SCIENCE AND SOCIETY

Be smart, exercise your heart: exercise effects on brain and cognition

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Abstract | An emerging body of multidisciplinary literature has documented the beneficial influence of physical activity engendered through aerobic exercise on selective aspects of brain function. Human and non-human animal studies have shown that aerobic exercise can improve a number of aspects of cognition and performance. Lack of physical activity, particularly among children in the developed world, is one of the major causes of obesity. Exercise might not only help to improve their physical health, but might also improve their academic performance. This article examines the positive effects of aerobic physical activity on cognition and brain function, at the molecular, cellular, systems and behavioural levels. A growing number of studies support the idea that physical exercise is a lifestyle factor that might lead to increased physical and mental health throughout life.

Participation in physical activity has been associated with the reduction of a number of physical (for example, cardiovascular disease, colon and breast cancer, and obesity) and mental (for example, depression and anxiety) disorders across the adult lifespan[1]. Despite mounting evidence for the importance of physical activity, 74% of adults in the United States do not meet the recommended guideline of at least 30 minutes of moderate-intensity physical activity on most days of the week[1,2]. Recent evidence further indicates that children are growing increasingly sedentary and unfit, and that these lifestyle factors are related to an earlier onset of several chronic diseases (such as type II diabetes and obesity), which typically do not emerge before adulthood[3]. As a result, recent estimates have indicated that younger generations, for the first time in United States history, might live less healthy lives than their parents[4–5]. The economic cost of this sedentary lifestyle is enormous in both developed and developing countries, with estimates indicating that inactivity was associated with 2.4% of healthcare expenditures in 1995 (REF. 6) and ~US$76 billion in medical costs in the year 2000 (REF. 7). Canadian estimates concur, as 2.5% (or $2.1 billion) of the total direct healthcare costs for the year 1999 were related to physical inactivity[8].

In addition to the physical and economic impact of physical inactivity, a growing body of literature has linked physical activity with improvements in brain function and cognition. Animal research has long shown that enriched environments, including access to exercise equipment (such as running wheels), has a positive effect on neuronal growth and on the neural systems that are involved in learning and memory, indicating that physically active behaviours influence cognitive function and the supporting brain structures[9]. A similar perspective has emerged in human research[10]; with recent advances in neuroimaging techniques showing that exercise leads to evident changes in brain structure and function. These findings allow for a better understanding of the implications of specific lifestyle factors for cognitive health.

Although the roots of a mind–body connection can be traced back to at least the ancient Greek civilization, the scientific investigation of the relation between physical activity and cognition began in the 1930s. Evidence for a relationship between physical conditioning and faster reaction time was observed during the next several decades[11–13] (although some studies indicated no such relationship[14]). The first systematic examination of this relationship began in the 1970s, with findings indicating that older adults who regularly participated in physical activity had faster psychomotor speed, relative to their sedentary counterparts, on simple and choice reaction-time tests. Interestingly, no such relationship was observed in comparable groups of younger adults[15–18], suggesting that the benefits of physical activity on cognition were specific to older adults (see REF. 19 for a review). With recent technical advancements, contemporary research has sought to understand the mechanisms that underlie the influence of exercise participation on cognition.

Here we describe the latest research, in both humans and non-human animals, on the relationship between physical activity (primarily aerobic exercise) and cognition. The research with humans has mostly focused on the effects of exercise on cognitive processes, as assessed with paper-and-pencil and computer-based tests. However, neuroimaging techniques, such as event-related brain potentials (ERP) and structural and functional MRI, are also being used to examine the link between exercise and cognition. Non-human animal research takes this investigation one step further, revealing some of the molecular and cellular changes that occur in the brain following exercise training. The findings we describe could have important implications for future healthcare and education policies.

