Physical Activity and Cognitive Vitality

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Annu. Rev. Psychol. 2015. 66:769–97

First published online as a Review in Advance on September 12, 2014

The *Annual Review of Psychology* is online at psych.annualreviews.org

This article's doi: 10.1146/annurev-psych-010814-015249

Keywords

physical activity, exercise, life span, cognitive functioning, neural plasticity, neurogenesis

Abstract

We examine evidence supporting the associations among physical activity (PA), cognitive vitality, neural functioning, and the moderation of these associations by genetic factors. Prospective epidemiological studies provide evidence for PA to be associated with a modest reduction in relative risk of cognitive decline. An evaluation of the PA-cognition link across the life span provides modest support for the effect of PA on preserving and even enhancing cognitive vitality and the associated neural circuitry in older adults, with the majority of benefits seen for tasks that are supported by the prefrontal cortex and the hippocampus. The literature on children and young adults, however, is in need of well-powered randomized controlled trials. Future directions include a more sophisticated understanding of the dose-response relationship, the integration of genetic and epigenetic approaches, inclusion of multimodal imaging of brain-behavior changes, and finally the design of multimodal interventions that may yield broader improvements in cognitive function.

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INTRODUCTION

Over the past decade, scientific, popular, and commercial interest in cognitive and brain plasticity has grown exponentially. For example, a recent Google search on the term "brain training" returned 226,000,000 documents (see also **http://www.sharpbrains.com**). Clearly, many of these hits referred to computer-based brain training games; a large number of these games are offered by start-up commercial companies. In many cases, these products are offered despite little convincing independent scientific validation of the claims that are made with regard to training, transfer, and retention of brain training. Similar claims are made for an increasing variety of dietary supplements often referred to as nutraceuticals. Although well-controlled scientific research on the potential efficacy of dietary supplements is certainly increasing (as is also the case for computer-based training products), product development still occurs at a much more rapid pace than research.

In the present review, we focus on a lifestyle factor that has shown promise in eliciting or taking advantage of brain plasticity—that is, physical activity (PA) and exercise. This growing interest occurs within the context of the increasingly inactive lifestyles of modern culture.

In 2008, the first comprehensive guidelines on PA were published by the US government. These recommendations, entitled *2008 Physical Activity Guidelines for Americans* (see **http://www.health.gov/paguidelines/guidelines/**), were the result of an extensive review of the scientific data on PA and health performed by a group of 13 leading experts from the fields of exercise science and public health (Haskell et al. 2007). The report was unique in that the science base available at the time was used to formulate practical guidelines for PA from young childhood through old age as well as for individuals with chronic medical conditions and physical disabilities. Recommendations were based both on the level of PA and its duration across the course of a week, and throughout most of the life span. Additionally, recommendations were formulated in terms of both aerobic and muscle strengthening activities that were appropriate for different populations.

For example, for general health benefits, adults between the ages of 18 and 65 years are recommended to engage in at least 30 minutes of moderate-intensity exercises five times a week (energy expenditure from 3 to 6 metabolic equivalents), or a minimum of 20 minutes of vigorous-intensity aerobic exercises at least three times per week (energy expenditure of >6.0 metabolic equivalents), or some combination of an equivalent amount of the two. Additionally, the recommendations

included engaging in moderate- to high-intensity muscle strengthening exercises involving all major muscle groups at least two times a week. Individuals over the age of 65 years are recommended to follow similar guidelines, but the guidelines for older adults further take into consideration older adults' fitness levels and include flexibility exercises for at least two days a week and balance exercises to reduce the risk of falls (Nelson et al. 2007). More recently, these PA guidelines were extended to even younger children in *PA Guidelines for Americans Midcourse Report: Strategies for Increasing Physical Activity Among Youth* (Phys. Act. Guidel. Am. Midcourse Rep. Subcomm. Pres. Counc. Fit. Sports Nutr. 2012) and in *PA Objectives for 2020* (see **http://www.healthypeople.gov**).

The recommendations in these reports were based on the large and growing body of studies that have examined the relationship between PA (and other factors) and health and disease. Lack of PA and exercise has been associated with an increased risk for a number of diseases including type II diabetes, hypertension, colon and breast cancer, obesity, and coronary heart disease (HealthyPeople.gov 2000). Indeed, lack of activity has even been associated with the onset of "adult" diseases, such as diabetes and hypertension, among children (Freedman et al. 2001, Sisson et al. 2009). Finally, PA has also been found to result in increased life expectancy and a substantial decrease in medical expenditures across the life span (Lee et al. 2012, Nagai et al. 2011). However, despite the well-documented relationship between lack of PA and disease and several government reports promoting PA, as of 2011, only 21% of US adults met the recommended weekly objectives for aerobic PA and muscle strengthening activities (see **http://healthypeople.gov/2020/topicsobjectives2020/nationaldata.aspx?topicId=33**).

As described above, abundant data now suggest that PA is important in reducing the risk of various diseases, including those diseases (e.g., heart disease, stroke, osteoporosis, cancers, and obesity) that have been associated with compromised cognitive and brain health and consequently reduced independence and quality of life. The development of these diseases and their effects on cognition and brain unfold over the course of several years to several decades. In the present review, we focus on shorter-acting but equally important effects of PA and exercise on brain and cognitive health.

