Review TRENDS in Cognitive Sciences Vol.11 No.8

Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function

Arthur F. Kramer and Kirk I. Erickson

Beckman Institute and Department of Psychology, University of Illinois, Urbana, IL 61801, USA

Given the aging populations in many countries throughout the world, there is an increasing interest in lifestyle factors and interventions that will enhance the cognitive vitality of older adults and reduce the risk for age-related neurological disorders, such as Alzheimer's disease. In this review, we evaluate the hypothesis that physical activity and exercise might serve to protect, and also enhance, cognitive and brain function across the adult lifespan. To this end, we critically review three separate literatures that have examined the influence of physical activity and exercise on cognition, brain function and brain structure of adults, including epidemiological or prospective observational studies, randomized human clinical interventions and non-human animal studies. We suggest that this literature supports the claim that physical activity enhances cognitive and brain function, and protects against the development of neurodegenerative diseases. We discuss future directions to address currently unresolved questions, such as interactions between multiple lifestyle factors on offsetting or protecting against cognitive and neural decline, and conclude that physical activity is an inexpensive treatment that could have substantial preventative and restorative properties for cognitive and brain function.

Introduction

Given our aging populations [1], the mantra of 'successful aging' seems to be ever present in our fast-paced, high-tech society. A visit to your local electronics store will quickly reveal an increasing number of computer games, such as Nintendo's Brain Age™ and Mattel's Brain Games™, which are touted to train your brain and keep you mentally young. These products, and many others, are also easily downloadable, for a fee, from a multitude of websites. The number of books offering solutions to age-related declines in cognitive function, including many aspects of memory, are also proliferating at a rapid pace. Claims in the media, and on the shelves of health food stores, also abound with regard to the beneficial effects of nutraceuticals and supplements on health and functioning throughout the lifespan. Unfortunately, physicians, researchers and the public need to wade through the sometimes disingenuous marketing of these products and treatments to select and prescribe the ones that are the most likely to enhance or maintain cognitive functioning in adulthood. Here, we focus on one factor that has been suggested to have a positive influence on cognition and brain function, that is, physical activity and exercise.

Relative to many other products that market a 'successful aging' byproduct, exercise is accessible to nearly everyone, low-cost and low-tech, thereby allowing for potentially widespread participation. Therefore, in this review, we evaluate the claim that staying physically active can maintain, and even enhance, cognition and brain function, as well as reduce the risk of age-associated neurological disorders, such as Alzheimer's disease. We begin by examining the epidemiological or prospective observational literature that has explored this issue, often with middle age and older adults. Next, we examine randomized clinical trials that have examined the influence of fitness training programs on cognition and, less frequently, measures of brain function and structure. We then provide a brief review of the ever expanding animal literature, which has begun to elucidate the cellular and molecular mechanisms of physical activity effects on brain and cognition. Finally, we conclude with a brief prescription of future directions for research on maintaining cognitive vitality across the adult lifespan.

Human observational studies of physical activity and exercise

In recent years, there has been an increasing interest in the relationship between physical activity and exercise at one point in the lifespan and cognition or the diagnosis of age-associated neurological diseases at a later point in time. One reason for this interest is the burgeoning literature on the reduction in risk for a multitude of diseases, including cardiovascular disease, breast and colon cancer, obesity, and type II diabetes, associated with physical activity [2]. However, another important factor influencing the interest in physical activity and cognition is the animal research on the positive effects of enriched environments, which often include a physical activity component, on learning, memory and brain function [3].

Observational studies generally assess physical activity and exercise with self-report questionnaires, and then follow-up, often 2–9 years later, with an examination of cognitive function or an assessment of Alzheimer's or other forms of dementia. Given that the decision to partake in physical activity is often related to other lifestyle choices

Corresponding author: Kramer, A.F. (a-kramer@uiuc.edu).
Available online 12 July 2007.

 1364-6613/$ – see front matter doi:10.1016/j.tics.2007.06.009

and medical conditions, such as obesity, socio-economic status, and smoking and drinking intake, these observational studies also assess such lifestyle and demographic factors, which are then used as covariates in the examination of physical activity effects on cognition.

