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The positive impact of physical activity on cognition during adulthood: a review of underlying mechanisms, evidence, and recommendations

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Abstract

A growing body of literature suggests that physical activity beneficially influences brain function during adulthood, particularly frontal lobe-mediated cognitive processes, such as planning, scheduling, inhibition, and working memory. For our hunter-gatherer ancestors, times of famine interspersed with times of feast necessitated bouts of intense physical activity balanced by periods of rest. However, the sedentary lifestyle that pervades modern society has overridden the necessity for a physically active lifestyle. The impact of inactivity on disease processes has been the focus of much attention; the growing understanding that physical activity also has the benefit of enhancing cognitive performance strengthens the imperative for interventions that are successful in increasing physical activity, with the outcomes of promoting health and productivity. Population health and performance programs that promote physical activity provide benefits for employees and employers through improvements in worker health and performance and financial returns for the company. In this review, we examine the mechanisms by which physical activity improves cognition. We also review studies that evaluate the effects of physical activity on cognitive executive performance in adulthood, including longitudinal studies that address the impact of physical activity during early adulthood and midlife on preservation of cognition later in life. This is of particular importance given that adulthood represents prime working years and that physical activity promotion is a key component of population health and performance programs. Finally, we provide recommendations for maximizing the lasting benefits of movement and physical activity on cognition in adulthood.

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Keywords: cognition; cognitive reserve; executive function; exercise; movement; physical activity; population health.

Introduction

A growing body of literature indicates that physical activity is associated with improvements in brain function and cognition during childhood (Sibley and Etnier, 2003; Hillman et al., 2008) and throughout adulthood (Colcombe and Kramer, 2003; Cotman et al., 2007; Angevaren et al., 2008; Hillman et al., 2008; Smith et al., 2010). Studies in older adults suggest that aerobic activity robustly and preferentially improves performance on tasks that involve executive cognition function, such as planning, scheduling, inhibition, and working memory (Kramer et al., 1999; Colcombe and Kramer, 2003). Executive cognitive processes are mediated by the frontal lobes of the brain and are subject to age-related declines (Hillman et al., 2008). Physical activity is an important component of healthy aging and preservation of cognitive function (Colcombe et al., 2006; Kramer et al., 2006; Larson et al., 2006). For example, better aerobic fitness in older adults reduces loss of brain volume in regions that mediate executive cognitive function (Colcombe et al., 2003; Colcombe et al., 2006) and is associated with more efficient performance of executive function tasks and increased activity in brain regions that subserve such tasks (Colcombe et al., 2004). Similarly, older adults with better aerobic fitness demonstrate better spatial memory performance and related increases in hippocampal volume (Erickson et al., 2009).

In addition to preservation of cognition during older adulthood, it is important to examine the acute and lasting effects of physical activity on cognition during early adulthood and midlife. In this review, we will examine potential mechanisms by which exercise and physical activity improve brain function, particularly with regard to executive processes and performance. We will also review studies evaluating the effects of acute bouts of exercise and longer-term physical activity interventions on cognitive performance in adulthood, as well as longitudinal studies that address the role of physical activity during early adulthood and midlife in preserving cognition later in life. Finally, we will provide evidence and recommendations for maximizing the benefits of physical activity on cognition through full engagement in physical activity programs, including population health and performance programs in the workplace. Population health and performance programs that promote physical activity have reported positive effects on employee health and productivity (Conn et al., 2009; Pronk, 2009; Pronk and Kottke, 2009) that translate into financial savings for employers (Pronk, 2009; Baicker et al., 2010). In light of the growing evidence that improved cognitive performance is one of the many benefits related to physical activity, workplace interventions that are successful in increasing physical activity can promote both physical and mental health. The rationale for population health and performance programs is further strengthened by their potential to optimize cognitive performance in addition to employee health.

Evolutionary perspective on physical activity and cognition

From an evolutionary perspective, the need for movement is probably programmed into our genes (Booth et al., 2002). Physical activity was required by our hunter-gatherer ancestors to compete for energy resources for survival. It is probable that the human genome evolved to support increased metabolic demands associated with hunting and foraging for food. Moreover, 'thrifty' genotypes (Neel, 1962) that maximized the human body's ability to efficiently store and utilize fuel sources such as muscle glycogen and triglycerides probably evolved to support survival during periods of famine (Chakravarthy and Booth, 2004). In other words, the intake of glucose and fat when food was plentiful allowed our hunter-gatherer ancestors to store fuel sources in adipose tissue during periods when little physical activity was required (i.e., feast). Periods of feast were balanced by periods of famine that required physical activity for food procurement; during periods of famine, fuel sources in adipose tissue were metabolized by skeletal muscle.

Thus, the human genome has adapted to support a constant demand for movement as well as bursts of physical activity and metabolic fluxes associated with proper energy homeostasis during periods of feast and famine (Booth et al., 2002; Chakravarthy and Booth, 2004). Although the human genome has remained relatively unchanged for the past 10 000 years, the sedentary lifestyle that pervades modern society, along with the unlimited food supply, has overridden the necessity for a physically active lifestyle and natural metabolic fluxes. The disruption of naturally evolved energy homeostasis brought on by physical inactivity contributes to the growing incidence of metabolic diseases (e.g., diabetes, obesity) in today's sedentary society (Booth et al., 2002; Chakravarthy and Booth, 2004; Dishman et al., 2006; Hamilton et al., 2007). According to data from the National Center for Health Statistics, physical inactivity accounts for approximately 200 000 or 1 in 10 disease-specific deaths each year in the US adult population (Danaei et al., 2009). In addition to being an individual risk factor for disease-specific deaths, physical inactivity contributes to other dietary, lifestyle, and metabolic risk factors for chronic diseases through effects on body mass index (BMI), blood pressure, glucose, and low-density lipoprotein cholesterol.

Physical activity can be evolutionarily related to cognition in that the need to generate movements for the purpose of successful food foraging could have necessitated mental activity (Vaynman and Gomez-Pinilla, 2006). As Rudolfo Llinás articulates in *I of the Vortex: From Neurons to Self* (Llinás, 2001), successful movements led to our thinking brain: 'That which we call thinking is the evolutionary internalization of movement'.

Potential mechanisms that mediate the beneficial effects of physical activity on cognition and performance

The effects of physical activity on cognition are seen at the systemic, molecular, and cellular levels (Figure 1). At the systems level, electrophysiologic and neuroimaging studies have shown that neural systems that underlie attention, learning, and memory are primed for efficient and flexible functioning by physical activity. At the molecular level, physical activity increases the availability of neurotrophins and growth factors in the brain. Signaling cascades induced by these factors regulate cellular effects that support brain function, including synaptic plasticity, neurogenesis, and angiogenesis.

Systems level: increased activity in brain regions mediating attention, learning, and memory

Many studies have shown that physical activity influences neural systems involved in attention, learning, and memory. Electrophysiologic studies have provided insight into the effects of exercise and fitness on cognition by using electrodes placed on the scalp to record event-related brain potentials, a measure of electrocortical activity. In particular, P300 is a well-studied component of event-related brain potentials

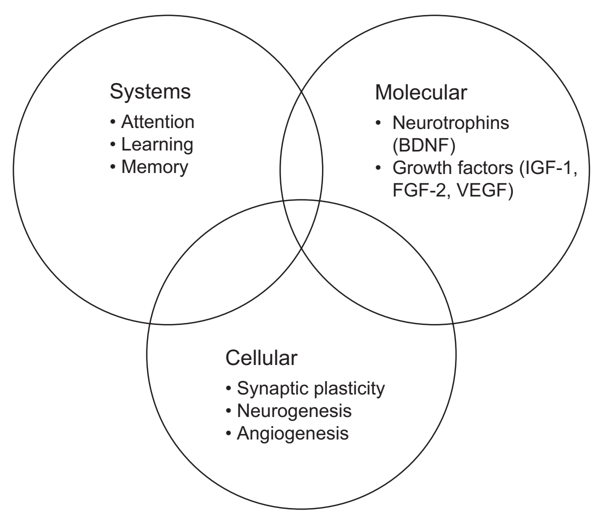

Figure 1 Exercise exerts systemic, molecular, and cellular effects to mediate executive cognitive function.
At the systems level, electrophysiologic and neuroimaging studies have shown that physical activity improves cognitive performance by increasing neuroelectric activity, brain volume, and blood flow in brain networks that mediate attention, learning, and memory. At the molecular level, physical activity increases the availability of neurotrophins and growth factors in the brain. Signaling cascades induced by these factors regulate cellular effects that support brain function, including synaptic plasticity, neurogenesis, and angiogenesis. BDNF, brain-derived neurotrophic factor; FGF-2, fibroblast growth factor-2; IGF-1, insulin-like growth factor-1; VEGF, vascular endothelial growth factor.

that occurs approximately 300–800 ms after stimulus onset and provides an indication of attentional resources allocated to the stimulus (Pontifex et al., 2009). This attention-driven neural activity signal is thought to be generated by multiple brain regions involved in information processing and memory encoding, including the frontal lobes, anterior cingulate cortex, temporal lobe, and parietal cortex (Polich, 2007). The frontal lobes mediate tasks that require executive cognitive function, such as planning, scheduling, inhibition, and working memory (Kramer et al., 1999; Etnier and Chang, 2009). The anterior cingulate cortex is a limbic structure in the medial wall of the brain and is thought to monitor response conflict and signal the need for adaptation in the attentional network (Colcombe et al., 2004). Temporoparietal activity is thought to be associated with attention and subsequent memory processing, particularly by the hippocampal formation in the medial temporal lobe (Polich, 2007).