Human research

Physical activity effects on cognition during childhood and young adulthood. Despite the fact that children in industrialized countries are growing increasingly unfit and unhealthy owing, in part, to the comforts of technological advancements, the investigation of the effects of physical activity on cognitive health during development has received surprisingly little attention. In fact, only a handful of studies using true experimental designs exist in the literature and, arguably, these studies have done little to advance our understanding of the mechanisms by which exercise influences brain function and cognition. A recent meta-analysis determined a positive relation between physical activity and cognitive performance in school-age children (aged 4–18 years) in eight measurement categories (perceptual skills, intelligence quotient, achievement, verbal tests, mathematic tests, memory, developmental level/academic readiness and other). A beneficial relationship was found for all categories, with the exception of memory, which was unrelated to physical activity behaviour[20], and for all age groups (although it was stronger for children in the age ranges of 4–7 and 11–13 years, compared with the age ranges of 8–10 and 14–18 years)[20]. The effect size (ES) observed by Sibley and Etnier[20] in their meta-analysis was 0.32 (standard deviation = 0.27), which is similar to that which was observed in a meta-analysis of the effects of physical activity on cognition (ES = 0.25) across the lifespan (6–90 years)[21]. These findings suggest that although physical activity might be beneficial at all stages of life, early intervention might be important for the improvement and/or maintenance of cognitive health and function throughout the adult lifespan.

Recently, research efforts have focused on the relation between physical activity and the academic performance of school-age children (BOX 1). Several studies have suggested that participation in physical activity has either a positive relation or is unrelated to academic performance, with differences across studies probably reflecting the techniques that were used to assess behaviour and/or the aspects of scholastic aptitude that were measured (achievement testing, grade-point average and academic records, for example)[22–24]. Regardless of the measure, these studies indicated that an increase in the amount of time dedicated towards physical health-based activities (such as physical education) is not accompanied by a decline in academic performance. The implications of these findings are important for promoting better physical health, without the loss of other educational benefits, in school-age children.

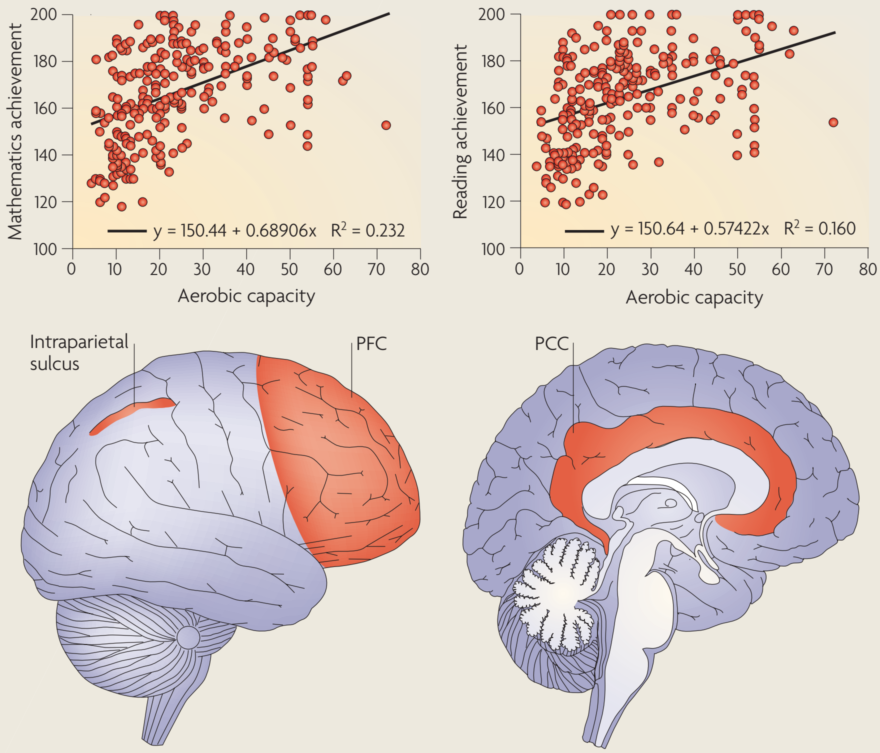
Similar to the situation with children, there is a dearth of research on exercise–cognition effects in young adults. Although exceptions exist, especially with regards to acute exercise effects on cognition[25–26] (see REF. 27 for a review), most research has used

Box 1 | **Physical activity and academic performance in school-age children**

Recently, owing to the increasing importance placed on standardized testing, many schools in the United States have reduced or eliminated physical education (PE) requirements, in an effort to increase students' academic performance. However, no empirical evidence exists to suggest that the elimination of non-academic programmes (such as PE) is related to higher academic achievement. In fact, empirical evidence suggests otherwise. Aerobic fitness has a small but positive relation to academic achievement, whereas body mass index (BMI) has a negative relation[23]. Recent studies have indicated that achievement in standardized tests of mathematics (the left-hand graph in the figure) and reading (the right-hand graph in the figure) was positively related to physical fitness scores, measured using the progressive aerobic cardiovascular endurance run (PACER) test (a 20 metre shuttle run that increases in difficulty and is considered a field test of aerobic capacity), in school-age children[88]. This relationship was selective to aerobic fitness, as muscle strength and flexibility fitness were unrelated to academic achievement[23]. Similarly, beneficial relationships have been observed between physical activity and other measures of academic performance, such as academic grades in the classroom[24,89–90].