We begin with a review of the prospective epidemiological literature of PA and exercise and their relationship to cognition and age-associated neurodegenerative diseases such as Alzheimer's disease (AD). Although such research does not establish a causal relationship between exercise and cognitive and brain health, it does set the stage for intervention studies that enable the establishment of causality. Randomized controlled exercise trials with both healthy individuals and individuals with different diseases are also discussed. As a means to understand the molecular and cellular mechanisms that support the beneficial effects of exercise, we review the animal literature. We follow this discussion with an examination of a relatively new literature on gene-by-exercise interactions. Finally, we conclude with a section on the limitations of our current knowledge and suggestions for where we might go next in our exploration of the effects of exercise and PA on brain and cognition.

EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

Epidemiological studies typically involve an observational, but longitudinal, examination of factors that are involved in and possibly contribute to the development of increased health, progression of infectious and noninfectious diseases, and ultimately mortality. These studies have identified PA as a potent lifestyle factor that plays a critical role in predicting rates of cognitive decline (Middleton et al. 2010, Yaffe et al. 2009), the subsequent development of age-related neurodegenerative diseases such as AD (Hamer & Chida 2009), and mortality rates (Katzmarzyk et al. 2003, Samitz et al. 2011).

Higher levels of PA have been found to be reliably associated with a reduction in all-cause mortality, with studies reporting a relative risk reduction of 20% to 30% (Katzmarzyk et al. 2003, Phys. Act. Guidel. Advis. Comm. 2008) after removing variance associated with a range of confounding variables, such as age, education, gender, intelligence quotient, socioeconomic status, and social support network. Similar reductions in mortality rates have also been observed with higher levels of physical fitness, a physiological surrogate of PA (Kampert et al. 1996), with estimates of survival rates being slightly higher for physical fitness than for PA. Although these findings support the association of PA with a reduced risk of dying, a critical question is the extent to which this lifestyle factor contributes to a reduced risk of cognitive decline, thus influencing not just longevity but also an enhanced quality of life in these later years.

The growing epidemiological literature has also contributed to our understanding of the potential for PA to prevent or delay late-life cognitive decline. A notable methodological strength of the majority of these studies is the large sample size used to differentiate the effects of PA from demographic, health, and socioeconomic factors that likely influence the rate of cognitive decline. However, given that the majority of these studies employ samples of greater than 1,000 participants, the assessment of cognitive functioning has been limited to a rather tertiary examination of global cognitive functioning using measures such as the Mini-Mental State Examination. Additionally, the studies have varied considerably in their assessment of PA, with the predictor variable often defined as the intensity, frequency, or duration of self-reported PA or some combination of these various measures. Thus, efforts to draw conclusions across studies can be mired by these limitations. However, despite such shortcomings, these studies have shown a remarkable consistency for self-reported PA, especially in individuals in their late fifties to early sixties, to predict later-life performance on general measures of cognitive functioning (Almeida et al. 2006, Etgen et al. 2010, Yaffe et al. 2009), processing speed (Chang et al. 2010, Stewart et al. 2003), episodic memory (Richards et al. 2003, Sabia et al. 2009, Stewart et al. 2003), and executive control (Chang et al. 2010, Sabia et al. 2009). A meta-analytic review of this literature, merging data across 15 prospective observational studies, demonstrated a 38% reduction in risk of cognitive decline in nondemented participants with high levels of PA, and a 35% reduction in risk of cognitive decline in participants with low to moderate levels of PA (Sofi et al. 2011). This meta-analysis, taken together with the mortality literature, indicates that engagement in PA is thus associated not just with increased longevity but also with an enhanced quality of life during the later years of life, manifesting as preserved cognitive functioning.

Within this literature, there is a growing need to clearly examine the dose-response relation between duration and intensity of PA with preserved cognition. The meta-analytic review by Sofi et al. (2011) provided no evidence for an increase in relative risk reduction in cognitive decline as a function of increasing levels of PA (38% reduction for individuals with high levels of PA and 35% reduction for individuals with low to moderate levels of PA). However, categorization of PA was based on a combination of frequency, duration, and intensity of the activities, and thus future research would need to parse the differential contribution of the facets of PA in yielding dose-response benefits. Additionally, epidemiological studies vary considerably with respect to the age of participants at baseline assessment, with the majority of studies conducting initial assessments on individuals in their mid sixties. It would thus be essential to parsimoniously examine the contributing role of engagement in PA over the life span on cognitive impairment later in life. In one retrospective study, low levels of PA during teenage years contributed the most to predicting cognitive impairment later in life (Middleton et al. 2010). These effects were found, in turn, to be counteracted by engagement in PA during midlife. Of the 15 studies included in the meta-analytic review by Sofi et al. (2011), the range of follow-up assessments was between 1 and 12 years, with the majority of studies conducting baseline assessments in individuals over 65 years of age. Given

the critical implications of such knowledge in relation to public health recommendations, as well as its influence in motivating individuals to adhere to health-enhancing behavior, there is a need to more systematically investigate through prospective longitudinal study designs the differential contributions of life-span PA on cognitive functioning.