The amplitude of P300 is proportional to the amount of attention needed to encode the stimulus in working memory, whereas the latency of P300 reflects the speed of cognitive evaluation of the stimulus (Hillman et al., 2003). In an electrophysiologic study of 20 young adults, Hillman et al. (2003) recorded P300 amplitude and latency during an executive cognitive task performed at baseline and after a single bout of treadmill exercise. Results indicated that P300 amplitude during task performance was larger after the exercise session than at baseline, suggesting that exercise increased allocation of attention and memory resources at the neuroelectric level. Other studies have reported that adults with better physical fitness have larger P300 amplitudes and shorter P300 latencies than less fit adults while they perform executive tasks (Polich and Lardon, 1997; Hillman et al., 2006a; Pontifex et al., 2009; Kamijo and Takeda, 2010). These studies support a role for physical activity in improving cognitive function through attentional mechanisms.

In addition to findings from electrophysiologic studies, neuroimaging studies have provided insights into the effects of physical activity on brain activity and cognition. Structural magnetic resonance imaging (MRI) studies in older adults have revealed that physical fitness is related to preservation of brain volume. Adults with better fitness have significantly greater brain volume in frontal, temporal, and parietal cortices compared with less fit adults (Colcombe et al., 2003; Gordon et al., 2008). Moreover, older adults who participated in a 6-month regimen of aerobic training had significant preservation of these brain areas (Colcombe et al., 2006). A recent study provided a more direct link between brain volume and preservation of cognition during aging; older adults with better aerobic fitness not only had increased hippocampal volume compared with less fit adults but also had better performance on a task of spatial memory, a cognitive process subserved by the hippocampus (Erickson et al., 2009).

Functional MRI studies support and extend the findings that exercise affects brain structure, by demonstrating changes in brain function/activity after participating in a regimen of physical exercise. Colcombe et al. (2004) observed increased brain activity coupled with better cognitive performance in older adults who were more fit or who underwent 6 months of aerobic training compared with less fit or untrained study participants. Participants underwent functional MRI while they performed an executive/attention task known as the Eriksen flanker task, a task-switching test in which a target stimulus (e.g., B) is flanked by congruent (e.g., BBBBB) or incongruent (e.g., AABAA) stimuli. A correct response during the incongruent condition requires participants to inhibit or filter misleading information (i.e., the incongruent flanking cues); successful inhibition of the misleading information is signified by faster reaction time to the incongruent cues. Highly fit and aerobically trained adults had faster reaction times during the incongruent condition of the task, indicating that these participants processed conflicting cues more efficiently than less fit and untrained participants. In addition, highly fit and aerobically trained adults had greater activity during the task in the attentional circuitry of the brain, including key regions of the frontal and parietal cortices. Thus, improved fitness was associated with better task performance, as well as enhancements in structure and function of brain areas thought to underlie executive functions.

In another study, 11 adults aged 21–45 years participated in a 3-month aerobic exercise regimen (Pereira et al., 2007). Performance on a word recall memory task, the Rey Auditory Verbal Learning Test, along with changes in regional cerebral blood volume (CBV) in the hippocampus, was assessed before and after the exercise training period. CBV in the hippocampal dentate gyrus significantly increased after aerobic training and was positively associated with the fitness level achieved (as assessed by the maximum volume of oxygen consumption). Moreover, performance on the Rey Auditory Verbal Learning Test improved after exercise training and correlated with dentate gyrus CBV. Thus, exercise induced a selective increase in CBV that correlated with fitness level and cognitive performance (Figure 2). The dentate gyrus is a hippocampal structure to which new neurons are added throughout life (Eriksson et al., 1998); the potential role of neurogenesis in mediating exercise-induced changes in the brain is discussed in more detail later.

Molecular level: neurotrophins and growth factors

In addition to studies reporting that neural systems underlying attention, learning, and memory are primed for efficient and flexible functioning after physical activity interventions, other studies have begun to elucidate molecular mechanisms by which physical activity affects cognition. Among various potential molecular mediators of the effect of exercise on cognition (Vaynman and Gomez-Pinilla, 2006; Cotman et al., 2007), two well-studied candidates are brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1).

Studies in rats and mice (Cotman and Berchtold, 2002) have shown that voluntary exercise on a running wheel increases hippocampal levels of BDNF, a molecule important for synaptic plasticity, learning, and memory. Animal studies have shown that exercise improves performance on the Morris water maze, a task that involves spatial learning and memory,

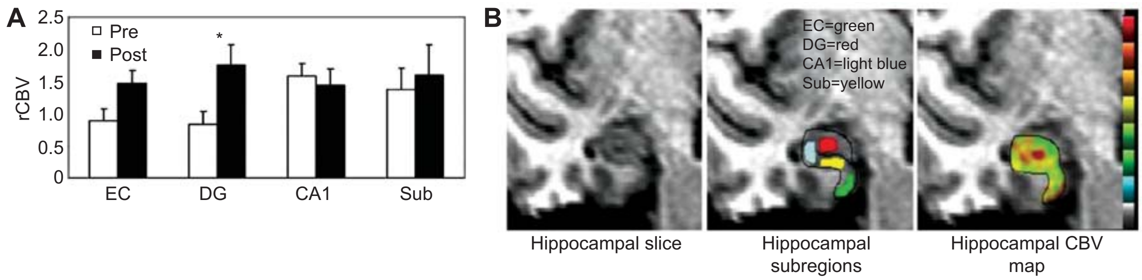

Figure 2 Increased CBV in the hippocampal dentate gyrus in adults who participated in a 12-week exercise training program. (A) Relative CBV (rCBV) in the dentate gyrus selectively increased after exercise training, whereas exercise did not significantly affect CBV in other hippocampal subregions. (B) A high-resolution MRI taken after exercise training in one of the adult participants shows the hippocampus (left image) with depiction of individual subregions (middle image). Higher CBV (indicated by warmer colors) is evident in the dentate gyrus (right image). CA1, *Cornu Ammonis* 1; CBV, cerebral blood volume; DG, dentate gyrus; EC, entorhinal cortex; Sub, subiculum. Figure reproduced with permission from Pereira et al. (2007). Figure used with permission from Pereira et al. (2007) National Academy of Sciences, USA, Copyright 2007.

and that injection of a drug that blocks BDNF activity in the hippocampus also blocked the benefit of exercise on the water maze task (Vaynman et al., 2004; Gomez-Pinilla et al., 2008). In exercising mice, hippocampal BDNF levels increased immediately after exercise and remained elevated for several weeks before returning to baseline levels (Berchtold et al., 2010). Moreover, the cognitive improvement in water maze training and memory performance paralleled the time course of hippocampal BDNF availability. In humans, acute exercise increased serum BDNF levels in young adults (Ferris et al., 2007). In older women (but not older men), decreased levels of plasma BDNF were significantly associated with poorer performance on multiple cognitive tasks (Komulainen, et al., 2008). Thus, the effects of BDNF on hippocampal function, learning, and plasticity make it a potentially important factor in the mediation of the effects of exercise on cognition (Cotman et al., 2007).

IGF-1 is produced mainly in the liver and works closely with growth hormone to mediate somatic growth and tissue remodeling (Trejo et al., 2001; Torres-Aleman, 2010). IGF-1 also provides trophic support to the brain, both through serum IGF-1 that crosses the blood-brain barrier and through IGF-1 produced locally in the brain (Torres-Aleman, 2010). Animal studies have shown that exercise stimulates uptake of IGF-1 from the bloodstream into specific brain areas, including the hippocampus, and that blocking IGF-1 uptake in the brain also blocks exercise-mediated increases in adult neurogenesis (Trejo et al., 2001). Animals with decreased IGF-1 levels have impaired learning and memory (Trejo et al., 2008). In humans, IGF-1 levels decrease with age, and in older adults, serum IGF-1 levels are positively correlated with cognitive performance (Arwert et al., 2005).

BDNF and IGF-1 appear to act in concert to mediate exercise-induced effects on the brain (Cotman et al., 2007). For example, IGF-1 influences BDNF production in the hippocampus in response to exercise. Other growth factors also contribute to the beneficial effects of exercise on the brain. For example, vascular endothelial growth factor (VEGF) can work together with IGF-1 to mediate exercise-induced vascular changes in the brain (Cotman et al., 2007). Moreover, experimentally increasing VEGF levels in the hippocampus in rats resulted in a 2-fold increase in neurogenesis that was associated with improved performance on the Morris water maze, and blocking VEGF levels inhibited both neurogenesis and learning (During and Cao, 2006). Fibroblast growth factor-2 (FGF-2) is another growth factor with effects on neurogenesis; animal studies have shown that FGF-2 increases neurogenesis in the hippocampus of adult and aged animals (Jin et al., 2003; Mudò et al., 2009). Similar to IGF-1, VEGF and FGF-2 exhibit age-related declines in the rat hippocampus, and the loss of growth factor activity with aging could contribute to age-related decreases in neurogenesis and brain function (Shetty et al., 2005).