Several prospective observational studies have found a reduction of risk for Alzheimer's disease and other forms of dementia for more physically active individuals. For example, Larson *et al*. [4] assessed 1740 adults over the age of 65 on the frequency of participation in a variety of physical activities (e.g. walking, hiking, bicycling and swimming). After a mean follow-up of 6.2 years, 158 of the original participants had developed dementia. After adjusting for age, sex and medical conditions, individuals who exercised more than three times per week during initial assessment were found to be 34% less likely to be diagnosed with dementia than those who exercised fewer than three times per week. Similar relationships between exercise and dementia have been reported in other studies [5–7]. Some studies have focused specifically on walking and its relationship to dementia. Abbott *et al.* [8] examined the distance that 2257 physically capable men, aged 71 to 93, walked on a daily basis and then followed up an average of 4.7 years later with an assessment of dementia. After adjusting for cognitive ability, education and medical conditions at baseline, both walking speed and distance were associated with a reduced risk for dementia.

A reduction of risk for cognitive decline, often measured with a general test of cognitive function, such as the mini-mental state examination (MMSE), has also been found for physically active individuals who have not been diagnosed with dementia [9–12]. A particularly noteworthy study was reported by Barnes *et al.* [13] who obtained both subjective and objective measures of cardiorespiratory fitness in a sample of 349 individuals over 55. Six years later these individuals were tested on both the MMSE and more focused tests of executive control, attention, verbal memory and verbal fluency. Individuals who were higher fit at the first assessment showed benefits on tests of all of these abilities at the final assessment, and the relationship between fitness and cognition was stronger for the objective than for the subjective measure of fitness.

Although, in general, the majority of the observational studies have found a positive relationship between physical activity and cognition, it is important to note that some observational studies have failed to find a relationship between fitness or physical activity and cognition or dementia [14–17]. It is difficult to know which factors are most important in moderating the influence of physical activity on later life cognition and dementia. However, some possibilities that merit further study include: the distinction between aerobic and nonaerobic physical activities [13]; the utility of self-report versus more objectively measured physical activities and fitness; the relative contribution of social, intellectual and physical factors to different everyday activities [18]; the role of physical activity duration, intensity, and frequency [19]; the nature of the components of cognition that serve as the criterion variables [20,21]; the age of participants at initial and final assessment; and genetic factors [6,22,23,24].

Beyond observation: randomized clinical trials in humans

Observational studies have provided intriguing support for the relationship between physical activity and cognition. However, such studies cannot establish causal links between these constructs. Over the past several decades there have been a relatively small but increasing number of clinical trials in which relatively sedentary individuals, often over the age of 60, are randomized to an aerobic training group (i.e. walking, swimming and bicycling) and a control group that often entails nonaerobic activity, such as toning and stretching. Training is usually conducted for an hour a day for several days a week and can last from several months to years. Cognition, and less frequently brain function and structure, is examined before and after the interventions.

Results of such studies have been mixed with some reporting that aerobic exercise differentially benefits aspects of cognition whereas other studies have failed to observe such a relationship. Several potential reasons for this mixed pattern of results include: (i) the manner in which cardiorespiratory fitness was characterized from resting heart rate to the gold standard, VO_2 max; (ii) the length, duration and intensity of exercise training; (iii) the cognitive processes examined in the studies; and (iv) the age, health, sex and fitness levels of participants. Given the substantial variability in individual and experimental characteristics, several meta-analyses have been conducted in recent years to determine, first, whether a robust relationship between exercise training and cognition can be discerned and, second, which factors moderate such a relationship [20,25,26].

The results are clear with respect to the first question, exercise training positively influences cognition. Several additional results are noteworthy. First, the effect size of exercise training, ~0.5 over various analyses, is similar for both normal and cognitively impaired adults. Thus, older adults with early dementia seem able to benefit from exercise training, albeit from a different cognitive baseline. Second, studies with more women generally show a larger effect of exercise training on cognition than studies with fewer women (see Box 1 for one potential explanation of this observation). Third, although exercise training has relatively broad effects across a variety of perceptual and cognitive processes, the benefits of exercise training seem to be larger for executive control processes (e.g. planning, scheduling, working memory, dealing with distraction and multi-tasking). This observation is interesting given that executive control processes show substantial declines over the adult lifespan.

Fourth, overall there was little evidence of a significant relationship between fitness change and cognitive change. At first glance this observation seems perplexing. However, upon further consideration this might not be surprising given that the measures of fitness obtained in these studies are global in nature (i.e. sensitive to both peripheral and central nervous system changes) and not specific to brain function (also see Ref. [25]).