Although there has been support for PA at baseline predicting cognitive vitality at follow-up, there is also evidence for a reverse association between cognitive functioning and physical functioning, specifically involving the ability to engage in physical tasks, such that baseline levels of cognitive functioning are associated with the ability to engage in walking and to maintain balance, grip strength, and gait speed later in life (Atkinson et al. 2007, Singh-Manoux et al. 2005, Tabbarah et al. 2002). For instance, data from the MacArthur studies of successful aging provide evidence for the change in cognitive functioning over a seven-year period to be associated with a change in physical functioning on both novel and routine physical tasks, thus supporting the hypothesis that the capacity to engage cognitive faculties could be an antecedent to the ability to engage in physical tasks rather than a consequence of enhanced physical capabilities (Tabbarah et al. 2002). In contrast, providing support against this reverse causality hypothesis, Deary et al. (2006) examined follow-up longitudinal data collected 68 years later on a group of 460 Scottish older adults. All participants had completed a measure of verbal and spatial reasoning, the Moray House Test, at baseline at the age of 11 and at follow-up at the age of 79. The latent physical fitness trait, a composite measure derived from the six-minute walk test, grip strength, and forced expiratory volume from the lungs in 1 second (FEV_1), at age 79 was found to be associated with cognitive functioning at follow-up, after removing variance associated with baseline cognitive performance. This composite measure explained 3.3% of the variance in cognitive functioning at follow-up. Interestingly, cognitive scores at baseline failed to predict physical performance later in life, thus providing preliminary support against the hypothesis that the associations between fitness and cognition are driven by better cognitive function associated with enhanced physical function. The relation between cognitive functioning and physical functioning is indeed complex, and the two are inextricably interrelated throughout the life span. Thus, although epidemiological studies provide modest support for PA in reducing cognitive decline, it is also important to note that pre-existing differences in cognitive vitality may interact with the ability to engage in physical functioning.

The notion that PA is protective against age-related cognitive decline is further supported by two neuroimaging studies that have examined the protective role of PA in guarding against age-related decline in brain atrophy (Erickson et al. 2010, Rovio et al. 2010). Although the two studies differed in the ages of participants at baseline assessment of PA, with the Rovio et al. study assessing the impact of PA during midlife (early fifties) and the Erickson et al. study assessing PA in individuals in their early seventies, the established association between PA at baseline and preserved structural integrity in these regions at follow-up ($\sim$21 years for the Rovio et al. study and $\sim$9 years for the Erickson et al. investigation) has critical implications for understanding the neuroprotective effect of PA. In both of these studies, PA at baseline was found to be protective of structural volume in the prefrontal cortices, thus providing corroboratory evidence for the protective effects of PA against age-related decline of brain volume. Additionally, Erickson et al. (2010) also found that PA at baseline was associated with greater structural integrity in the temporal cortices after an average of nine years of follow-up, thus establishing further specificity to the nature of the association between PA and neuroprotective benefits. Juxtaposed with the behavioral effects of the epidemiological literature, there seems to be converging evidence for the efficacy of PA to attenuate age-related decline in cognitive domains supported by the prefrontal and temporal cortices, such as executive control and episodic memory, respectively. In this study, after a further follow-up of four years, preserved gray matter volume in several cortical and subcortical regions,

including the hippocampus, was associated with a twofold-reduced risk of developing clinically significant cognitive impairment.

The role of physical inactivity as a risk factor for the development of all-cause dementia, particularly AD, is further supported by research studies providing strong evidence that higher levels of PA, measured subjectively using self-report questionnaires, as well as objectively using quantitative measures of PA, such as actigraphy, may guard against the development of these age-related, neurodegenerative disorders. With the exception of a few prospective studies (Carlson et al. 2008, Sturman et al. 2005, Verghese et al. 2006), the majority of studies have found evidence for lower rates of dementia, particularly AD, in individuals with higher levels of PA. Meta-analytic reviews of this literature suggest an odds ratio ranging from 0.72 against the risk for all-cause dementia to 0.55 against the risk of developing AD in individuals engaging in higher levels of PA (Daviglus et al. 2011, Hamer & Chida 2009). Employing actigraphs to gain a more thorough and objective assessment of PA levels, Buchman et al. (2012) reported a twofold-increased risk of developing AD in participants in the lowest PA percentiles (10th percentile), relative to participants in the highest PA percentiles (90th percentile). Interestingly, these results remained significant even after controlling for self-reported physical, cognitive, and social activities, indicating that objective measures of activity are providing information above and beyond that of self-reported measures. Similar to the cognitive decline literature, there is considerable heterogeneity in the ages at which baseline assessments of PA were conducted across studies. For example, in the meta-analytic review by Hamer & Chida (2009), 16 cohort studies examining the link between PA and neurodegenerative disease risk were identified. Ages at which PA assessments were conducted ranged from the individuals in their thirties to nineties, with follow-up periods ranging from three years to thirty years.