Cellular level: synaptic plasticity, neurogenesis, and angiogenesis

Neurotrophins and growth factors can promote a cellular environment that supports cognition by increasing synaptic plasticity, neurogenesis, and vascular function (Cotman et al., 2007).

Exercise increases long-term potentiation (LTP) in the hippocampus, a neural correlate of learning (Farmer et al., 2004); rats given access to a running wheel had significantly greater LTP induction than did sedentary litter mates, indicating that exercise lowers the threshold for synaptic plasticity. In addition, expression of BDNF and specific glutamate receptor subtypes in the hippocampal dentate gyrus was increased in running rats, indicating that increased BDNF signaling and glutamate-mediated synaptic transmission could have contributed to the exercise-induced enhancement of synaptic plasticity. Additional research has shown that exercise affects synaptic plasticity through BDNF- and IGF-1-activated kinase signaling cascades (e.g., mitogen-activated protein kinase, calcium/calmodulin protein kinase II), which in turn promote transmission at the synapse through upregulation of synaptic proteins, such as synapsin I (Vaynman and Gomez-Pinilla, 2006).

Research studies in rodents have demonstrated that voluntary running increases the production of new neurons in the dentate gyrus of the hippocampus (van Praag et al., 1999a,b). Moreover, running increases neurogenesis in aged mice that had been sedentary until old age (van Praag et al., 2005). Mice with access to a running wheel also had better performance on the Morris water maze than did non-running controls. Running increases neurogenesis in mice through effects on cell proliferation (McAlpine et al., 2007), cell survival (van Praag et al., 1999a,b, 2005; Snyder et al., 2009), and functional maturation and incorporation of newly generated cells into hippocampal circuitry (Snyder et al., 2009).

Exercise can promote the survival of newly generated cells in the dentate gyrus through effects on the phosphatidylinositol 3-kinase/protein kinase B (PI3K-Akt) signaling pathway (Bruel-Jungerman et al., 2009). A recent rodent study found that phosphorylation/activation of Akt and several of its downstream antiapoptotic targets occurs in the dentate gyrus in response to running wheel exercise and that inhibiting PI3K blocks exercise-induced activation of these prosurvival proteins as well as reduces exercise-induced neurogenesis (Bruel-Jungerman et al., 2009). In addition, inhibition of PI3K blocked LTP induction, indicating that synaptic plasticity in the dentate gyrus depends on PI3K signaling. These results collectively suggest that neurogenesis is a key mechanism by which physical activity can improve synaptic plasticity and cognition and that growth factor cascades such as the PI3K-Akt signaling pathway induced by IGF-1 (Bondy and Cheng, 2004) can contribute to the exercise-induced effects on cognition (Trejo et al., 2008; Bruel-Jungerman et al., 2009).

Running increases the growth of new microvessels in the cerebral vasculature of young and old rats (Swain et al., 2003; Ding et al., 2006). In addition, angiogenesis is coupled with neurogenesis; the vascular environment in the dentate gyrus can help circulating growth factors influence the proliferation and survival of newly generated cells (Palmer et al., 2000). Expression of VEGF is increased in running rats (Ding et al., 2006), and blocking VEGF abolishes the exercise-induced increase in neurogenesis in running animals (Fabel et al., 2003). Exercise increases the size of blood vessels in the dentate gyrus in mice, potentially increasing the blood supply to support neurogenesis (van Praag et al., 2005).

Mice with low levels of circulating IGF-1 (and thus reduced uptake of IGF-1 into the brain) have deficiencies in both angiogenesis (Lopez-Lopez et al., 2004) and neurogenesis (Trejo et al., 2001), suggesting that the vascular environment in the hippocampus affects the delivery of important, neurogenic growth factors to the dentate gyrus. Consistent with these findings, another study showed that exercising mice have increased CBV and neurogenesis in the dentate gyrus (Pereira et al., 2007). Blocking neurogenesis by exposing the mice to irradiation also blocked changes in CBV, suggesting that neurogenesis is the mechanism by which exercise directs blood flow to the dentate gyrus. Taken together, these studies indicate that exercise promotes angiogenesis by increasing the effects of VEGF and IGF-1 on vessel growth (Cotman et al., 2007) and that angiogenesis is linked with neurogenesis.

Overall, mechanistic studies have demonstrated that physical activity has a role in priming mental function at the systems level and directly influencing cognition at the molecular and cellular levels, maximizing the potential of the brain to process new information (Ratey and Hagerman, 2008). Studies that have evaluated the connection between physical activity and cognitive performance on a variety of tasks in humans are discussed in detail later.

Beneficial effects of physical activity on cognition and performance

Published studies on the impact of physical activity on cognitive performance generally have two types of designs: controlled studies of the effects of exercise interventions and studies of the correlation between exercise and cognitive performance. Exercise interventions range from a single bout of acute exercise to weeks-long fitness programs. Correlation studies have addressed whether adults who are already physically active are more likely than inactive adults to have better performance on various cognitive tasks, or whether better fitness in early adulthood and midlife is associated with better cognition later in life.

A single bout of exercise can improve specific aspects of cognition

Studies have shown that a single bout of exercise, such as 30 min of cycling or running, can improve automatic aspects of cognition such as reaction time and speed of information processing (Hogervorst et al., 1996; McMorris and Graydon, 1997; Audiffren et al., 2008; Joyce et al., 2009). Acute exercise also improves performance on higher-order cognitive processes, including executive cognitive tasks such as planning, scheduling, inhibition, and working memory (Kramer et al., 1999).

One common test of attention and executive function that has been used to measure the effects of exercise is the Stroop test (Stroop, 1935). This test measures the amount of time it takes to do three tasks: reading words, naming ink colors, and naming the ink color of words that are color names (e.g., the word ‘red’ printed in green ink). Although people find the first two tasks to be simple, the third is much more difficult because it involves inhibiting the automatic response to read the word rather than name the color. Thus, whereas the word and color subtasks of the Stroop test evaluate speed of information processing, the incongruent color-word subtask assesses the executive functions of selective attention, shifting, and inhibition of habitual responses (Chang and Etnier, 2009b).

Improved executive function as demonstrated by better performance on the Stroop color-word subtask has been shown in young adults after a single bout of aerobic exercise (Hogervorst et al., 1996; Sibley et al., 2006) or resistance exercise (Chang and Etnier, 2009b). In a study of 41 middle-aged adults (mean age: 49 years), improvement in information processing speed and a trend toward improvement in executive function were found after resistance exercise (Chang and Etnier, 2009a). Other studies have shown increased working memory performance (e.g., verbal memory, visual memory) after acute aerobic exercise in young adults (Sibley and Beilock, 2007; Winter et al., 2007; Coles and Tomporowski, 2008) and enhanced cognitive flexibility (i.e., thinking beyond conventional uses of objects to alternate uses) after acute aerobic exercise in middle-aged adults (aged 50–64 years) (Netz et al., 2007).

Longer-term exercise interventions improve cognition

Prospective studies have shown that exercise interventions that range from 2 to 12 weeks can effectively improve cognitive function. In a report published more than 30 years ago, Young (1979) found that a 10-week exercise program for 32 adults aged 23–62 years improved performance on executive function tasks, including the Wechsler Adult Intelligence Scale Digit Symbol and Block Design subtests and the Trail Making Test, along with other tests of learning and information processing speed (Figure 3). In addition, participants reported improved health status and decreased levels of anxiety at the end of the program.

In another study of 66 adults aged 18–48 years, participants who improved 15% or more in physical fitness after a 10- to 12-week exercise regimen had more efficient information processing compared with adults with stable fitness levels (Blomquist and Danner, 1987). Similarly, a smaller study of 30 women aged 27–66 years showed that participation in a physical fitness program consisting of three exercise sessions per week for 8 months improved physical fitness by 17% and was associated with significant gains in information processing and decision-making capabilities (Suominen-Troyer et al., 1986).

A short-term exercise program can also be an effective way to improve working memory and cognitive flexibility. A 14-day healthy lifestyle program that combined mental and physical exercise, stress reduction, and healthy diet was associated with significant improvement in a verbal fluency test of working memory in 17 adults aged 35–69 years with mild self-reported memory problems (Small et al., 2006). Another study reported that 6 weeks of running (30 min three times weekly) by 14 adults aged 17–29 years improved visuospatial memory and positive mood (Stroth et al., 2009). Another recent study of 91 adults aged 18–70 years randomized participants to minimal aerobic exercise (0–2 days/week, the control group), moderate aerobic exercise (3–4 days/week), or high aerobic exercise (5–7 days/week) for 10 weeks (Masley et al., 2009). Participants took the CNS Vital Signs battery of cognitive tests at study entry and after the 10-week intervention. Compared with the control group, the moderate and high exercise groups had significantly improved cognitive