As compared with the study of the relationship between exercise training and cognition, relatively few studies have been conducted to examine exercise training influences on human brain structure and function. Colcombe *et al.* [27]

Box 1. Exercise and estrogen

Exercise and estrogen upregulate many of the same biochemical markers in the brain that enhance the capability for cognitive and neural plasticity. For example, the production of brain-derived neurotrophic factor (BDNF), a molecule involved in neurogenesis, neuroprotection, and learning and memory operations, is increased with both exercise and estrogen replacement [50,51]. In addition, the combination of treatments produces different results compared with each treatment in isolation. For example, in ovariectomized young and middle-aged female rats, the combination of both voluntary exercise and estrogen administration increases levels of BDNF in the hippocampus above that of either treatment alone, whereas levels in the striatum and cerebellum are unaffected [50,51]. Such an interaction might enhance learning and memory operations subsumed by the hippocampus [52]. Some evidence for a synergistic relationship between hormone therapy and aerobic exercise is also apparent in humans. For example, women who receive hormone replacement therapy report greater levels of physical activity and exercise participation than women who do not receive hormone therapy [53]. Furthermore, a recent meta-analysis reported that exercise interventions with a higher ratio of females to males showed greater enhancing effects of exercise on cognition than those studies with more males [20]. In a systematic study of this relationship, Erickson *et al.* [54] examined the interactive effects of hormone replacement therapy and aerobic fitness levels on cortical volume and executive functioning in postmenopausal women (Figure I). They reported that higher levels of aerobic fitness reliably augmented the cortical and cognitive sparing effects of short durations of therapy and offset the deteriorating effects of long durations of hormone therapy. They concluded that interactions between hormone therapy and aerobic exercise affect both prefrontal cortex volume and executive function in postmenopausal women (Figure I). It is possible that other factors, such as age since menopause or type of hormone therapy, also moderate this effect.