Collectively, the epidemiological literature points to the potential capacity for PA to maintain cognitive functioning and promote neural plasticity later in life. Although researchers have made substantial progress in understanding the capacity of PA to delay cognitive impairment later in life, as well as to delay the onset of neurodegenerative diseases, there is a need to more closely examine how PA might differentially enhance cognitive function and brain structure and function during childhood, young and middle adulthood, and old age. To better understand the developmental course of this potentially beneficial lifestyle factor, it is critical that longitudinal studies involve an examination of outcomes at several points in the developmental trajectory, and do so with both objective and subjective measures of PA parameters. Additionally, the inclusion of brain imaging metrics, specifically structural indices, as well as task-free measures of hemodynamic activity will allow for a further understanding of the changes in the neurobiological substrates that are not influenced by practice effects and can be reliably combined across multiple sites.

PHYSICAL ACTIVITY AND COGNITIVE AND NEURAL FUNCTIONING ACROSS THE LIFE SPAN

The literature reviewed above presents strong evidence for a rationale for the systematic scientific study of PA as a modifiable lifestyle factor that could improve cognition and brain plasticity. As such, the study of PA through cross-sectional investigations and randomized controlled trials (RCTs) has become a vibrant area of research, with new evidence supporting the beneficial associations between PA and cognitive vitality throughout the life span. In this section, we review evidence from cross-sectional investigations, RCTs, and meta-analytic reviews to present the current state of the literature examining the behavioral and neural correlates of PA, with a special emphasis on cardiorespiratory fitness (CRF).

Behavioral Evidence

Although the majority of the epidemiological literature has examined cognitive functioning during late life, recent cross-sectional studies and RCTs provide support for the beneficial effect of PA and CRF in children, young adults, and older adults. In a series of cross-sectional studies, Hillman and colleagues have provided evidence that objective measures of CRF are associated with behavioral measures of attentional and inhibitory control (Chaddock et al. 2010b, Hillman et al. 2009), and relational memory (Chaddock et al. 2010a, 2011) in children. Meta-analytic reviews of cross-sectional and RCTs of PA in children provide modest support for its association with cognitive performance in this age group (Fedewa & Ahn, 2011, Lees & Hopkins 2013, Sibley & Etnier 2003). For instance, Sibley & Etnier (2003) examined whether PA was associated with cognitive performance in children between the ages of 4 and 18 by pooling data across 44 studies. Cognitive domains were coded on eight separate categories: perceptual skills, intelligence quotients, achievement, verbal tests, mathematic tests, memory, developmental level/academic readiness, and other; PA was associated with functioning on all domains (range of significant effect sizes 0.17 to 0.49) but memory (effect size = 0.03). This meta-analytic review, however, was limited by its inclusion of studies with methodological shortcomings, combining data across research designs, and merging data across children with and without learning disabilities. Despite an impressive set of cross-sectional studies within this cohort, few RCTs with active control groups and psychometrically sound cognitive measures have been conducted. In a recent review of this literature in children, Lees & Hopkins (2013) identified only eight studies: two were crossover designs, and of the remaining six RCTs, only two studies had follow-up data greater than six months.

In addition to children, PA may explain variation in cognitive performance in older adults. Several RCTs have been conducted to examine whether inactive older adults, through participation in randomized longitudinal training programs, demonstrate gains in cognitive function. Although varied in their definition of the cognitive domains assessed, as well as in the length of the training program, the majority of these studies have examined the influence of moderate-intensity aerobic exercise training in mitigating age-related declines. In fact, within the past decade there has been growing interest in the scientific study of exercise as a potential low-cost psychosocial intervention for older adults. As such, several meta-analytic reviews quantifying the magnitude of this effect in reducing age-related cognitive decrements have been conducted, either focusing exclusively on older adults without cognitive impairment (Angevaren et al. 2008, Colcombe & Kramer 2003) or examining age as a potential moderator of treatment effects (Etnier et al. 2006, Smith et al. 2010). In one of the first such meta-analytic reviews, Colcombe & Kramer (2003) found support for the executive control hypothesis, reporting that although exercise interventions yielded benefits across several domains of cognition for older adults, the largest gains were incurred for higher-order executive control operations, which are known to be subserved by the complex interactions of top-down prefrontal mechanisms and bottom-up ventral visual cortices (Miller & Cohen 2001, Tamber-Rosenau et al. 2011). Additional moderators that impacted treatment effect sizes were the duration of the treatment, with RCTs of at least a six-month training period yielding larger effect sizes; the duration of the session within the training period, with sessions exceeding 30 minutes of training reporting larger effect sizes; and the combination of training interventions, with treatments incorporating elements of strength training with aerobic exercise yielding more benefit than aerobic exercise alone. Interestingly, this review did not find support for the CRF hypothesis, such that the effect sizes in the studies reporting the maximum change in CRF levels did not differ from studies reporting no change in fitness levels. The notion that changes in CRF are not associated with the observed effects of the intervention on cognition has

been corroborated by two additional meta-analytic reviews (Angevaren et al. 2008, Etnier et al. 2006) in which the observed changes in cognitive function were not explained by changes in CRF levels.