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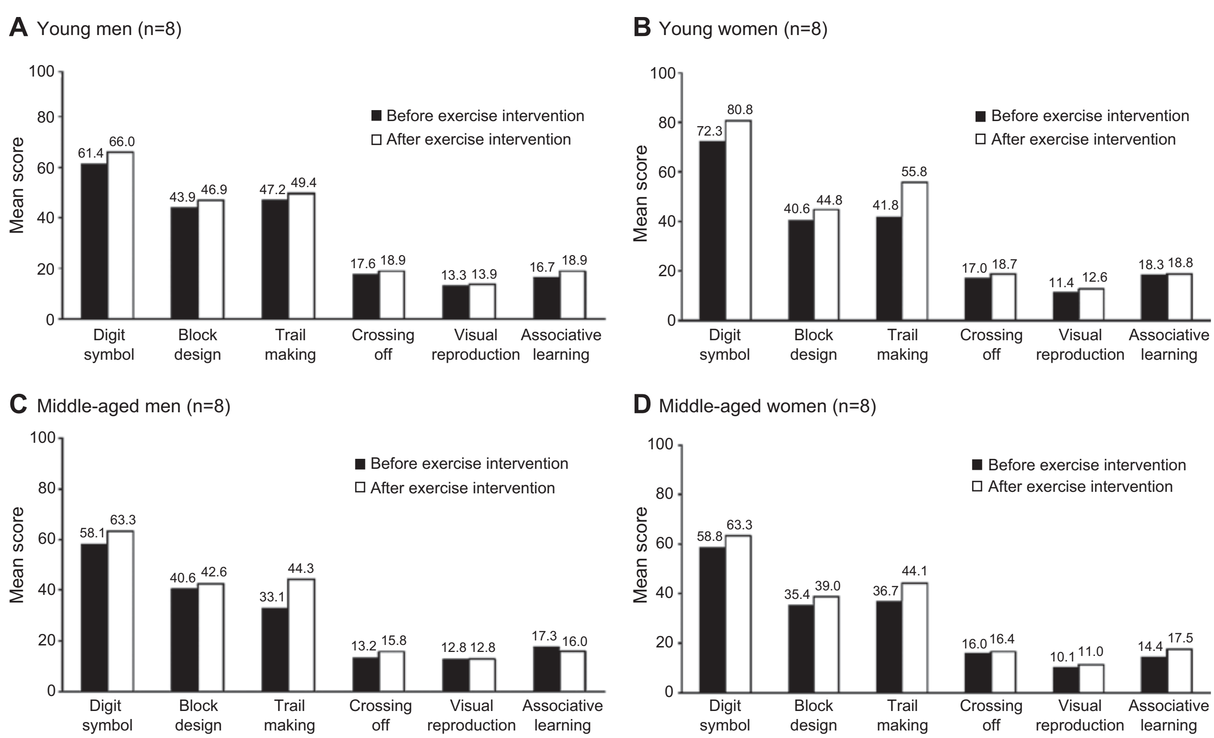

Figure 3 Improved executive function after exercise intervention.
The mean performance on various tasks of executive function improved after a 10-week exercise program in young (A, B) and middle-aged (C, D) adults. Across all four groups, regardless of age or sex, significant improvement was observed after the exercise intervention on all tasks except the Visual Reproduction Memory task. Data are reproduced with permission from Young (1979). Reproduced with permission from BMJ Publishing Group Ltd., Copyright 1979.

flexibility. In addition, participants who exercised 5–7 days per week had better reaction time, attention, and cognitive flexibility than participants who exercised 3–4 days per week (Masley et al., 2009).

Higher levels of physical activity are associated with better cognition

In addition to promising results from randomized studies of short-term exercise interventions, correlation studies have shown that adults who are generally more physically active are more likely than adults who are generally inactive to have better performance on various cognitive tasks, including those involving executive functions. In a study of 241 community-dwelling individuals aged 15–71 years, Hillman et al. (2006b) evaluated whether participants' self-reported physical activity levels were associated with performance on the Eriksen flanker task, a task that requires focusing attention and inhibiting responses to the incongruent stimuli. The authors found that younger (mean age: 26 years) and older (mean age: 50 years) participants who participated in more physical activity had faster reaction times for congruent and incongruent conditions of the flanker task. In addition, older participants with higher physical activity levels displayed better response accuracy on the incongruent condition (Hillman et al., 2006b). Smaller studies in young adults showed an association between physical activity and task-switching performance (Themanson et al., 2008; Kamijo and Takeda, 2010); together, these studies provide evidence that regular physical activity during adulthood improves executive function.

In a study that used a battery of neuropsychological tests on 1927 healthy adults aged 45–70 years revealed that individuals with more intense weekly physical activity had better processing speed, memory, mental flexibility, and overall cognitive function (Angevaren et al., 2007). In addition, participation in a greater variety of activities (e.g., walking, cycling, housekeeping, doing odd jobs, gardening, sports activities) was associated with significantly better performance on all evaluated cognitive domains.

Furthermore, in a prospective, occupational cohort study of 10 308 adults aged 46–68 years who were employed by 20 London-based civil servant departments revealed that those who reported lower levels of physical activity had lower scores on various cognitive tests of executive function, including measures of inductive reasoning and verbal fluency (Singh-Manoux et al., 2005).

Physical activity in early and middle adulthood can preserve cognition in later life

Several studies have investigated the lasting benefit of physical activity on cognition in later years. The largest study included a population-based analysis of all Swedish men born from 1950 to 1976 who enlisted for military service at the age of 18 years (n=1 221 727) (Åberg et al., 2009). This large population represented approximately 97% of the male Swedish population born from 1950 to 1976. Cardiovascular fitness was measured with ergometer cycling, and cognitive ability and performance were assessed with a combination of four tests: a logical performance test, a verbal test of synonyms and opposites, a test of visuospatial/geometric perception, and a test of technical/mechanical skills with mathematical/physics problems, as measures of general cognitive ability. Cardiovascular fitness as well as performance on the individual cognitive domains (logic, verbal, visuospatial, and technical) at age 18 years was significantly associated with general cognitive ability. Interestingly, additional analyses of brother pairs (n=268 496) and twin pairs (n=3147, of which 1432 were monozygotic twin pairs) showed that the positive correlation between fitness and cognition was mainly due to environmental rather than genetic factors. The authors also examined the longitudinal effect of cardiovascular fitness on cognitive performance. They found that changes in fitness from 15 to 18 years of age were linked to changes in cognition; participants with improved fitness had better scores on global, logic, verbal, visuospatial, and technical cognitive tests compared with participants with a decline in fitness levels. Finally, cardiovascular fitness at age 18 years predicted educational attainment (university vs. high school) and socioeconomic status (professions ranked with high vs. low socioeconomic index) later in life (Åberg et al., 2009).

In addition to this large, longitudinal study of young adults (Åberg et al., 2009), other studies have found that physical activity during midlife can preserve cognition later in life (Bosma et al., 2002; Richards et al., 2003; Rovio et al., 2005; Singh-Manoux et al., 2005; Andel et al., 2008; Hassing et al., 2009; Sabia et al., 2009; Geda et al., 2010). These studies, outlined in Table 1, report that participation in physical activity can significantly slow the rate of cognitive decline during later adulthood (Bosma et al., 2002; Richards et al., 2003; Singh-Manoux et al., 2005) or reduce the risk of developing dementia or Alzheimer's disease (Rovio et al., 2005 Andel et al., 2008; Geda et al., 2010) and that being overweight or obese during midlife can be associated with poorer cognition or increased odds of developing dementia later in life (Hassing et al., 2009; Sabia et al., 2009).

Additional insights and recommendations for maximizing the benefits of physical activity on cognition

The American College of Sports Medicine and the American Heart Association recommend that to promote and maintain health, all healthy adults aged 18–65 years should partake in a minimum of 150 min per week (i.e., 30 min for 5 days) of moderate-intensity aerobic physical activity as well as at least 2 days per week of muscle-strengthening activities that work the major muscle groups (Haskell et al., 2007). Unfortunately, most adults in the United States currently do not obtain the recommended level of physical activity (Troiano et al., 2008). In light of the large body of evidence that supports the positive effects of physical activity on

Table 1 Physical activity during midlife preserves cognition in later adulthood.

