahn, S., Cohen, N.J., Banich, M., McAuley, E., Harrison, C.R., Chason, J., Vakil, E., Bardell, L., Boileau, R.A., Colcombe, A., 1999. Aging, fitness, and neurocognitive function. Nature 400, 418–419.

LeBlanc, E.S., Janowsky, J., Chan, B.K.S., Nelson, H.D., 2001. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 285, 1489–1499.

Mackay, K.B., Loddick, S.A., Naeve, G.S., Vana, A.M., Verge, G.M., Foster, A.C., 2003. Neuroprotective effects of insulin-like growth factor-binding protein ligand inhibitors in vitro and in vivo. J. Cereb. Blood Flow Metab. 23, 1160–1167.

Maki, P., Zonderman, A., Resnick, S., 2001. Enhanced verbal memory in nondemented elderly women receiving hormone replacement therapy. Am. J. Psychiatry 158, 227–233.

McAuley, E., Jerome, G.J., Marquez, D.X., Elavsky, S., Blissmer, B., 2003a. Exercise self-efficacy in older adults: social, affective, and behavioral influences. Ann. Behav. Med. 25, 1–7.

McAuley, E., Jerome, G., Elavsky, S., Marquez, D.X., Ramsey, S.N., 2003b. Predicting long-term maintenance of physical activity in older adults. Prev. Med. 37, 110–118.

Raz, N., 2000. Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In: Craik, F.M., Salthouse, T.A. (Eds.), The Handbook of Aging and Cognition, vol. 2. Lawrence Erlbaum Associates, Mahweh, NJ, pp. 1–90.

Rhodes, R.E., Martin, A.D., Taunton, J.E., Rhodes, E.C., Donnelly, M., Elliot, J., 1999. Factors associated with exercise adherence among older adults. Sports Med. 6, 397–411.

Rosenzweig, M.R., Bennett, E.L., 1996. Psychobiology of plasticity: effects of training and experience on brain and behavior. Behav. Brain Res. 78, 57–65.

Swain, R.A., Harris, E.C., Weiner, M.V., Dutka, H.D., Theien, S., Konda, S., Engberg, K., Lauterbur, P.C., Greenough, W.T., 2003. Prolonged Exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience 117, 1037–1046.

Shumaker, S.A., Legault, C., Rapp, S.R., Thal, L., Wallace, R.B., Ockene, J.K., Hendrix, S.L., Jones III, B.N., Assaf, A.R., Jackson, R.D., Kotchen, J.M., Wassertheil-Smoller, S., Wactawski-Wendeumaker, J., 2003. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in post-menopausal women. JAMA 289, 2651–2662.

Stewart, A.L., King, A.C., 1991. Evaluating the efficacy of physical activity for influencing quality-of-life outcomes in older adults. Ann. Behav. Med. 13, 108–116.

van Praag, H., Kempermann, G., Gage, F.H., 1999. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat. Neurosci. 2, 266–270.

West, R., 1996. An application of prefrontal cortex function theory to cognitive aging. Psychol. Bull. 20, 272–292.

Wilson, R.S., Bennett, D.A., Bienias, J.L., Aggarwal, N.T., Mendes de Leon, C.F., Morris, M.C., Schneider, J.A., Evans, D.A., 2002. Cognitive activity and incident AD in a population-based sample of older adults. Neurology 59, 1910–1914.

Zek, R.F., Trivedi, M.A., 2002. The effects of estrogen replacement therapy on neuropsychological functioning in post-menopausal women with and without dementia: a critical and theoretical review. Neuropsychol. Rev. 12, 65–109.