In a more recent review of this literature across adult development, Smith et al. (2010) examined the age-dependent effects of PA on four domains of cognition: attention and processing speed, executive functioning, working memory, and declarative memory. Although there seems to be emerging consensus on the positive relationship between PA and behavioral indices of cognitive performance in older adults, the literature on the impact of PA on the middle of the developmental course is still in its infancy, with debate on the potency of this lifestyle factor in sustaining cognitive performance within this age range (Aberg et al. 2009; Stroth et al. 2009, 2010). Aggregating studies from 1966 to 2010, Smith et al.'s (2010) review included 29 studies, with 17 RCTs on healthy older adults. Only 4 of the 29 RCTs included either young adults or adults in midlife, thus highlighting a critical gap in this literature. Interestingly, exercise training was found to have a weak to modest effect across all domains (Hedge's *g* ranging from 0.12 to 0.16) except working memory. Age was not found to moderate the effects of exercise training on any of the significant cognitive domains but was found to moderate the effects of exercise on working memory.

In summary, although the most consistent evidence indicates that PA, particularly moderate-intensity exercise, affects the cognitive vitality of older adults, there is mixed evidence for its role in improving cognitive functioning across the life span. Correlational studies support a positive relationship in childhood and late adulthood, but there is a clear need for well-powered RCTs to causally examine this relationship in multiple domains of cognition. It is also important to note that the majority of the behavioral literature within the field has focused on employing mean reaction time (RT) data and accuracy scores as the primary dependent variables. One of the next steps is to employ more nuanced computational models, such as diffusion models (Ratcliff 1978, Ratcliff & McKoon 2008), that take into account all aspects of the experimental data, including RT, error rates, and shapes of the RT distributions to finely parse the contribution of various facets of information processing and decisional processes that may contribute to developmental differences in the PA-related effects on cognition. For example, although both children and older adults, in comparison with young adults, show slower RT on cognitive tasks, Ratcliff and colleagues, employing diffusion models, have found that compromised cognitive functioning in children is due to the quality of acquired information (Ratcliff et al. 2012), whereas differences in decision boundaries seem to be the reason behind age-related differences in cognitive performance (Ratcliff et al. 2001, 2004). It would be interesting to examine the association of PA with the various components of the diffusion model, taking into account both RT and error scores. Such a careful examination of these components in children, young adults, and older adults would contribute to our understanding of the theoretical model of PA and its impact on cognition.

Neural Evidence

The promising findings in the behavioral domain have led researchers to quantify and qualify the nature of neural changes observed in relation to PA (Hayes et al. 2013, Thomas et al. 2012). With the growth of data analytic techniques in the field of neuroimaging (Bressler & Menon, 2010, Bullmore & Sporns 2009), studies have begun to employ sophisticated methodologies to better understand the nuanced neural correlates of the observed behavioral relationships. In this section, we discuss the literature aimed at understanding the correlational and causal relationships between PA and brain structure and function indices, such as volume of gray matter, white matter, and subcortical structures as assessed through voxel-based morphometry and automated segmentation

of magnetic resonance imaging (MRI) data; integrity of white matter tracts as assessed employing techniques such as diffusion tensor imaging; neuroelectric indices as measured by event-related brain potentials (ERP); brain activation patterns in response to exogenous processing as measured through task-based functional MRI (fMRI); and functional connectivity between distinct brain regions using techniques such as seed-based correlation and graph-theory analyses.

Structural MRI metrics. The development of neuroimaging techniques, such as voxel-based morphometry (Ashburner & Friston 2000) and diffusion imaging (Pierpaoli et al. 1996), has been critical in advancing our understanding of the structural architecture of the brain; the associated changes as a result of development, psychiatric, and neurodegenerative disorders; and plasticity associated with health-enhancing behaviors such as PA (Thomas et al. 2012). These techniques to measure the structural integrity of the brain have become widely used because of their reliability and semiautomatization. Although much of the current literature examining morphometric differences as a function of PA has investigated cross-sectional associations (Chaddock et al. 2010a,b; Colcombe et al. 2003; Erickson et al. 2009), results from a few randomized trials of PA show promising support for increased structural plasticity (Colcombe et al. 2006, Erickson et al. 2011, Ruscheweyh et al. 2011, Voss et al. 2013).

For instance, Colcombe et al. (2006) examined changes in the volume of gray matter and white matter in a group of inactive older adults following randomization to either a six-month aerobic exercise training group (walking) or a six-month stretching and toning control group. Using whole-brain voxel-based morphometry, their study provided evidence for the preservation of and gains in both gray matter and white matter volumes in regions traditionally known to show cortical atrophy as a function of aging (Raz et al. 2005, Ziegler et al. 2012), as well as in regions known to show exercise-induced plasticity in animal models (Voss et al. 2013a). Specifically, participants in the walking group, at postintervention, demonstrated an increase in the volume of the dorsal anterior cingulate cortex (dACC), supplementary motor area, the dorsolateral prefrontal cortices, and the left superior temporal lobule. Walking-induced changes were also noted for the volume of the anterior white matter tracts. Although the volumes of these structures do not show a direct correspondence with the microscopic cytoarchitectonic properties of the underlying tissue, the change in these measures provides promising evidence for the influence of PA, specifically aerobic exercise, in preserving the structural properties of the brain.