Study	Participants	Assessments	Results
Andel et al. (2008)	264 seniors with dementia and 2870 controls enrolled in the HARMONY study, which included members of the Swedish Twin Registry who were aged 65 years and older in 1998.	Assessment of dementia occurred an average of 31 years after assessment of exercise in the following: 1) regular exercise involving sports; 2) light exercise such as walking or gardening; 3) hardly any exercise.	Compared with participants who reported getting hardly any exercise, those who reported regular exercise or light exercise had significantly reduced odds of developing dementia 31 years later.
Bosma et al. (2002)	830 adults aged 49–81 years without dementia who participated in the Maastricht Aging Study.	Participants with no engagement vs. at least 1 h/week of engagement in physical activity were tested at baseline and at follow-up 3 years later on six cognitive tests (Stroop color–word incongruent task, Rey Auditory Verbal Learning Test, Letter Digit Coding Test, Word Fluency Test, and MMSE).	Compared with inactive participants, those who reported at least 1 h/week of physical activity had less cognitive decline over 3 years on the Stroop and Letter Digit Coding Test tasks.
Geda et al. (2010)	198 adults (median age: 83 years) with MCI and 1126 adults (median age: 80 years) with normal cognition who participated in the Mayo Clinic Study of Aging.	Participants reported their level of physical exercise (light, moderate, or vigorous) during midlife (aged 50–65 years). A battery of neuropsychological tests was administered to determine whether participants had MCI in one or more cognitive domains (memory, executive function, language, visuospatial skills).	Participation in moderate exercise during midlife was associated with significantly reduced odds of developing MCI in late life; exercise reduced the risk of MCI by 39%.
Hassing et al. (2009)	1152 adults, including 312 with dementia and 181 with Alzheimer's disease, from the Swedish Twin Registry who participated in a BMI survey in 1963 and were aged 45–65 years in 1963.	Participants were screened for dementia, including Alzheimer's disease, over a follow-up period of 40 years. Correlation analyses were conducted to determine whether being overweight in midlife (BMI$\geq$26.5 kg/m^2) increased the risk of developing dementia.	Being overweight during midlife significantly increased the risk of developing any dementia (59% greater risk) or Alzheimer's disease (71% greater risk).
Richards et al. (2003)	1919 adults enrolled in the Medical Research Council National Survey of Health and Development (the British 1946 birth cohort).	Participants reported their level of physical exercise (e.g., aerobic activities, sports) and spare-time activities (e.g., social activities) at age 36 years. Verbal memory was assessed at ages 43 and 53 years using a word-learning task.	Engagement in physical exercise and spare-time activity at age 36 years was significantly associated with better verbal memory at age 43 years. In addition, participants who reported engaging in physical exercise at age 36 years had a significantly slower rate of decline in memory from ages 43 to 53 years. Moreover, protection against memory decline was evident in participants who reported engaging in physical exercise at age 43 years (either new or continuing exercisers) but not in participants who gave up exercise after 36 years, suggesting that continuing physical exercise after age 36 years was important for protection of cognition.
Rovio et al. (2005)	1449 adults, including 117 who developed dementia and 76 who developed Alzheimer's disease, in the Finnish CAIDE study who had assessments at midlife (mean age, 51 years) and follow-up (mean age, 72 years).	Participants reported their level of physical activity and were categorized as active (participated in leisure-time physical activity at least twice a week) or sedentary (participated in leisure-time physical activity less than twice a week). Correlation analyses were conducted to determine whether engagement in physical activity decreased the risk of developing dementia or Alzheimer's disease.	Compared with the sedentary group, participants who reported engaging in physical activity at least twice a week during midlife had a significantly reduced risk of developing dementia (52% lesser risk) or Alzheimer's disease (60% lesser risk).

Table 1 (Continued)

Study	Participants	Assessments	Results
Sabia et al. (2009)	5131 civil servants in London who participated in the Whitehall II study.	BMI was self-reported or measured at age 25 years (early adulthood), early midlife (mean age: 44 years), and late midlife (61 years). Cognition was assessed at late midlife using a battery of tests and categorized as measuring global cognition (MMSE), memory (20-word free recall test), and executive function (Alice Heim 4-I test of inductive reasoning and tests of verbal fluency).	Being obese (BMI≥30 kg/m^2) at late midlife was associated with poorer cognition on all measures (MMSE, memory, and executive function tests). In addition, cumulative obesity (being obese at two to three of the study time points) was associated with lower MMSE, memory, and executive function scores, suggesting that the effect of obesity on cognition accumulates over the adult life course, examined over a mean duration of 36 years in this study.
Singh-Manoux et al. (2005)	10 308 civil servants in London who participated in the Whitehall II study, a prospective, occupational cohort study that began in 1985, when participants were aged 35–55 years.	Participants reported their level of physical activity (low, medium, or high) at study baseline and other time points. Cognitive function was assessed from 1997 to 1999, when the participants were aged 46–68 years, using a battery of tests that included measures of fluid intelligence (i.e., Alice Heim 4-I test of inductive reasoning) and verbal fluency.	A low level of physical activity at study baseline was significantly associated with poorer performance on a measure of fluid intelligence (which involves short-term memory, abstract thinking, creativity, ability to solve novel problems, and reaction time) 11 years later, when workers were aged 46–68 years.

BMI, Body mass index; CAIDE, cardiovascular risk factors, aging and incidence of dementia; MCI, mild cognitive impairment; MMSE, mini-mental state examination.

cognition, and the ample evidence of the impact of exercise on physical health and disease, effective interventions to increase level of exercise and effectiveness of exercise regimens are needed. In this section, we will discuss evidence that engaging in focused periods of exercise and rest, along with avoiding prolonged periods of sedentary behavior at work and at home, can improve physical health and cognitive performance. We also review evidence supporting participation in population health and performance programs that promote physical activity. Given that employed adults spend around half of their waking hours at work (Conn et al., 2009) and that the nature of contemporary work is increasingly sedentary owing to automation and process efficiencies (Pronk, 2009), workplace interventions that promote physical activity are urgently needed and uniquely positioned to impact employee health and productivity. Our recommendations for focused periods of exercise and participation in workplace programs support both physical and mental health benefits (Table 2).

Engage in focused periods of exercise and rest

The recommended amount of weekly physical activity for healthy adults is a minimum of 150 min of moderate-intensity aerobic physical activity or 60 min of vigorous-intensity activity in addition to muscle-strengthening activities on 2 or more days (Haskell et al., 2007). The level of intensity of physical activity can affect cognitive performance. Although the impact of exercise on cognition is not uniform across individuals (Sibley and Beilock, 2007), several studies have suggested a dose-response relationship between exercise intensity and cognitive function (Themanson et al., 2008; Chang and Etnier, 2009b). Among 1927 adults aged 45–70 years, individuals with more intense weekly physical activity (assessed by summing weekly physical activities and calculating the metabolic equivalent value of the summed activity) had better processing speed, memory, mental flexibility, and overall cognitive function (Themanson et al., 2008). However, the time spent weekly on physical activities did not affect cognitive performance, suggesting a selective effect of exercise intensity on cognitive function. A more recent study reported that the relationship between exercise intensity and cognitive performance depended on the type of cognitive task (Chang and Etnier, 2009b); in this study of 68 adults (mean age: 26 years) who participated in an acute bout of resistance exercise, high-intensity exercise was found to benefit speed of information processing, whereas moderate-intensity exercise was most beneficial for executive performance (i.e., inhibition, working memory, attentional flexibility).

Regardless of the level of intensity applied during physical activity, a highly focused, purposeful routine can provide motivation to stay engaged in an exercise regimen over the long-term (Loehr and Schwartz, 2003). A study of 50 adults aged 20–40 years reported that mindfulness was associated with better cognitive function. The study included meditators and non-meditators across a wide range of professions and reported that mindfulness was associated with better

Table 2 Recommendations for maximizing the benefits of physical activity on physical and mental health.

Recommendation	Rationale
Engage in focused periods of physical activity and rest	• Exercise intensity is related to information processing speed, memory, mental flexibility, and overall cognitive function (Angevaren et al., 2007; Chang and Etnier, 2009b). • Taking frequent physical activity breaks (i.e., avoiding prolonged periods of uninterrupted sitting) has important health benefits (Healy et al., 2008) that could promote preservation of cognitive performance. • Participation in mental, social, and physical activities preserves cognitive function (Bosma et al., 2002; Richards et al., 2003; Singh-Manoux et al., 2003; Small et al., 2006) and improves emotional satisfaction and health-related quality of life (Bize et al., 2007; Stubbe et al., 2007).
Participate in workplace wellness programs	• Participation in wellness programs that promote physical activity improves worker health and productivity (Benedict and Arterburn, 2008; Anderson et al., 2009; Conn et al., 2009; Pronk, 2009). • Financial gains for employers include decreased medical costs and reduced absenteeism costs (Baicker et al., 2010).

performance on the Stroop task and d2-concentration and endurance test (Moore and Malinowski, 2009). Meditators demonstrated greater mindfulness than did non-meditators and had better attentional control, accuracy, and cognitive flexibility. Practical suggestions for increasing mindfulness during physical activity include commitment, focus, and elimination of distractions during the exercise period.

Periods of intense physical activity should be balanced by periods of rest and energy renewal (Loehr and Schwartz, 2003). Balance is key, because prolonged periods of sedentary behavior during waking hours have been associated with poorer health (Healy et al., 2008). Healy et al. (2008) reported an association between metabolic health and avoidance of prolonged periods of sitting in 168 adults aged 30–87 years (mean age: 53 years). Sedentary time and physical activity breaks (i.e., avoiding prolonged periods of physical inactivity) were monitored during waking hours for 7 days, and biomarkers of metabolic risk were assessed. Findings indicated that the number of physical activity breaks was associated with lower waist circumference, BMI, triglycerides, and 2-h plasma glucose levels. The recorded breaks were relatively short in duration and light in intensity, suggesting that brief, simple disruptions in sedentary time can have a significant impact on metabolic health. The authors provided practical suggestions for implementing easy physical activity breaks at home and in the workplace, such as taking brief ambulatory breaks during commercial breaks on television and during prolonged periods of sitting at work. Other approaches for avoiding prolonged periods of sedentary behavior at work by expending energy in the office setting include innovative office equipment, such as treadmill workstations, or holding meetings while walking (Levine et al., 2006; Levine and Miller, 2007; McAlpine et al., 2007; John et al., 2009).

In a study of 20 self-professed ‘couch potatoes’, including 10 lean (BMI, 23±2 kg/m^2) and 10 mildly obese (BMI, 33±2 kg/m^2) participants, Levine et al. (2005) used microsensors to record participants’ movements and body positions every 0.5 s for 10 days. Obese participants were seated an average of 2 h longer per day than lean participants. This result is consistent with the finding that prolonged sedentary time has detrimental effects on physical health. Moreover, in light of evidence that being overweight or obese during midlife is associated with poorer cognition or increased odds of developing dementia later in life (Hassing et al., 2009; Sabia et al., 2009), these findings suggest that avoiding prolonged periods of sedentary behavior can have positive effects not only on physical health but also on preservation of cognition.