Relevant neural networks have been identified for component processes that might be involved in mathematics and reading performance (see the lower two panels of the figure). Research that examined the functional neuroanatomy of reading comprehension revealed an activation of the prefrontal cortex (PFC) and parietal/posterior cingulate cortex (PCC)[91]. Likewise, mathematical calculations and numerical magnitude processing have been linked to bilateral regions of the intraparietal sulcus in children and adults[92–94]. However, children also recruit the right dorsolateral prefrontal cortex[92,94]. Given that both mathematics and reading elicit activation in the frontoparietal network, there is a sound basis for examining these structures in relation to academic performance. As fitness has also been related to the frontoparietal network[48,53,55], it would follow that children might derive benefits in school performance from increased participation in physical activity.

Finally, a few studies have indicated that physical activity is unrelated to academic performance. For example, a study that relied on the self-reported teacher perception of students' physical activity did not find a relation with academic performance[22]. However, another study[95] reported that pupils who engaged in vigorous physical activity performed better in school than those that performed moderate or no physical activity. Sallis *et al.*[96] observed a trend for improved achievement test scores following physical activity, but the relationship might have been blunted because the school district examined was one with historically high test scores. Collectively these data indicate that, at the very least, time spent in physical activity programmes does not hinder academic performance, and it might indeed improve performance. Given the positive health benefits that are derived from physical activity, these studies support PE as an important component of children's health and wellbeing. Bottom panels adapted from REF. 97 © (1996) Appleton & Lange.



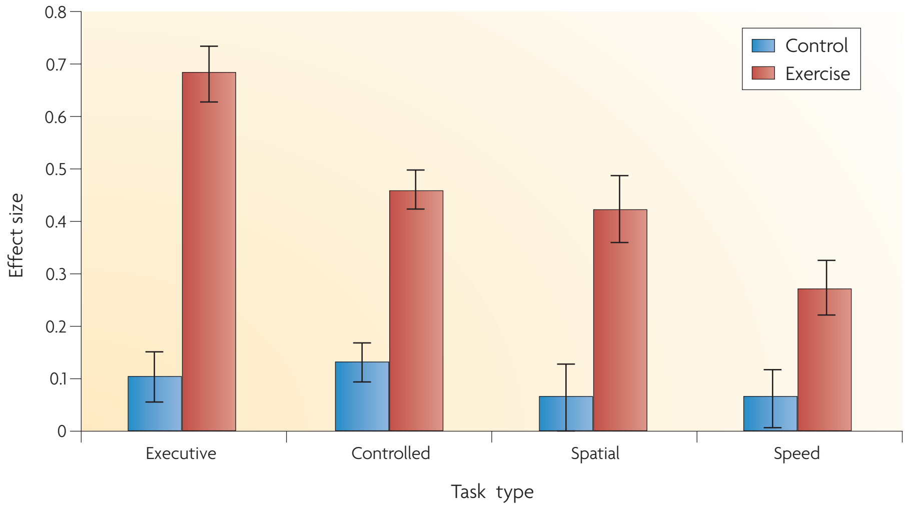


Figure 1 | **Meta-analytic findings of exercise-training effects on cognition in older adults.** The results of a meta-analysis of the effects of fitness training on cognition showed that the benefits of fitness training on four different cognitive tasks were significant. As illustrated in the figure, fitness training has both broad and specific effects. The effects are broad in the sense that individuals in aerobic fitness training groups (represented by the red bars) showed larger fitness training effects across the different categories of cognitive processes illustrated on the x-axis. They are specific in the sense that fitness training effects were larger for some cognitive processes, in particular executive control processes, than for other cognitive processes. Figure reproduced, with permission, from REF. 32 © (2003) Blackwell Publishers.

younger adults merely for the purpose of comparison with older adults, to provide a basis for age-related deficits in cognitive function and to better understand the prophylactic or ameliorative effects of chronic physical activity participation on cognitive ageing. One obvious reason for this paucity of literature is that cognitive health peaks during young adulthood[28], suggesting that there is little room for exercise-related improvement to cognitive function during this period of the lifespan. However, recent trends indicating a declining health status among children[3] suggests that future research should extend to periods of the lifespan that are characterized by peak cognitive health.