The specific findings of the Colcombe et al. (2006) study of brain regions typically showing age-related decline, such as the prefrontal and temporal cortices, evince support for the role of this lifestyle factor in reducing age-related structural decline. The extent to which these structural changes associate with behavioral performance were examined in another RCT (Erickson et al. 2011). This study provided evidence for an association between increases in the volume of the hippocampus, specifically the anterior hippocampus, and performance on a task of spatial short-term memory following a 12-month aerobic exercise intervention. The walking group demonstrated about a 2% increase in hippocampal volume, whereas the control group showed a 1.4% decline after one year; gains in volume were circumscribed to the anterior hippocampus that included the dentate gyrus, subiculum, and CA1 subfields, relative to the posterior hippocampus. The walking group did not show better performance on the measure of spatial memory relative to the control group. However, the changes in hippocampal volume for the walking group were associated with improvements in spatial memory performance, thus providing support for the possible facilitation of cognitive vitality, potentially mediated through aerobic exercise–induced gains in hippocampal volume. Interestingly, greater change in CRF across the two groups over a one-year period was associated with greater increases in hippocampal volume ($r = 0.37$ and 0.40 for left and right

hippocampus, respectively), suggesting that changes in CRF, irrespective of group participation, explain between 13% and 16% of the variance in hippocampal change.

Although these studies provide evidence for moderate-intensity aerobic exercise (walking) to facilitate gains in structural plasticity, at least two other studies have failed to find differential gains in structural metrics as a function of the type of exercise (Ruscheweyh et al. 2011, Voss et al. 2013). For example, physically inactive older adults in the Ruscheweyh et al. (2011) study were randomized into one of three groups: a medium-intensity Nordic walking group, a low-intensity stretching and toning group, or an assessment-only control group. The study results showed no differences between the three groups on measures of cognitive performance, structural brain volume, or neurotrophic or catecholamine levels. Merging across groups, the authors found evidence for an association between changes in total PA levels, quantified as total energy expenditure per week, and improved behavioral performance on the auditory verbal learning test as well as increased gray matter in the prefrontal cortices, specifically the left prefrontal cortex, and the anterior cingulate cortex. Similarly, Voss et al. (2013), employing diffusion imaging, investigated the change in white matter integrity as a result of exercise training. Moderate-intensity walking, relative to stretching and toning, did not yield significant changes in any of the examined metrics following a one-year period, though trending results were observed for the prefrontal cortex in favor of the aerobic training group. However, changes in CRF levels were associated with increased white matter integrity in the prefrontal and temporal regions of interest, but only for the walking group and not for the stretching and toning group.

Collectively, although there is some support for the type of training (e.g., aerobic exercise) influencing structural plasticity, other studies provide evidence that the change in either CRF levels or the total amount of energy expenditure is associated with the facilitative effects of the intervention. Despite these differences, there is converging evidence across these studies that the largest gains are in prefrontal and hippocampal regions, with both volumetric and diffusion data evincing support for these effects. Given the transformative role played by the prefrontal cortices and hippocampus on both sides of the developmental course, these findings suggest that PA could be a promising, low-cost intervention in shaping the tectonics of the human brain. The critical issue for future research is to systematically examine whether it is the type of exercise, such as aerobic exercise, that is vital for producing benefits in structural plasticity or if it is the change in various facets of PA, such as energy expenditure or CRF levels, that facilitates gains in brain structure. Much of the reviewed literature provides support for PA to incur gains in structural plasticity in older adults, and although cross-sectional support exists for the association between PA and brain volume in children (Chaddock et al. 2010a,b), well-powered RCTs examining changes in structural metrics in children, young adults, and individuals in middle age are needed to assess the impact of PA training across the life span.

Neuroelectric correlates. Event-related brain potentials allow for the study of real-time stimulus-locked or response-locked electrical potentials generated via the synchronous activity of underlying neurons (Rugg & Coles 1995). As such, this technique allows for a quantification of the precise temporal response associated either with the presentation of the stimulus or the generated response, thus allowing for a finer examination of the association between PA and the temporal magnitude of various cognitive operations.

The majority of ERP studies conducted within this literature have examined associations with neuroelectric indices within the context of stimulus discrimination tasks (Dustman et al. 1990, Hillman et al. 2005) and cognitive control tasks (Hillman et al. 2004, 2006, 2009; Pontifex et al. 2010; Themanson & Hillman 2006), with a particular emphasis on the P300 and error-related negativity (ERN) components. Although much of this literature is cross-sectional, support exists

for a positive relationship across the developmental life span between various facets of PA and neuroelectric indices.

In preadolescents, Hillman and colleagues have found evidence for increased P300 amplitude and decreased P300 latency in higher-fit children relative to lower-fit children during performance on various cognitive control tasks (Hillman et al. 2009, Pontifex et al. 2010). This increase in P300 amplitude, coupled with a shortened latency, was interpreted to reflect greater attentional allocation to the task-relevant attributes, with faster processing time. Similar results with these ERP components were also reported on stimulus discrimination tasks (Hillman et al. 2005), thus providing corroborating evidence that higher levels of fitness in preadolescent children are associated with neuroelectric indices of attentional allocation.