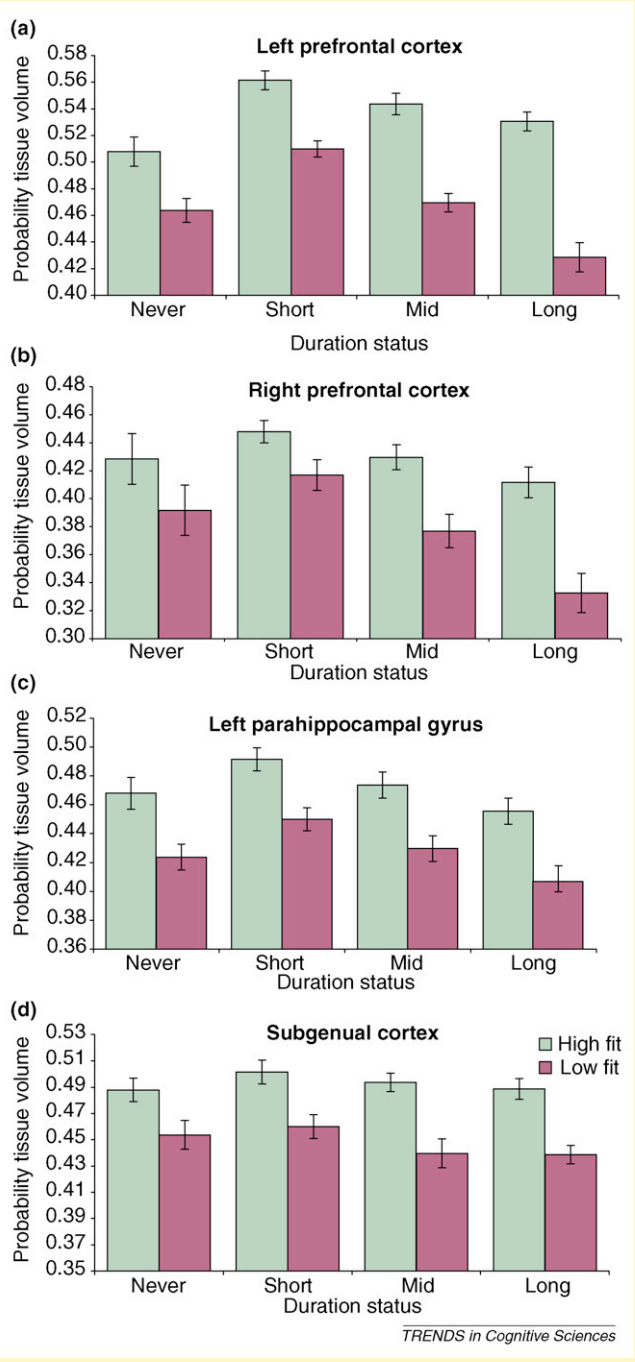

Figure I. Mean brain volume measures in the **(a)** left prefrontal cortex, **(b)** right prefrontal cortex, **(c)** left parahippocampal gyrus, and **(d)** subgenual cortex for never users, short-term users (less than 10 years), mid-term users (11 to 15 years) and long-term (greater than 15 years) users of hormone therapy. The green bars represent high-fit participants and pink bars represent low-fit participants. Main effects were found in all four regions for duration of treatment and VO_2. The left and right prefrontal cortex and the subgenual cortex showed significant interactions between duration of hormone therapy and fitness levels. In addition, the left prefrontal and right prefrontal tissue volume measures were significantly correlated with perseverative errors on the Wisconsin Card Sorting Test (i.e. greater volume is associated with fewer errors). Reproduced, with permission, from Ref. [54].

investigated changes in a neural network, which supports attentional control, as indexed by functional magnetic resonance imaging (fMRI) activation obtained in a high field magnet, over the course of a six month aerobic exercise program. Older adults performed the flanker task, which entails focusing on a subset of information presented on a visual display and ignoring task-irrelevant distractors, before and after the exercise training interventions. Individuals in the aerobic training group (i.e. walking) showed a reduced behavioral distraction effect and change in pattern of fMRI activation similar to that displayed by younger controls (i.e. increased right middle frontal gyrus and superior parietal activation). Participants in the toning and stretching control group did not show such behavioral and fMRI changes. More recently, Colcombe *et al.* [28] employed a semi-automated segmentation technique on high-resolution MRI data from older adults who were randomly assigned to either six months of an exercise intervention or a stretching and toning, nonaerobic control group. The older adults who walked three days a week for ~1 h per day for six months displayed increases in gray matter volume in the frontal and temporal cortex, as well as increases in the volume of anterior white matter (Figure 1). There were no volumetric increases for the nonaerobic control group or in a group of college-student control participants. Although such structural changes as

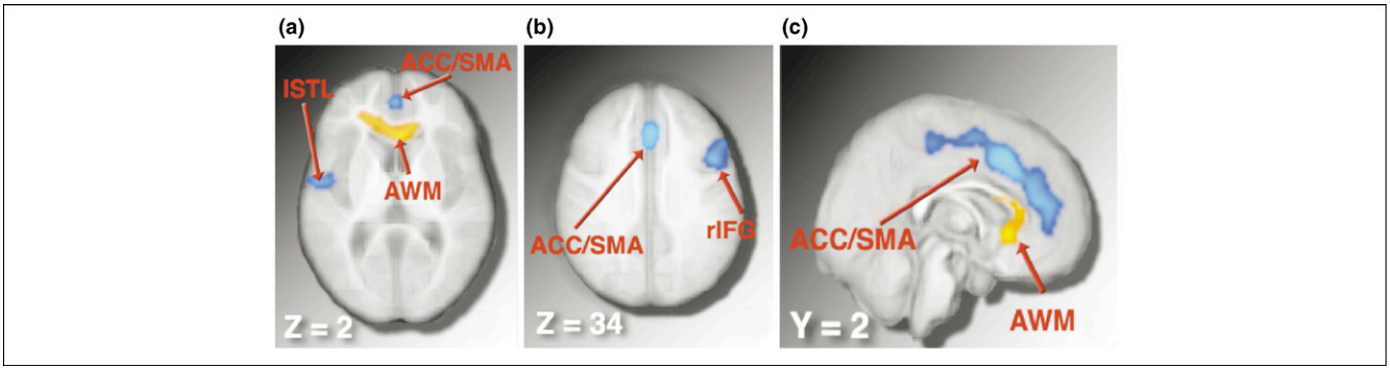

Figure 1. The brain regions showing a significant increase in volume for older adults who participated in an aerobic fitness training program, compared with nonaerobic (stretching and toning) control older adults. **(a,b)** Neurologically oriented axial slices through the brain at (a) +2 and (b) +34 mm in stereotaxic space. **(c)** A sagittal slice 2 mm to the right of the midline of the brain. Blue regions show where gray matter volume was increased for aerobic exercisers, relative to non-aerobic controls. Areas in yellow show where white matter volume was increased for aerobic exercisers, relative to controls. Reproduced, with permission, from Ref. [28].

a function of an exercise intervention parallels cognitive improvements observed with six months of exercise, it is unknown whether increases in cortical volume are directly related to enhanced cognitive performance. Finally, Pereira *et al.* [29] reported increases in MRI measures of cerebral blood volume (CBV) in the dentate gyrus of the hippocampus for a group of 11 middle-aged individuals who participated in a three month aerobic exercise program. These CBV changes were related to both improvements in cardiorespiratory fitness and performance on a test of verbal learning and memory. Increases in CBV in a parallel study of exercising mice were found to be related to enhanced neurogenesis [29]. Therefore, the results of this study are particularly exciting in suggesting that CBV might serve as a biomarker for neurogenesis in humans.