In addition to evidence supporting intense physical activity and avoidance of prolonged sedentary time, other studies have reported positive associations between participation in leisure activities and cognition. Studies in middle-aged adults have shown that participation in leisure activities involving mental engagement (e.g., brain teasers, courses or evening classes, playing chess or bridge), social engagement (e.g., volunteer work, attending the cinema, theatre, or concerts), or spiritual engagement (e.g., church or religious activities) improved performance on various cognitive tests of executive function, including measures of inductive reasoning and memory (Richards et al., 2003; Singh-Manoux et al., 2003; Small et al., 2006). Moreover, participation in mental, social, and physical activities protected against cognitive decline in 830 adults aged 49–81 years assessed at baseline and 3 years later (Bosma et al., 2002).

Engaging in physical and leisure activities affects not only cognitive function but also emotional satisfaction and quality of life. The association between exercise participation and well-being was assessed in approximately 8000 adults aged 18–65 years from the Netherlands Twin Registry. Exercisers were more satisfied with their life and happier than non-exercisers at all ages (Stubbe et al., 2007). A systematic review of 14 studies related to physical activity and health-related quality of life reported that higher levels of physical activity in healthy adults were linked to better health-related quality of life outcomes (Bize et al., 2007).

Taken together, these studies suggest that engaging in focused periods of physical activity and rest has significant physical and mental health benefits. In addition, the likelihood of preserving physical health and cognition throughout adulthood can be maximized by avoiding prolonged sedentary time and participating in leisure activities that provide opportunities for physical, emotional, mental, and spiritual engagement.

Participate in workplace wellness programs

An increasing body of evidence suggests that promoting physical activity in the workplace has a significant positive effect on worker health and productivity (Conn et al., 2009; Pronk, 2009). The workplace is an opportune setting for implementing and monitoring physical activity interventions that support the employee population and, indirectly, their families (Pronk and Kottke, 2009). The corporate environment is well suited to leverage resources to increase employees' awareness of the benefits of physical activity and to encourage adoption and maintenance of physical activity regimens. For example, companies can use e-mail communications, departmental meetings, and online programs to promote tailored strategies (e.g., walking programs, integrated work breaks, comprehensive population health and performance programs) to increase physical activity and improve employee health and performance. Companies can also provide meaningful incentives and awards (e.g., financial incentives, health insurance benefits) to promote ongoing participation in health risk assessments and physical activity programs (Pronk and Kottke, 2009).

In a comprehensive meta-analysis summarizing health and physical activity behavior outcomes associated with workplace wellness programs, Conn et al. (2009) reviewed nearly 150 reports including more than 38 000 participants. Significant improvements were observed for physical activity behavior, fitness, lipids, anthropometric measures, work attendance, and job stress (Figure 4). Other systematic reviews reported that wellness programs are effective for improving weight loss and BMI (Benedict and Arterburn, 2008; Anderson et al., 2009). Taken together, studies of population health and performance programs provide evidence that workplace interventions can successfully increase the physical activity behavior of employees. Moreover, these programs can provide significant benefits in terms of employee health and productivity. Although wellness programs generally do not assess cognitive function as an outcome measure, the growing body of literature that connects physical activity with cognition suggests that workplace programs that promote engagement in physical activity can also promote improved cognitive performance among employees.

Workplace wellness programs have significant benefits for employers as well as employees. A meta-analysis evaluating the costs and savings associated with workplace wellness programs showed that medical costs decrease by approximately $3.27 for every dollar spent on wellness programs and that absenteeism costs decrease by approximately $2.73 for every dollar spent (Baicker et al., 2010). Thus, integrated population health and performance programs that promote physical activity provide benefits for employees and employers through improvements in worker health and performance and financial returns for the company. In light of the increasing evidence that improved cognitive performance is one of the many benefits related to physical activity, workplace interventions that promote physical activity are likely to have lasting benefits on employees' physical fitness and cognitive productivity.

Conclusion

Extensive evidence suggests that physical activity beneficially influences brain function and executive cognitive processes in

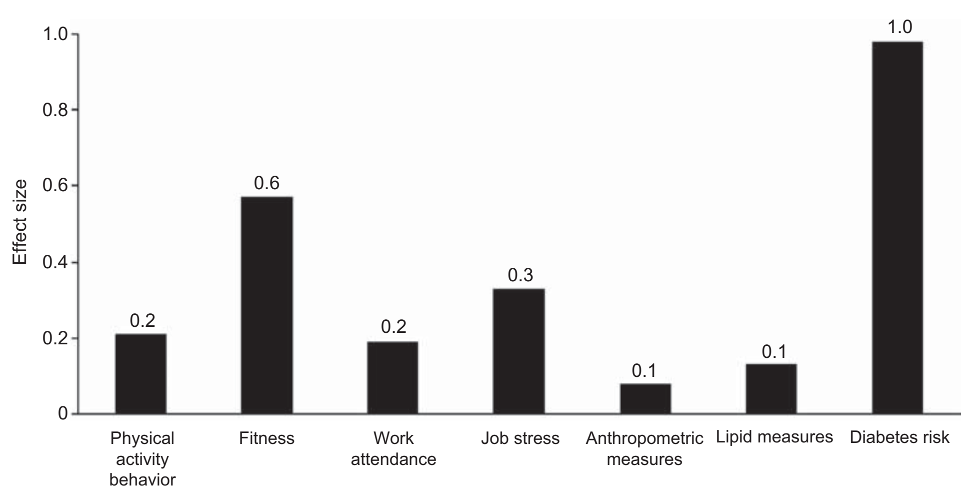

Figure 4 Meta-analytic findings of effects of workplace physical activity interventions on physical activity behavior, health, and work-related outcomes.

A meta-analysis of the effects of workplace physical activity interventions reported significant benefits on physical activity behavior, fitness (oxygen consumption), work attendance (derived from company records), job stress (self-reported), anthropometric measures (BMI, weight, abdominal girth, and percent body fat), lipid measures (total cholesterol, high-density lipoproteins, or the ratio of total cholesterol to high-density lipoproteins), and diabetes risk (fasting glucose or insulin levels). Data are reproduced with permission from Conn et al. (2009). Reproduced with permission from Elsevier, Copyright 2009.

particular. The effects of physical activity on cognition are exerted at the systemic, molecular, and cellular levels and are associated with changes in brain volume, cerebral blood flow, and growth factor availability and signaling cascades. Published studies suggest that physical activity in adulthood has a significant, lasting impact on cognition. Not only does acute exercise improve executive cognitive performance but regular physical activity in midlife has a protective effect against cognitive decline in later adulthood. Recommendations for maximizing the lasting benefits of movement and physical activity on cognition in adulthood include bouts of intense exercise, avoidance of prolonged periods of sedentary behavior (i.e., sitting), engagement in leisure activities, and participation in workplace wellness programs. Population health and performance programs that promote physical activity can provide lasting benefits for employees in terms of physical health and brain function, translating into improved employee performance and increased financial returns for the company. In summary, humans were designed to move. Movement improves cognitive performance and delays age-related cognitive declines through multiple neural mechanisms that support improved brain function. Additional insights from future studies will continue to clarify the beneficial effects of physical activity – and the detrimental effects of inactivity – on cognitive performance throughout adulthood.

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References

Åberg, M.A., Pedersen, N.L., Torén, K., Svartengren, M., Bäckstrand, B., Johnsson, T., et al. (2009). Cardiovascular fitness is associated with cognition in young adulthood. Proc. Natl. Acad. Sci. USA *106*, 20906–20911.

Andel, R., Crowe, M., Pedersen, N.L., Fratiglioni, L., Johansson, B., and Gatz, M. (2008). Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. J. Gerontol. A Biol. Sci. Med. Sci. 63, 62–66.

Anderson, L.M., Quinn, T.A., Glanz, K., Ramirez, G., Kahwati, L.C., Johnson, D.B., et al., Task Force on Community Preventive Services. (2009). The effectiveness of worksite nutrition and physical activity interventions for controlling employee overweight and obesity: a systematic review. Am. J. Prev. Med. *37*, 340–357.

Q4: Please supply the names of 10 authors followed by et al.

Angevaren, M., Vanhees, L., Wendel-Vos, W., Verhaar, H.J., Aufdemkampe, G., Aleman, A., et al. (2007). Intensity, but not duration, of physical activities is related to cognitive function. Eur. J. Cardiovasc. Prev. Rehabil. *14*, 825–830.

Angevaren, M., Aufdemkampe, G., Verhaar, H.J., Aleman, A., and Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst. Rev. *3*, CD005381.

Arwert, L.I., Deijen, J.B., and Drent, M.L. (2005). The relation between insulin-like growth factor I levels and cognition in healthy elderly: a meta-analysis. Growth Horm. IGF Res. *15*, 416–422.

Audiffren, M., Tomporowski, P.D., and Zagrodnik, J. (2008). Acute aerobic exercise and information processing: energizing motor processes during a choice reaction time task. Acta Psychol. (Amst.) *129*, 410–419.

Baicker, K., Cutler, D., and Song, Z. (2010). Workplace wellness programs can generate savings. Health Aff. (Millwood) *29* (Suppl. 2), 304–311.