Using more nuanced cognitive tasks with older and young adults, Hillman and colleagues (Hillman et al. 2002, 2006; Pontifex et al. 2009; Themanson & Hillman 2006; Themanson et al. 2008) have systematically parsed the neuroelectric correlates associated with PA. Whereas the behavioral support for PA in young adults is more equivocal, ERP data, with the exception of a few studies (Dustman et al. 1990, Hillman et al. 2002, Scisco et al. 2008), supports the notion that CRF is associated with the amplitude of the P300 component, specifically P3b relative to P3a. A stimulus discrimination task in both young and older adults (Pontifex et al. 2009) provides some support for the selective benefits of CRF on the allocation of attentional resources rather than on attentional orienting. The positive association between CRF and the P300 component has also been found in the context of a cognitive control task for both young and older adults (Hillman et al. 2006, Pontifex et al. 2009), with older adults displaying a preferential increase in amplitude over the frontal scalp sites relative to an increased amplitude for young adults in the parietal scalp sites. Given that the P300 component of the ERP reflects the attentional processes devoted to the stimuli, greater P300 amplitude in physically active individuals provides preliminary support for a greater ability to allocate top-down attentional resources. Coupled with the greater P300 amplitude, there is also cross-sectional support for PA and shorter P300 latency in both young and older adults, suggesting faster cognitive processing speed in active individuals.

The stimulus-locked ERPs can contribute substantially to our understanding of the preparatory processes that are presumably engaged in formulation of the response. In contrast, response-locked components, such as the ERN and the error-related positivity, are traditionally linked to neuronal activity following an incorrect response. PA is associated with reduced ERN amplitude and increased error-related positivity across the developmental life span (Hillman et al. 2009, Pontifex et al. 2010, Themanson et al. 2008). This association signifies the potential relation between increased levels of PA and more efficient processing during conflict monitoring and subsequent awareness of error. For instance, Themanson et al. (2008) found reduced ERN amplitude in active older adults during set-shifting, followed by a slower rate of responding posterror. The posterror slowing of performance is usually considered to be a by-product of enhanced activation of the top-down neural circuitry to yield more efficient and accurate behavioral adjustments (Gehring et al. 1993). Given the associations between PA and neuroelectric response-locked components, it is reasonable to hypothesize that, at least cross-sectionally, this lifestyle factor is involved not only in allocation of attentional resources but even with electrophysiological activity initiated in the face of conflict and error processing. These promising cross-sectional findings across the developmental life span necessitate the further study of well-conducted RCTs of PA to causally examine its influence in modulating electrophysiological brain activity.

fMRI activity and connectivity correlates. The above-reviewed neuroelectric correlates suggest that higher PA is associated with greater allocation of attentional resources to the stimulus environment as well as reduced activity related to the monitoring of error responses. Although the

use of ERPs allows us to investigate the neural correlates of cognitive functioning with temporal precision, it gives a relatively imprecise account of the topographical distribution of the observed effects. The use of functional MRI (fMRI) has garnered increasing attention to examine the distinct spatial regions that demonstrate associations with PA, either through examinations of the magnitude of blood-oxygen-level-dependent (BOLD) activity or through interactions of distinct spatial regions with other brain regions, examined in terms of functional coherency among brain regions.

Supporting and extending the executive control hypothesis, which posits a selective benefit of PA for performance on measures of executive control, much of the functional neuroimaging literature provides support for an association between PA and neural correlates of cognitive control. In a first examination of its kind, Colcombe et al. (2004), employing an analysis of brain imaging data, found higher CRF levels were associated with greater recruitment of the dorsolateral prefrontal cortices and the parietal cortices during performance on a flanker task. In this task, participants are presented with a series of five arrows, and they were asked to respond to the direction of the central arrow while ignoring the two flanking arrows on either side. Interestingly, higher levels of CRF were also found to be associated with less recruitment of the ACC, suggesting not just an upregulation of neural activity with higher levels of CRF, but rather a more selective, region-specific change in the magnitude of the BOLD response. As discussed above, the successful operation of cognitive control abilities is dependent on a critical balance between the top-down, prefrontal mediated circuitry in biasing the selection and inhibition of the posterior processing regions that process stimulus attributes. For instance, in the classic Stroop task (Stroop 1935), participants are asked to respond to the color of ink in which the word is printed, while ignoring the semantic meaning of the word. The ability to perform the task involves the successful activation of the dorsolateral prefrontal cortices, which then initiates a cascade of metabolic activity in the posterior processing regions to selectively upregulate the color-processing regions while impeding activity in the competing inferior temporal cortices, which are known to play a critical role in word identification (Erickson et al. 2009, Prakash et al. 2009). Thus, performance on the Stroop task benefits from a well-functioning prefrontal cortex, as well as the regulatory, controlled modulation of the posterior regions.