Animal research: cellular and molecular mechanisms

Research using non-human animals complements human research in several ways. First, many of the uncontrolled variables in human research can be more easily controlled or systematically manipulated in non-human animal research, thereby enabling a more precise examination of some of the factors influencing brain and cognition. Second, the technical capabilities to assess the molecular and cellular mechanisms of exercise are substantially greater in non-human animals than in humans. Therefore, non-human animal research provides an important translational approach to understanding neurocognitive plasticity in humans.

In rodents, voluntary exercise enhances the rate of learning on swimming tasks, such as the Morris Water maze, that require the use of extra-maze cues to determine the location of a submerged platform [30,31]. For example, in older animals, van Praag *et al.* [32] reported that 45 days of access to a running wheel resulted in faster acquisition and greater retention on the water maze than age-matched sedentary controls. Other tasks, such as the passive avoidance task, in which animals are trained via foot-shock to refrain from entering into a dark chamber, also show performance improvements with exercise [33]. Similar behavioral benefits of exercise have been reported in rodent models of Alzheimer's disease [34] and Huntington's disease [35]. Therefore, there is ample evidence that exercise promotes faster rates of learning and improved retention on tasks mediated by the hippocampus.

Enhanced learning on water maze tasks has been associated with an increased production of neurotrophic molecules, such as brain-derived neurotrophic factor (BDNF), and a series of molecular and cellular cascades. BDNF is involved in neuroprotection and promotes cell survival, neurite outgrowth and synaptic plasticity [36]. For example, direct administration of BDNF increases cell proliferation in the hippocampus, whereas blocking BDNF reduces cell proliferation. Voluntary exercise increases both mRNA and protein levels of BDNF in the hippocampus, cerebellum and frontal cortex, and blocking the binding of BDNF to its receptor abolishes the exercise-induced performance benefits on the Morris water maze [31]. Therefore, exercise increases BDNF levels, which seem to be inextricably related to the behavioral improvements observed with an exercise treatment.

BDNF is not the only molecule in the brain affected by exercise. For example, insulin-like growth factor-1 (IGF-1) is crucial for both exercise-induced angiogenesis [37] and neurogenesis [38]. By blocking IGF-1 influx into the brain, exercise-induced cellular proliferation and BDNF production are effectively rescinded. In addition, IGF-1 moderates the secretion of other molecules, such as vascular endothelial growth factor (VEGF), a prominent molecule involved in blood vessel growth. For example, Lopez-Lopez *et al.* [37] reported that blocking IGF-1 blocked the secretion of VEGF, which resulted in a significant reduction in new capillaries. Furthermore, blocking the influx of VEGF into the brain abolishes exercise-induced neurogenesis, but baseline levels of neurogenesis are unaffected [39]. Therefore, a plethora of molecules and molecular cascades are upregulated with exercise that influence learning and memory operations, cortical morphology, angiogenesis and cell proliferation.

Exercise induces the development of new capillaries in the hippocampus, cerebellum and motor cortex of young rats [40–42], and reduces the volume of cortical damage caused by the induction of stroke [43]. One function of new capillaries is to deliver necessary nutrients to existing or newly dividing neurons. In relation to this, exercise increases both cell proliferation and cell survival, which has been related to enhanced learning rates on the Morris

water maze [44]. Neurogenesis is diminished with age, but exercise reliably reverses the normal decline in neurogenesis and is accompanied by improved Morris water maze performance [32,45].

It is clear that rodent research provides strong support for the positive effects of exercise on the brain and cognition. Voluntary wheel running in rodents results in enhanced learning and retention on hippocampal-dependent tasks, the induction of a variety of molecular cascades, including BDNF, IGF-1 and VEGF. In addition, both angiogenesis and neurogenesis are upregulated with exercise in young and old animals. This evidence provides an important mechanistic and molecular basis for understanding the effects of exercise on the human brain and cognition.

Conclusions and future directions

Our brief review of the literature suggests that exercise provides multiple routes to enhancing cognitive vitality across the lifespan – through the reduction of disease risk, and in the improvement in the molecular and cellular structure and function of the brain. We present here six directions for future research to isolate and delineate the cognitive and neural effects of exercise.