There is a small body of literature that examines neurophysiological indices of the benefits of chronic physical activity participation on cognitive function in young adults; however, the vast majority of this research is focused on cognitive ageing (see below). Future research in this area needs to continue to build the physical activity–cognition literature base, similar to that for older adults and, if it is to have societal implications, it should also focus on bridging the gap between the basic mechanisms that underlie the effects of exercise on the brain and applied aspects of cognition related to classroom and job performance.

Physical-activity effects on cognition during older adulthood. The study of exercise and cognition with older adults dates back several decades. Recently the exercise–cognition relation in older adults has been strengthened by the observation, in prospective epidemiological studies, that there are a number of lifestyle factors — including intellectual engagement, social interaction, diet and physical activity — that are associated with the maintenance of cognitive function and a reduction in risk for age-associated neurodegenerative disorders, such as Alzheimer's disease and vascular dementia[9,29–30].

A small but growing number of randomized intervention studies have examined whether fitness training has a positive effect on different aspects of perception and cognition in older adults. These studies generally enrol healthy but sedentary adults between the ages of 60 and 85 years and ask them to participate in an exercise regime several times per week over the course of several months to several years. Cognition and fitness is assessed before and after the intervention. The central question is whether individuals who participate in an aerobic training regime show larger gains in cognition than wait-list control subjects or control subjects who participate in non-aerobic regimes, such as toning and stretching. In one example[31], older adults were randomized into a pool-based aerobic exercise group or a wait-list control. All participants were tested with a series of single and dual auditory and visual discrimination tasks both before and after the 10-week intervention. Participants in the aerobic training programme, but not those in the control group, showed significant improvement in dual-task performance over the 10-week period. Improvements in single-task performance were equivalent for the two groups.

Although a number of intervention studies have found improvements in performance on cognitive tasks for aerobically trained but not control subjects, other studies have found equivalent performance improvements for both aerobic and control subjects across cognitive tests. Given that the number of randomized intervention trials that have examined fitness training effects on cognition is relatively small, and that the particulars of these studies were varied, there are a number of factors that might be responsible for the mixed pattern of results. Some of these factors include: the cognitive processes examined; the length, intensity and type of exercise programme; the age range, health and education of participants; and the manner in which fitness improvements were measured. Fortunately, a few meta-analyses have been conducted in recent years to determine first whether the fitness–cognition effect is robust across the literature and second which factors might moderate this relation[32–34]. Several important results have been obtained from these meta-analyses, which examined partially overlapping sets of studies. First, and perhaps most importantly, the effect size in each meta-analysis was significant. That is, in all studies, physical activity had a positive effect on cognition. Second, a significant relationship between physical activity training and improved cognition was obtained for both normal adults and patients with early signs of Alzheimer's disease, in which memory or cognitive ability was mildly impaired[32–34]. Thus, it appears that physical activity can have a positive effect on a wide range of cognitive functions. Several other moderator variables were also revealed[32]. As indicated in FIG. 1, physical-activity training appears to have both broad and specific cognitive effects: broad in the sense that various different cognitive processes benefit from exercise participation, and specific in the sense that the effects on some cognitive processes, especially executive control processes (which include scheduling, planning, working memory, multi-tasking and dealing with ambiguity), are disproportionately larger. This is particularly interesting as executive control processes, and the brain regions that support them (chiefly the prefrontal cortex), show substantial age-related deterioration — the findings suggest that even processes that display substantial age-related change are amenable to intervention. Additionally, the relationship between physical activity training and cognition was also influenced by programme duration, age, gender[35] and type[32].

In summary, although there are a multitude of unanswered questions regarding physical activity and cognition in older adults, there is evidence of a relationship between fitness training and improvements in various aspects of cognition across a broad range of ages. Collectively, the findings suggest that physical activity is beneficial across the human lifespan. However, the mechanisms that underlie this relationship are unclear and might differ during development and ageing, as the brains of children are still developing and undergoing organization whereas the brains of adults are not. Physical activity during childhood might encourage optimal cortical development, promoting lasting changes in brain structure and function. Future research should address whether the mechanisms that support the physical activity–cognition relationship are different in children and adults.