Benedict, M.A. and Arterburn, D. (2008). Worksite-based weight loss programs: a systematic review of recent literature. Am. J. Health Promot. *22*, 408–416.

Berchtold, N.C., Castello, N., and Cotman, C.W. (2010). Exercise and time-dependent benefits to learning and memory. Neuroscience *167*, 588–597.

Bize, R., Johnson, J.A., and Plotnikoff, R.C. (2007). Physical activity level and health-related quality of life in the general adult population: a systematic review. Prev. Med. *45*, 401–415.

Blomquist, K.B. and Danner, F. (1987). Effects of physical conditioning on information-processing efficiency. Percept. Mot. Skills *65*, 175–186.

Bondy, C.A. and Cheng, C.M. (2004). Signaling by insulin-like growth factor 1 in brain. Eur. J. Pharmacol. *490*, 25–31.

Booth, F.W., Chakravarthy, M.V., Gordon, S.E., and Spangenburg, E.E. (2002). Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. J. Appl. Physiol. *93*, 3–30.

Bosma, H., van Boxtel, M.P., Ponds, R.W., Jelicic, M., Houx, P., Metsemakers, J., et al. (2002). Engaged lifestyle and cognitive function in middle and old-aged, non-demented persons: a reciprocal association? Z. Gerontol. Geriatr. *35*, 575–581.

Bruel-Jungerman, E., Veyrac, A., Dufour, F., Horwood, J., Laroche, S., and Davis, S. (2009). Inhibition of PI3K-Akt signaling blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in the dentate gyrus. PLoS One *4*, e7901.

Chakravarthy, M.V. and Booth, F.W. (2004). Eating, exercise, and “thrifty” genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. J. Appl. Physiol. *96*, 3–10.

Chang, Y.K. and Etnier, J.L. (2009a). Effects of an acute bout of localized resistance exercise on cognitive performance in middle-aged adults: a randomized controlled trial study. Psychol. Sport Exerc. *10*, 19–24.

Chang, Y.K. and Etnier, J.L. (2009b). Exploring the dose-response relationship between resistance exercise intensity and cognitive function. J. Sport Exerc. Psychol. *31*, 640–656.

Q5: In Chang and Etnier (2009), ‘a’ and ‘b’ has been added for year in text and Ref. list. Please confirm that a and b have been properly assigned in the text.

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.

Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J., McAuley, E., et al. (2003). Aerobic fitness reduces brain tissue loss in aging humans. J. Gerontol. A Biol. Sci. Med. Sci. *58*, 176–180.

Colcombe, S.J., Kramer, A.F., Erickson, K.I., Scalf, P., McAuley, E., Cohen, N.J., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. Proc. Natl. Acad. Sci. USA *101*, 3316–3321.

Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kim, J.S., Prakash, R., McAuley, E., et al. (2006). Aerobic exercise training increases brain volume in aging humans. J. Gerontol. A Biol. Sci. Med. Sci. *61*, 1166–1170.

Coles, K. and Tomporowski, P.D. (2008). Effects of acute exercise on executive processing, short-term and long-term memory. J. Sports Sci. *26*, 333–344.

Conn, V.S., Hafdahl, A.R., Cooper, P.S., Brown, L.M., and Lusk, S.L. (2009). Meta-analysis of workplace physical activity interventions. Am. J. Prev. Med. *37*, 330–339.

Cotman, C.W. and Berchtold, N.C. (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. *25*, 295–301.

Cotman, C.W., Berchtold, N.C., and Christie, L.A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. *30*, 464–472.

Danaei, G., Ding, E.L., Mozaffarian, D., Taylor, B., Rehm, J., Murray, C.J., et al. (2009). The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. *6*, e1000058.

Ding, Y.H., Li, J., Zhou, Y., Rafols, J.A., Clark, J.C., and Ding, Y. (2006). Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. Curr. Neurovasc. Res. *3*, 15–23.

Dishman, R.K., Berthoud, H.R., Booth, F.W., Cotman, C.W., Edgerton, V.R., Fleshner, M.R., et al. (2006). Neurobiology of exercise. Obesity (Silver Spring) *14*, 345–356.

During, M.J. and Cao, L. (2006). VEGF, a mediator of the effect of experience on hippocampal neurogenesis. Curr. Alzheimer Res. *3*, 29–33.

Eriksson, P.S., Perfilieva, E., Björk-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D.A., et al. (1998). Neurogenesis in the adult human hippocampus. Nat. Med. *4*, 1313–1317.

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Hu, L., Morris, K.S., et al. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus *19*, 1030–1039.

Etnier, J.L. and Chang, Y.K. (2009). The effect of physical activity on executive function: a brief commentary on definitions, measurement issues, and the current state of the literature. J. Sport Exerc. Psychol. *31*, 469–483.

Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., et al. (2003). VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur. J. Neurosci. *18*, 2803–2812.

Farmer, J., Zhao, X., van Praag, H., Wodtke, K., Gage, F.H., and Christie, B.R. (2004). Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience *124*, 71–79.

Ferris, L.T., Williams, J.S., and Shen, C.L. (2007). The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med. Sci. Sports Exerc. *39*, 728–734.

Geda, Y.E., Roberts, R.O., Knopman, D.S., Christianson, T.J., Pankratz, V.S., Ivnik, R.J., et al. (2010). Physical exercise, aging, and mild cognitive impairment: a population-based study. Arch. Neurol. *67*, 80–86.

Gomez-Pinilla, F., Vaynman, S., and Ying, Z. (2008). Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. Eur. J. Neurosci. *28*, 2278–2287.

Gordon, B.A., Rykhlevskaia, E.I., Brumback, C.R., Lee, Y., Elavsky, S., Konopack, J.F., et al. (2008). Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. Psychophysiology *45*, 825–838.

Hamilton, M.T., Hamilton, D.G., and Zderic, T.W. (2007). Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes *56*, 2655–2667.

Haskell, W.L., Lee, I.M., Pate, R.R., Powell, K.E., Blair, S.N., Franklin, B.A., et al., American College of Sports Medicine; American Heart Association. (2007). Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation *116*, 1081–1093.

Hassing, L.B., Dahl, A.K., Thorvaldsson, V., Berg, S., Gatz, M., Pedersen, N.L., et al. (2009). Overweight in midlife and risk of dementia: a 40-year follow-up study. Int. J. Obes. (Lond.) *33*, 893–898.

Healy, G.N., Dunstan, D.W., Salmon, J., Cerin, E., Shaw, J.E., Zimmet, P.Z., et al. (2008). Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 31, 661–666.

Hillman, C.H., Snook, E.M., and Jerome, G.J. (2003). Acute cardiovascular exercise and executive control function. Int. J. Psychophysiol. *48*, 307–314.

Hillman, C.H., Kramer, A.F., Belopolsky, A.V., and Smith, D.P. (2006a). A cross-sectional examination of age and physical activity on performance and event-related brain potentials in a task switching paradigm. Int. J. Psychophysiol. *59*, 30–39.

Q6: In Hillman et al. (2006), 'a' and 'b' has been added for year in text and Ref. list. Please confirm that a and b have been properly assigned in text.

Hillman, C.H., Motl, R.W., Pontifex, M.B., Posthuma, D., Stubbe, J.H., Boomsma, D.I., et al. (2006b). Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals. Health Psychol. *25*, 678–687.

Hillman, C.H., Erickson, K.I., and Kramer, A.F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. Nat. Rev. Neurosci. *9*, 58–65.

Hogervorst, E., Riedel, W., Jeukendrup, A., and Jolles, J. (1996). Cognitive performance after strenuous physical exercise. Percept. Mot. Skills *83*, 479–488.

Jin, K., Sun, Y., Xie, L., Batteur, S., Mao, X.O., Smelick, C., et al. (2003). Neurogenesis and aging: FGF-2 and HB-EGF restore neurogenesis in hippocampus and subventricular zone of aged mice. Aging Cell *2*, 175–183.

John, D., Bassett, D., Thompson, D., Fairbrother, J., and Baldwin, D. (2009). Effect of using a treadmill workstation on performance of simulated office work tasks. J. Phys. Act. Health *6*, 617–624.

Joyce, J., Graydon, J., McMorris, T., and Davranche, K. (2009). The time course effect of moderate intensity exercise on response execution and response inhibition. Brain Cogn. *71*, 14–19.

Kamijo, K. and Takeda, Y. (2010). Regular physical activity improves executive function during task switching in young adults. Int. J. Psychophysiol. *75*, 304–311.

Komulainen, P., Pedersen, M., Hänninen, T., Bruunsgaard, H., Lakka, T.A., Kivipelto, M., et al. (2008). BDNF is a novel marker of cognitive function in ageing women: the DR's EXTRA study. Neurobiol. Learn. Mem. *90*, 596–603.

Kramer, A.F., Hahn, S., Cohen, N.J., Banich, M.T., McAuley, E., Harrison, C.R., et al. (1999) Ageing, fitness and neurocognitive function. Nature *400*, 418–419.

Kramer, A.F., Erickson, K.I., and Colcombe, S.J. (2006). Exercise, cognition, and the aging brain. J. Appl. Physiol. *101*, 1237–1242.

Larson, E.B., Wang, L., Bowen, J.D., McCormick, W.C., Teri, L., Crane, P., et al. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann. Intern. Med. *144*, 73–81.