First, whether the molecular mechanisms of exercise are the same in both humans and rodents remains unknown. An important avenue for future research will be to assess the concentration of molecular markers in human blood and brain tissue as a function of an aerobic exercise treatment [46–48]. Such a link would provide compelling evidence that the same molecular mechanisms are functioning in both humans and rodents.

Second, a few studies have reported that the effects of aerobic exercise are not independent of factors such as estrogen, diet and social engagement [49]. However, the study of such interactions is in its infancy, and the degree and direction of these interactions needs to be more fully elucidated. An important future direction is to examine the effects of exercise within a multi-factorial framework in which a variety of lifestyle factors, or pharmacological treatments, are measured and manipulated (Box 2).

A third avenue involves determining the relationship between aerobic exercise and certain genetic profiles [6,22–24]. For example, people with certain alleles have higher risks for dementia, disease or cognitive dysfunction. Variation in genes, such as the BDNF gene, whose protein and mRNA concentrations are affected by exercise, might have a key role in determining the efficacy of an exercise intervention on cognitive and cortical outcome variables. Whether aerobic exercise offsets or diminishes the risks associated with such genetic predispositions remains an understudied question. Characterizing the genetic profiles of those people who benefit the most and those that benefit the least from an aerobic exercise regimen is needed.

Fourth, the benefits and limitations of aerobic exercise in preventing or reversing the cognitive and neural deterioration associated with neurological diseases have not been fully investigated [26]. It will be important for future research to examine the efficacy of aerobic exercise in relation to symptom severity, duration of illness, comorbidity of diseases, the brain areas and molecular factors most affected in the disease, and possible interactions with pharmaceutical treatments. Given the medical and social significance of this research, these questions should be pursued with vigor.

Box 2. Nutrition, social engagement and exercise

The effect of exercise on the brain and cognition does not occur independently of other lifestyle factors, such as diet and participation in social functions. For example, a diet rich in antioxidants, omega-3 fatty acids and B vitamins enhances cortical function and cognitive performance [55]. Conversely, diets rich in saturated fats and high calories vitiates learning and memory operations, and reduces the production of key neurotrophic factors involved in plasticity, such as BDNF [56]. However, the negative molecular and behavioral consequences of a diet high in saturated fats are reversed by exercise participation. For example, two months of voluntary exercise reverses the harmful effects of a high saturated fat diet on hippocampal BDNF levels and cognitive performance in a Morris water maze task [57]. Social engagement and participation is another lifestyle activity that can influence cognitive function, mood and psychopathology. A recent study in rodents reported that individually housed animals that voluntarily exercised for twelve days failed to exhibit exercise-induced neurogenesis in the hippocampus, and instead showed a reliable decrease in cell proliferation [58]. However, when animals were socially housed in groups of three, exercise reliably induced the proliferation of new neurons and protected against the negative influence of stress on neurogenesis. Forty-eight days of exercise was required before socially isolated rats displayed equivalent amounts of new neurons to that of socially housed animals. These results indicate the importance of social engagement on neuron proliferation and suggest that many of the benefits of exercise are dependent upon social involvement. Although assessing the interactions between exercise and other lifestyle factors, such as diet and social engagement, is in its infancy, it is apparent that such factors and interactions are crucial for a thorough understanding of the phenomena that best maintain, protect and rehabilitate cortical and cognitive function.

Fifth, another direction for future research is to specify which cognitive operations are most affected by aerobic exercise. For example, it seems that in humans aerobic exercise affects executive functions more than other cognitive processes [20]. However, what remains unaddressed is what aspect(s) of executive function is most affected with exercise: response preparation, response selection, conflict detection, task-switching, task and goal maintenance in working memory, etc. The nature of exercise effects on tasks that rely on the temporal lobes, consistent with the demonstration of hippocampal neurogenesis in non-human animals [29,32], is also an important research topic. Therefore, more refined task manipulations in the context of exercise interventions will enable a detailed characterization of the cognitive processes that are most affected by exercise.

Finally, few experimental studies investigate whether the benefits of exercise extend outside the laboratory to everyday cognitive functioning. Although the effects are often assumed to transfer outside the laboratory, evidence to support such a claim does not currently exist. It will be important for future research on aerobic exercise to investigate the transfer of such cognitive and neural benefits to everyday functions.