Neuroimaging studies of physical activity in humans. Neurophysiological studies have revealed differences in cognitive function that are related to physical activity behaviour. Examination of baseline spectral frequency distributions of electroencephalograms (EEGs) has revealed increased activation in the theta (4–8 Hz), alpha (8–13 Hz) and beta (13–20 Hz) spectral bands, and higher mean frequency in the delta (0.25–4 Hz), theta and beta bands in more active or aerobically fit individuals[36–39]. These findings suggest that physical activity influences baseline electrocortical function and, thus, that it might affect cognitive operations. Support for this influence is garnered from the finding that inter-individual variability in spectral frequency activation is related to individual variations in the P3 component of the ERP[40–41], which has been found to be especially sensitive to changes in physical activity participation and aerobic fitness.

Research conducted over the past two decades has described both aerobic fitness- and physical activity-related differences in the amplitude and latency of the P3 component in pre-adolescent children[42], young adults[43–44] and older adults[37,45–46]. This component appears to be generated by a network of neural structures, including the frontal lobe, the anterior cingulate cortex (ACC), the infero-temporal lobe and the parietal cortex, that are involved in cognitive operations, including stimulus processing and memory updating[47]. Consistent and robust findings have emerged: larger amplitude and shorter latency P3s are observed across a variety of cognitive tasks in individuals with high aerobic fitness compared with unfit individuals. These results indicate that greater amounts of physical activity or aerobic fitness are generally beneficial to cognitive processes that are related to the allocation of attentional resources and faster cognitive processing during stimulus encoding. In agreement with these findings, functional MRI (fMRI)[48] and behavioural[49–50] data show a physical activity-related modulation that is disproportionately larger for task components that necessitate greater amounts of executive control[49].

More recently, neurophysiological research has focused on response-monitoring processes elicited by the evaluation of conflict during instances of erroneous action. Specifically, smaller error-related negativity (ERN) amplitude following error commission has been observed in more active older adults[51] and fit young adults than in unfit individuals of similar age[26]. Given that source-localization techniques, such as dipole modelling[52], have localized the generation of the ERN to the caudal portion of the ACC, these findings corroborate previous fMRI research that showed reduced activation of the ACC in fit older adults during participation in tasks that required variable amounts of executive control relative to unfit individuals[48] (BOX 2). The implication of these findings is that greater amounts of physical activity and/or fitness might be associated with a reduction in task-related response conflict owing to increased top-down control during task execution. Physical activity-related influences on task performance are further observed through the regulation of top-down control, as more active and fit individuals exhibit longer reaction times on trials following erroneous action[26,51].

MRI has also been used to examine the effects of fitness on cognition. For example, in cross-sectional comparisons between individuals with high and low levels of fitness and aerobic fitness training studies, Colcombe and colleagues[48,53] found that higher levels of fitness and fitness improvements were related to larger volumes of prefrontal and temporal grey matter, as well as anterior white matter (see also REFS 54,55). Such increases in brain volume have previously been shown to be predictive of performance in older adults[35,55].

Aerobic fitness training has also been found to induce changes in patterns of functional activation using fMRI. For example, older adults who participated in a walking intervention over a 6-month period showed increases in activation in the middle frontal gyrus and superior parietal cortex and decreases in activation in the ACC, relative to a non-aerobic toning and stretching control group[48]. These changes in patterns of fMRI activation were related to significant and substantial improvements in the performance of a selective-attention task. More recently, increases in measures

Glossary

Aerobic fitness
The maximal capacity of the cardiorespiratory system to take up and use oxygen.

Behavioural conflict
The indecision that arises when multiple conflicting responses can be elicited in response to a stimulus.

Dipole modelling
A method to determine the location of the sources that underlie the responses measured in an electro-encephalographic experiment. It provides an estimate of the location, orientation and strength of the source as a function of time after the stimulus was presented.

Error-related negativity
(ERN). A negative deflection in a response-locked ERP that reflects neural correlates of action monitoring that is associated with the evaluation of conflict.

Event-related brain potential
(ERP). A time-locked index of neuroelectrical activation that is associated with specific cognitive processes.

Executive control
Computational processes involved in the selection, scheduling and coordination of complex cognitive functions.