Levine, J.A. and Miller, J.M. (2007). The energy expenditure of using a "walk-and-work" desk for office workers with obesity. Br. J. Sports Med. *41*, 558–561.

Levine, J.A., Lanningham-Foster, L.M., McCrady, S.K., Krizan, A.C., Olson, L.R., Kane, P.H., et al. (2005). Interindividual variation in posture allocation: possible role in human obesity. Science *307*, 584–586.

Levine, J.A., Vander Weg, M.W., Hill, J.O., and Klesges, R.C. (2006). Non-exercise activity thermogenesis: the crouching tiger hidden dragon of societal weight gain. Arterioscler. Thromb. Vasc. Biol. *26*, 729–736.

Llinás, R.R. (2001). I of the Vortex: From Neurons to Self (Cambridge: MIT Press).

Q7: Please supply the names of the editors, Chapter title for Refs. Ratey and Hagerman (2008), Loehr and Schwartz (2003).

Loehr, J. and Schwartz, T. (2003). The Power of Full Engagement (New York: Free Press), pp. 3–18.
Lopez-Lopez, C., LeRoith, D., and Torres-Aleman, I. (2004). Insulin-like growth factor I is required for vessel remodeling in the adult brain. Proc. Natl. Acad. Sci. USA 101, 9833–9838.
Masley, S., Roetzheim, R., and Gualtieri, T. (2009). Aerobic exercise enhances cognitive flexibility. J. Clin. Psychol. Med. Settings *16*, 186–193.
McAlpine, D.A., Manohar, C.U., McCrady, S.K., Hensrud, D., and Levine, J.A. (2007). An office-place stepping device to promote workplace physical activity. Br. J. Sports Med. *41*, 903–907.
McMorris, T. and Graydon, J. (1997). The effect of exercise on cognitive performance in soccer-specific tests. J. Sports Sci. *15*, 459–468.
Moore, A. and Malinowski, P. (2009). Meditation, mindfulness and cognitive flexibility. Conscious Cogn. *18*, 176–186.
Mudò, G., Bonomo, A., Di Liberto, V., Frinchi, M., Fuxe, K., and Belluardo, N. (2009). The FGF-2/FGFRs neurotrophic system promotes neurogenesis in the adult brain. J. Neural Transm. *116*, 995–1005.
Neel, J.V. (1962). Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”? Am. J. Hum. Genet. *14*, 353–362.
Netz, Y., Tomer, R., Axelrad, S., Argov, E., and Inbar, O. (2007). The effect of a single aerobic training session on cognitive flexibility in late middle-aged adults. Int. J. Sports Med. *28*, 82–87.
Palmer, T.D., Willhoite, A.R., and Gage, F.H. (2000). Vascular niche for adult hippocampal neurogenesis. J. Comp. Neurol. *425*, 479–494.
Pereira, A.C., Huddleston, D.E., Brickman, A.M., Sosunov, A.A., Hen, R., McKhann, G.M., et al. (2007). An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc. Natl. Acad. Sci. USA *104*, 5638–5643.
Polich, J. and Lardon, M.T. (1997). P300 and long-term physical exercise. Electroencephalogr. Clin. Neurophysiol. *103*, 493–498.
Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. *118*, 2128–2148.
Pontifex, M.B., Hillman, C.H., Fernhall, B., Thompson, K.M., and Valentini, T.A. (2009). The effect of acute aerobic and resistance exercise on working memory. Med. Sci. Sports Exerc. *41*, 927–934.
Pronk, N.P. (2009). Physical activity promotion in business and industry: evidence, context, and recommendations for a national plan. J. Phys. Act. Health *6* (Suppl. 2), S220–S235.
Pronk, N.P. and Kottke, T.E. (2009). Physical activity promotion as a strategic corporate priority to improve worker health and business performance. Prev. Med. *49*, 316–321.
Ratey, J.J. and Hagerman, E. (2008). Spark: The Revolutionary New Science of Exercise and the Brain (New York: Little, Brown and Company), pp. 35–56.
Richards, M., Hardy, R., and Wadsworth, M.E. (2003). Does active leisure protect cognition? Evidence from a national birth cohort. Soc. Sci. Med. *56*, 785–792.
Rovio, S., Kåreholt, I., Helkala, E.L., Viitanen, M., Winblad, B., Tuomilehto, J., et al. (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer’s disease. Lancet Neurol. *4*, 705–711.
Sabia, S., Kivimaki, M., Shipley, M.J., Marmot, M.G., and Singh-Manoux, A. (2009). Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. Am. J. Clin. Nutr. *89*, 601–607.
Shetty, A.K., Hattiangady, B., and Shetty, G.A. (2005). Stem/progenitor cell proliferation factors FGF-2, IGF-1, and VEGF exhibit early decline during the course of aging in the hippocampus: role of astrocytes. Glia *51*, 173–186.
Sibley, B.A. and Beilock, S.L. (2007). Exercise and working memory: an individual differences investigation. J. Sport Exerc. Psychol. *29*, 783–791.
Sibley, B.A. and Etnier, J.L. (2003). The relationship between physical activity and cognition in children: a meta-analysis. Pediatr. Exerc. Sci. *15*, 243–256.
Sibley, B.A., Etnier, J.L., and Le Masurier, G.C. (2006). Effects of an acute bout of exercise on cognitive aspects of Stroop performance. J. Sport Exerc. Psychol. *28*, 285–299.
Singh-Manoux, A., Richards, M., and Marmot, M. (2003). Leisure activities and cognitive function in middle age: evidence from the Whitehall II study. J. Epidemiol. Community Health *57*, 907–913.
Singh-Manoux, A., Hillsdon, M., Brunner, E., and Marmot, M. (2005). Effects of physical activity on cognitive functioning in middle age: evidence from the Whitehall II Prospective Cohort Study. Am. J. Public Health *95*, 2252–2258.
Small, G.W., Silverman, D.H., Siddarth, P., Ercoli, L.M., Miller, K.J., Lavretsky, H., et al. (2006). Effects of a 14-day healthy longevity lifestyle program on cognition and brain function. Am. J. Geriatr. Psychiatry *14*, 538–545.
Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., et al. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom. Med. *72*, 239–252.
Snyder, J.S., Glover, L.R., Sanzone, K.M., Kamhi, J.F., and Cameron, H.A. (2009). The effects of exercise and stress on the survival and maturation of adult-generated granule cells. Hippocampus *19*, 898–906.
Stroop, J.R. (1935). Studies of interference in serial verbal reactions. J. Exp. Psychol. *18*, 643–662.
Stroth, S., Hille, K., Spitzer, M., and Reinhardt, R. (2009). Aerobic endurance exercise benefits memory and affect in young adults. Neuropsychol. Rehabil. *19*, 223–243.
Stubbe, J.H., de Moor, M.H., Boomsma, D.I., and de Geus, E.J. (2007). The association between exercise participation and well-being: a co-twin study. Prev. Med. *44*, 148–152.
Suominen-Troyer, S., Davis, K.J., Ismail, A.H., and Salvendy, G. (1986). Impact of physical fitness on strategy development in decision-making tasks. Percept. Mot. Skills *62*, 71–77.
Swain, R.A., Harris, A.B., Wiener, E.C., Dutka, M.V., Morris, H.D., Theien, B.E., et al. (2003). Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience *117*, 1037–1046.
Themanson, J.R., Pontifex, M.B., and Hillman, C.H. (2008). Fitness and action monitoring: evidence for improved cognitive flexibility in young adults. Neuroscience *157*, 319–328.
Torres-Aleman, I. (2010). Toward a comprehensive neurobiology of IGF-I. Dev. Neurobiol. *70*, 384–396.
Trejo, J.L., Carro, E., and Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J. Neurosci. *21*, 1628–1634.
Trejo, J.L., Llorens-Martín, M.V., and Torres-Alemán, I. (2008). The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-I-dependent mechanism related to hippocampal neurogenesis. Mol. Cell. Neurosci. *37*, 402–411.
Troiano, R.P., Berrigan, D., Dodd, K.W., Mâsse, L.C., Tilert, T., and McDowell, M. (2008). Physical activity in the United

Q8:
In van Praag et al. (1999), ‘a’ and ‘b’ has been added for year in text and Ref. list. Please confirm that a and b have been properly assigned in text.

States measured by accelerometer. Med. Sci. Sports Exerc. *40*, 181–188.

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

van Praag, H., Christie, B.R., Sejnowski, T.J., and Gage, F.H. (1999b). Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc. Natl. Acad. Sci. USA *96*, 13427–13431.

van Praag, H., Shubert, T., Zhao, C., and Gage, F.H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. J. Neurosci. *25*, 8680–8685.

Vaynman, S. and Gomez-Pinilla, F. (2006). Revenge of the “sit”: how lifestyle impacts neuronal and cognitive health through molecular systems that interface energy metabolism with neuronal plasticity. J. Neurosci. Res. *84*, 699–715.

Vaynman, S., Ying, Z., and Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur. J. Neurosci. *20*, 2580–2590.

Winter, B., Breitenstein, C., Mooren, F.C., Voelker, K., Fobker, M., Lechtermann, A., et al. (2007). High impact running improves learning. Neurobiol. Learn. Mem. *87*, 597–609.

Young, R.J. (1979). The effect of regular exercise on cognitive functioning and personality. Br. J. Sports Med. *13*, 110–117.