Acknowledgements

We would like to thank the National Institute on Aging (RO1 AG25667 and RO1 AG25032) and the Institute for the Study of Aging for their support of our research and the preparation of this review.

References

1 Administration on Aging, U.S. Department of Health and Human Services (2005) A Profile of Older Americans: 2005. http://www.aoa.gov/PROF/Statistics/profile/2005/profiles2005.asp
2 Dishman, R.K. *et al.* (2006) The neurobiology of exercise. *Obes. Res.* 14, 345–356
3 Rosenzweig, M.R. and Bennett, E.L. (1996) Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav. Brain Res.* 78, 57–65
4 Larson, E.B. *et al.* (2006) Exercise is associated with reduced risk for incident dementia among persons 65 years of age or older. *Ann. Intern. Med.* 144, 73–81
5 Laurin, D. *et al.* (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch. Neurol.* 58, 498–504
6 Podewils, L.J. *et al.* (2005) Physical activity, apoe genotype, and dementia risk: findings from the cardiovascular health cognition study. *Am. J. Epidemiol.* 161, 639–651
7 Scarmeas, N. *et al.* (2001) Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology* 57, 2236–2242
8 Abbott, R.D. *et al.* (2004) Walking and dementia in physically capable men. *J. Am. Med. Assoc.* 292, 1447–1453
9 Almeida, O.P. *et al.* (2006) Successful mental health aging: results from a longitudinal study of older Australian men. *Am. J. Geriatr. Psychiatry* 14, 27–35
10 Lytle, M.E. *et al.* (2004) Exercise level and cognitive decline: the MoVIES project. *Alzheimer Dis. Assoc. Disord.* 18, 57–63
11 Weuve, J. *et al.* (2004) Physical activity including walking and cognitive function in older women. *J. Am. Med. Assoc.* 292, 1454–1461
12 Yaffe, K. *et al.* (2001) A prospective study of physical activity and cognitive decline in elderly women. *Arch. Intern. Med.* 161, 1703–1708
13 Barnes, D.E. *et al.* (2003) A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *J. Am. Geriatr. Soc.* 51, 459–465
14 Sturman, M.T. *et al.* (2005) Physical activity, cognitive activity, and cognitive decline in a biracial community population. *Arch. Neurol.* 62, 1750–1754
15 Verghese, J. *et al.* (2003) Leisure activities and the risk of dementia in the elderly. *N. Engl. J. Med.* 348, 2508–2516
16 Wilson, R.S. *et al.* (2002) Cognitive activity and incident AD in a population-based sample of older persons. *Neurology* 59, 1910–1914
17 Yamada, M. *et al.* (2003) Association between dementia and midlife risk factors: the radiation effects research foundation adult health study. *J. Am. Geriatr. Soc.* 51, 410–414
18 Karp, A. *et al.* (2006) Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dement. Geriatr. Cogn. Disord.* 21, 65–73
19 Van Gelder, B.M. *et al.* (2004) Physical activity in relation to cognitive decline in elderly men: the FINE study. *Neurology* 63, 2316–2321
20 Colcombe, S. and Kramer, A.F. (2003) Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol. Sci.* 14, 125–130
21 Hall, C.D. *et al.* (2001) The impact of aerobic activity on cognitive function in older adults: a new synthesis based on the concept of executive control. *Eur. J. Cogn. Psychol.* 13, 279–300
22 Etnier, J.L. *et al.* (2007) Cognitive performance in older women relative to ApoE-e4 genotype and aerobic fitness. *Med. Sci. Sports Exerc.* 39, 199–207
23 Rovio, S. *et al.* (2005) Leisure time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol.* 4, 705–711
24 Schuit, A.J. *et al.* (2001) Physical activity and cognitive decline, the role of apoliprotein e4 allele. *Med. Sci. Sports Exerc.* 26, 772–777
25 Etnier, J.L. *et al.* (2006) A meta-regression to examine the relationship between aerobic fitness and cognitive performance. *Brain Res. Rev.* 52, 119–130
26 Heyn, P. *et al.* (2004) The effects of exercise training on elderly persons with cognitive impairments and dementia: a meta-analysis. *Arch. Phys. Med. Rehabil.* 85, 1694–1704
27 Colcombe, S.J. *et al.* (2004) Cardiovascular fitness, cortical plasticity, and aging. *Proc. Natl. Acad. Sci. U. S. A.* 101, 3316–3321
28 Colcombe, S.J. *et al.* (2006) Aerobic exercise training increases brain volume in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 61, 1166–1170
29 Pereira, A.C. *et al.* (2007) An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci. U. S. A.* 104, 5638–5643