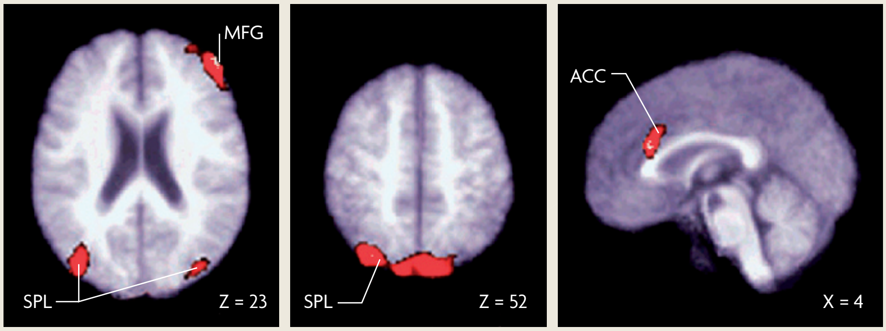
Exercise
Repetitive and planned physical activity with the goal of maintaining or improving physical fitness.

P3
A positive deflection in a stimulus-locked ERP that reflects changes in the neural representation of the stimulus environment and is proportional to the amount of attention that is required to encode a given stimulus (amplitude) as well as the speed of stimulus evaluation (latency).

Physical activity
Bodily movement produced by skeletal muscles with the expenditure of energy.

Top-down control
Refers to an individual's ability to selectively process information in the environment. Top-down control relies on an observer's expectancies about events in the environment, knowledge of and experience with similar environments, and the ability to develop and maintain an attentional set for particular kinds of environmental events.

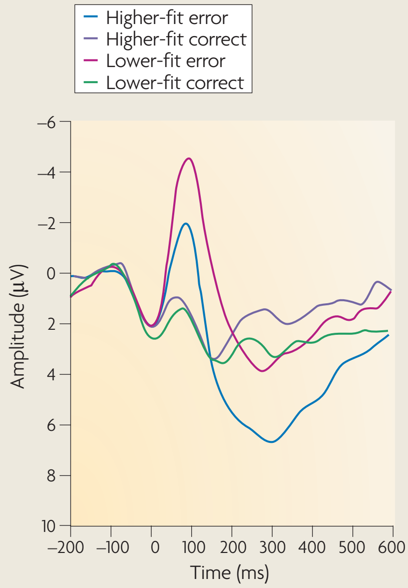
Box 2 | Physical activity and the anterior cingulate cortex



Physical activity has been found to enhance cognition, with a selectively larger effect on executive control functions compared with other cognitive processes[32,50,98]. Accordingly, brain structures that mediate executive functions would be expected to show disproportionate changes as a result of participation in physical activity. One such structure is the anterior cingulate cortex (ACC), which is part of the brain's limbic system and has connections with multiple brain structures that process sensory, motor, emotional and cognitive information[99]. Two convergent lines of research indicate that physical activity exerts a substantial influence on the ACC and the concomitant executive processes that it mediates.

Neuroimaging research that examined the effects of changes in fitness on the ACC found that aerobically trained older adults exhibited a reduction in activation (see figure, top panels), with a concomitant decrease in behavioural conflict, during a task that required variable amounts of executive control, relative to untrained individuals[48]. Furthermore, increased activation of the dorsal prefrontal and parietal brain regions involved with task-related inhibitory functioning was observed[48], suggesting an increased ability of the frontal attentional network to bias task-relevant activation in the posterior cortex[48].

These findings are supported by neurophysiological and task-performance data[26,51], which demonstrated a reduction in error-related negativity (ERN) amplitude[52]; an event-related brain potential (ERP) component with its primary neural generator in the caudal ACC (see figure, bottom panel) . This reduction in the ERN amplitude was associated with greater regulation of behavioural responses for physically active younger and older adults compared with inactive individuals. These findings suggest an improvement in task performance in aerobically active individuals through a reduction in conflict-related activation of action monitoring processes, resulting in a more efficient neurophysiological profile. Collectively, convergent evidence supports the view that higher levels of physical activity correlate with increased top-down control, which could be mediated through more efficient activation of the ACC, resulting in better performance during tasks requiring executive control. MFG, middle frontal gyrus; SPL, superior parietal lobule. Coordinates for the locations of the clusters are given in Montreal Neurological Institute space. Top panel reproduced, with permission, from REF. 48 © (2004) National Academy of Sciences. Bottom panel reproduced, with permission, from REF. 26 © (2006) Elsevier Science.



of cerebral blood volume (CBV) in the dentate gyrus of the hippocampus were observed in a small group of middle aged participants in a 3-month fitness training study[56]. The increases in CBV were associated with improvements in verbal learning and memory and cardiorespiratory fitness. The regional specificity of the CBV changes are particularly interesting, given previous demonstrations of neurogenesis in the dentate gyrus[57–59] as well as the association between increased CBV and neurogenesis in mice[56]. CBV changes in the hippocampus might serve as a biomarker for neurogenesis in humans.

Non-human animal research

Research on humans has demonstrated improved cognitive performance as a result of physical activity in both children and older adults. However, there are clearly limitations on the extent to which the human brain can be examined with neuroimaging techniques. Non-human animal research can directly examine the cellular and molecular cascades that are triggered by exercise, which in humans can only be indirectly examined and inferred. Additionally, investigating the effect of exercise in non-human animal populations has the benefit of markedly reducing some of the inherent confounding variables that are often present in human studies (for example, lack of adherence to treatment protocols, and covariation with other lifestyle factors, such as social interaction and diet with an exercise intervention) while also providing a translational and cross-species approach to studying exercise-induced neural and cognitive plasticity.

An increase in cell proliferation and cell survival in the dentate gyrus of the hippocampus is one of the most consistently observed effects of exercise treatment[57–61]. Exercise-induced hippocampal cell proliferation and cell survival can occur at many stages of development, including young adulthood[58], and in old age[62]. Even newborn pups with mothers that had carried out aerobic exercise during the gestational period of the pregnancy exhibited a greater number of surviving cells in the hippocampus than pups born from sedentary mothers[63–64]. The functional significance of hippocampal neurogenesis and the survival of the new neurons is a source of great controversy, but the behavioural performance improvements that are associated with exercise treatments suggest that these newborn cells might facilitate learning and memory. Furthermore, dementias such as Alzheimer's disease are characterized by a marked reduction in the number of neurons in the hippocampus, which might be alleviated, in part, by increased neurogenesis resulting from aerobic activity.

The proliferation of new cells in the brain is accompanied by an increased need for nutrients. This demand is met by the stimulation of new blood vessel growth in the cortex[65], the cerebellum[66], the striatum[67] and the hippocampus[68]. The growth of new vasculature might be dependent on the presence of molecules such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF1). For example, systemic injection of IGF1 effectively stimulates angiogenesis in the brain, and inhibiting IGF1 reduces angiogenesis. IGF1 might induce new blood vessel formation through the regulation of VEGF[68], a growth factor that is prominently involved in blood vessel formation and development. Aerobic exercise increases the production and release of both IGF1 and VEGF in young rodents, leading to the formation of new blood vessels. It is likely that angiogenic processes resulting from aerobic activity occur both in childhood and in old adulthood[67] (however, see REF. 62 for an exception).

Besides IGF1 and VEGF, brain-derived neurotrophic factor (BDNF) is another molecule that is consistently demonstrated to be upregulated with exercise treatments[69]. BDNF has been shown to be necessary for long-term potentiation (LTP), a neural analogue of long-term memory formation, and for the growth and survival of new neurons. Blocking the binding of BDNF to its tyrosine kinase receptor (TRKB) abolishes LTP and neurogenesis. Additionally, BDNF levels in the hippocampus have been directly related to the enhanced learning and memory processes that are observed with exercise treatments in rodents[70]. Even in humans, serum concentrations of BDNF are increased after acute exercise regimens[71] in both young adults and patients with multiple sclerosis[72]. Increases in BDNF levels in response to an exercise treatment could be an important finding, as serum and cortical concentrations of BDNF are reduced in Alzheimer's disease, Parkinson's disease, depression, anorexia and many other diseases. Aerobic activity might be neuroprotective, preventing the development of certain cognitive and neural symptoms that are associated with these diseases, through the regulation of BDNF secretion[73].

In summary, non-human research strongly supports the positive effects of exercise on cognition: aerobic activity improves learning and task acquisition, increases the secretion of key neurochemicals associated with synaptic plasticity and promotes the development of new neuronal architecture. In addition, non-human animal research is not only consistent with human literature on aerobic activity, but also provides some important mechanistic claims for how exercise exerts its effects on the nervous system in humans (see REF. 74 for an in-depth review of the cellular and molecular effects of exercise in non-human animals). Despite having gained some mechanistic insights, a large number of questions regarding the generality of the effects of exercise on learning, the molecular and genetic transcription cascades that result from exercise and the durability of the effects, remain unresolved. Although there are many missing links between the human neuroimaging results and non-human molecular and cellular work, both bodies of research suggest that aerobic exercise is an important lifestyle factor that influences cognitive function throughout the lifespan.