30 Adlard, P.A. *et al.* (2004) The time course of induction of brain-derived neurotrophic factor mRNA and protein in the rat hippocampus following voluntary exercise. *Neurosci. Lett.* 363, 43–48
31 Vaynman, S. *et al.* (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur. J. Neurosci.* 20, 1030–1034
32 van Praag, H. *et al.* (2005) Exercise enhances learning and hippocampal neurogenesis in aged mice. *J. Neurosci.* 25, 8680–8685
33 Alaei, H. *et al.* (2006) Treadmill running reverses retention deficit induced by morphine. *Eur. J. Pharmacol.* 536, 138–141
34 Adlard, P.A. *et al.* (2005) The exercise-induced expression of BDNF within the hippocampus varies across life-span. *Neurobiol. Aging* 26, 511–520
35 Pang, T.Y.C. *et al.* (2006) Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice. *Neuroscience* 141, 569–584
36 Cotman, C.W. and Berchtold, N.C. (2002) Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 25, 295–301
37 Lopez-Lopez, C. *et al.* (2004) Insulin-like growth factor I is required for vessel remodeling in the adult brain. *Proc. Natl. Acad. Sci. U. S. A.* 101, 9833–9838
38 Trejo, J.L. *et al.* (2001) Circulating insulin-like growth factor mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J. Neurosci.* 21, 1628–1634
39 Fabel, K. *et al.* (2003) VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur. J. Neurosci.* 18, 2803–2812
40 Black, J.E. *et al.* (1990) Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc. Natl. Acad. Sci. U. S. A.* 87, 5568–5572
41 Kleim, J.A. *et al.* (2002) Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. *Brain Res.* 934, 1–6
42 Swain, R.A. *et al.* (2003) Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience* 117, 1037–1046
43 Ding, Y.H. *et al.* (2004) Exercise-induced over expression of angiogenic factors and reduction of ischemia/reperfusion injury in stroke. *Curr. Neurovasc. Res.* 1, 411–420
44 Van Praag, H. *et al.* (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* 2, 266–270
45 Kronenberg, G. *et al.* (2006) Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiol. Aging* 27, 1505–1513
46 Reuben, D.B. *et al.* (2003) The associations between physical activity and inflammatory markers in high functioning older persons: MacArthur studies of successful aging. *J. Am. Geriatr. Soc.* 51, 1125–1130
47 Ferris, L.T. *et al.* (2007) The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med. Sci. Sports Exerc.* 39, 728–734
48 Rojas Vega, S. *et al.* (2006) Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Res.* 1121, 59–65
49 Vaynman, S. and Gomez-Pinilla, F. (2006) Revenge of the "sit": how lifestyle impacts neuronal and cognitive health though molecular systems that interface energy metabolism with neuronal plasticity. *J. Neurosci. Res.* 84, 699–715
50 Berchtold, N.C. *et al.* (2001) Estrogen and exercise interact to regulate brain-derived neurotrophic factor mRNA and protein expression in the hippocampus. *Eur. J. Neurosci.* 14, 1992–2002
51 Erickson, K.I. *et al.* (2006) Estrogen and exercise interact to up-regulate BDNF levels in the hippocampus but not striatum of middle-aged Brown-Norway rats. Program No. 266.17. *Soc. Neurosci. Abstr. 2006*

52 Korol, D.L. and Pruis, T.A. (2004) Estrogen and exercise modulate learning strategy in middle-aged female rats. Program No. 770.7. *Soc. Neurosci. Abstr. 2004*
53 Perrson, I. *et al.* (1997) Hormone replacement therapy and major risk factors for reproductive cancers, osteoporosis, and cardiovascular diseases: evidence of confounding by exposure characteristics. *J. Clin. Epidemiol.* 50, 611–618
54 Erickson, K.I. *et al.* (2007) Interactive effects of hormone treatment on brain health in postmenopausal women. *Neurobiol. Aging* 28, 179–185
55 Mattson, M.P. (2000) Neuroprotective signaling and the aging brain: take away my food and let me run. *Brain Res.* 886, 47–53
56 Molteni, R. *et al.* (2002) A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 112, 803–814
57 Molteni, R. *et al.* (2004) Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. *Neuroscience* 123, 429–440
58 Stranahan, A.M. *et al.* (2006) Social isolation delays the positive effects of running on adult neurogenesis. *Nat. Neurosci.* 9, 526–533