Conclusions and future directions

The human and non-human animal research discussed above suggests that physical activity, and aerobic fitness training in particular, can have a positive effect on multiple aspects of brain function and cognition. Although the number of studies on physical activity is certainly larger for older adults than for other age groups, the data suggest that physical activity can have beneficial effects throughout the lifespan, even for individuals with neurodegenerative diseases[34,75]. Studies with non-human animals have begun to shed light on the molecular and cellular changes that are engendered by exercise and that appear to underlie the effects of fitness on cognition and performance. Fitness training has been observed to selectively enhance angiogenesis, synaptogenesis and neurogenesis (in the dentate gyrus of the hippocampus), as well as to upregulate a number of neurotrophic factors in the mouse brain[9,74].

Despite the wealth of knowledge that has been obtained concerning the effects of exercise and physical activity on brain and cognition, there are a multitude of important questions that remain to be answered. From a practical perspective, at present we know little about how to design exercise interventions that optimize the effects on cognition and brain health. Future research might be able to answer questions such as: when is it best to begin? What are the best varieties, intensities, frequencies and durations of exercise? Is it ever too late to start an exercise programme? Can exercise be used to reduce the deleterious effects of neurodegenerative diseases[32,77]?

Some intriguing research has begun the important task of exploring how exercise interacts with other lifestyle factors in influencing cognition and brain health. For example, Molteni and colleagues[78] investigated the interaction of diet and exercise at the behavioural and molecular levels through their effects on learning and BDNF. Exercise served to reverse the negative effects of high-fat diets on BDNF levels and learning. In another recent study, the effects of exercise on hippocampal neurogenesis were substantially delayed and reduced for a group of socially isolated rodents compared with animals that were housed in a group setting[79]. Such results suggest the need to further study the potential relationship between social interaction (and social isolation) and exercise on brain function and cognition in humans. Finally, several recent studies have described the benefits of exercise training for the treatment of depression[79–80].

Although the prospective epidemiological literature has examined the influence of various lifestyle factors on cognition and neurodegenerative disease, few studies have explored the separate and interactive effects of lifestyle factors. Karp *et al.*[29] recently reported that cognitive, physical and social engagement had served to decrease the risk of dementia in a group of 778 adults over a period of three years, with those adults with high scores in all three factors showing the greatest benefit. The results of these studies are both intriguing and provocative; however, they only scratch the surface in terms of explaining the manner in which different lifestyle factors interact to promote healthy brains and minds. Clearly, additional observational and experimental studies are needed to further explain the effects of these interactions with regards to cognition.

In recent years there has also been increased acknowledgment of the role of genetic polymorphisms on the heterogeneity of treatment effects in drug trials, especially with regards to the speed with which individuals metabolize different agents[81]. The study of the potential moderating effect of genetic variability has also begun to have a role in the study of exercise effects on cognition. More specifically, a number of observational studies have examined whether the presence of the e4 allele on the *APOE* gene (which encodes apolipoprotein E) influences the relationship between fitness and cognition in older adults[82–85]. The answer to this question is, at present, unclear. However, given that single nucleotide polymorphisms exist on a number of genes that influence proteins implicated in fitness-training effects[86–87] (like BDNF and IGF1, for example) future studies will certainly benefit from the examination of the moderating influence of genetic variability on relevant target systems.

In conclusion, there is converging evidence at the molecular, cellular, behavioural and systems levels that physical activity participation is beneficial to cognition. Such evidence highlights the importance of promoting physical activity across the lifespan to reverse recent obesity and disease trends, as well as to prevent or reverse cognitive and neural decline. Accordingly, physical activity can serve to promote health and function in individuals, while also lessening the health and economic burden placed on society.

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DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
APOE | BDNF | IGF1 | TRKB| VEGF
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Alzheimer's disease | Parkinson's disease

FURTHER INFORMATION
Charles H. Hillman's homepage: http://www.kch.uiuc.edu/labs/neurocognitive%2Dkinesiology/default.htm

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