To further evaluate whether PA was associated with these nuanced operations of cognitive control, Prakash et al. (2011) examined if CRF, the physiological surrogate of PA, was differentially and selectively associated with the activity of the prefrontal cortices during the Stroop task or if CRF conferred benefits for both top-down and bottom-up components of this controlled, regulatory behavior. They first identified areas of the posterior cortices that showed differential neural activity in response to color relative to black-and-white checkerboards and words, relative to nonwords and strings of letters. CRF in older adults was associated with an increase in recruitment of the right prefrontal cortices; notably, the association was not found for all conditions of the Stroop task but rather for the most challenging condition. This association suggested that CRF was associated with an increase in recruitment of the prefrontal cortices, but only under conditions of increasing task demands and not with an increase in blood flow to the prefrontal regions during all conditions. The study also provided support for an upregulation of the color-processing regions relative to the word-processing regions during all conditions of the Stroop task. The increased BOLD response in the color-processing regions, however, was not associated with CRF levels.

Causal support for the role of PA to modulate neural activity to support cognitive performance has been provided through studies investigating alterations in neural activity following a long-term training program. Mirroring the cross-sectional investigation, Colcombe et al. (2004) found participation in a six-month aerobic exercise program to result in increased recruitment of the right middle frontal gyrus and bilateral parietal lobules, as well as reduced activity of the ACC,

during performance on the flanker task. The localized effects of the intervention to the right prefrontal cortex in the context of the flanker task was particularly interesting given previous reports of this region being critical to cognitive performance in the elderly (Colcombe et al. 2005); the training-induced benefits were thus observed in cortical regions known to play a role in behavioral performance. The reduced activation of the ACC as a result of training was hypothesized to reflect a reduced need to engage in conflict monitoring. Additionally, in another study, two-year follow-up fMRI data collected on older adults (mean age ~80 years) who had participated in a one-year RCT of moderate-intensity exercise provide similar findings of increased recruitment of the prefrontal and parietal cortices (relative to a health education group) during a task of processing speed (Rosano et al. 2010).

Taken together, these studies suggest that the prefrontal cortices are responsive to a moderate-intensity walking intervention, especially in older adults. The structural and functional deterioration of the prefrontal cortex is one of the most ubiquitous observations of the cognitive neuroscience literature on aging adults (Cabeza 2002, Raz et al. 2005, Ziegler et al. 2012). Older adults often show cortical overactivation in these regions relative to young adults (Cabeza 2002, Colcombe et al. 2005, Grady et al. 2002, Prakash et al. 2009), along with a reduced modulation in response to increased task demands (Prakash et al. 2009, Reuter-Lorenz & Mikels 2006). The benefits conferred by PA to prefrontal cortex function—specifically, enhancing neural activity in a load-dependent fashion—provide a theoretical foundation for the implementation of a low-cost walking intervention, at least for the elderly. The extent to which the associations between PA and hemodynamic activity are maintained across other domains of cognitive functioning—and perhaps even across other tasks of cognitive control—that show behavioral benefits as a function of PA is an important issue for future research.

Although the majority of RCTs have focused on aerobic exercise interventions, with moderate-intensity walking programs being the widely studied modality, at least one study has examined the change in BOLD activity as a function of resistance training (Liu-Ambrose et al. 2012). Participants were elderly women who were randomized to a once-weekly resistance training group (RT1), a twice-weekly resistance training group (RT2), or a balance and toning group (BAT) for 52 weeks. All participants completed the Eriksen flanker task at pre- and post-training. Participants in the RT2 group showed reduced interference on the flanker task relative to the BAT group. In addition, participants in the RT2 group showed increased recruitment of the left anterior insula and left middle temporal gyrus during the incongruent condition, coupled with a decreased recruitment during the congruent condition. These gains were not observed for the RT1 group. Thus, there seems to be support for resistance training programs in incurring benefits on brain function; however, these results need to be corroborated by additional studies. Furthermore, given the differential change in neural activity as a function of a walking program (Colcombe et al. 2004) and a resistance program (Liu-Ambrose et al. 2012), it would be beneficial for future research to examine the comparative efficacy of these two training programs, both behaviorally and with regard to mechanisms.

Extending this literature of task-based activation, other studies have provided evidence for increased coherence in functional brain systems as a function of moderate-intensity aerobic exercise training (Burdette et al. 2010, Voss et al. 2010). In this case, the dependent variable involves increased synchrony of functional brain activity in cortical and subcortical regions that interact with various functional brain networks. Voss et al. (2010) found support for increased synchrony of two networks known to be negatively affected by aging, the default mode network and frontal executive network, in older adults participating in a one-year moderate-intensity walking intervention program, relative to a stretching and toning group. The majority of regions responsive to walking training in the default mode network involved the hippocampus, which is considered to

be a core component of the medial temporal network (Andrews-Hanna et al. 2010, Buckner et al. 2008). In another study using a functional connectivity approach, the authors employed graph theory methodology to demonstrate differences in network connectivity in participants engaged in a four-month aerobic exercise training group, relative to a health education and stretching control group (Burdette et al. 2010). A limitation of this study was the assessment of brain functioning only after the intervention. The results further underscored the involvement of the hippocampus in the context of an aerobic exercise intervention. Specifically, participants in the aerobic exercise group, relative to the health education and stretching group, demonstrated greater blood flow to the hippocampus, and the hippocampi were shown to be the most highly connected hubs in the exercise group.

Thus, another critical theme that emerges from the topographic study of the effects of PA on the brain is the responsiveness of the hippocampus to moderate-intensity aerobic training. The reviewed functional studies corroborate extant animal literature and other structural and functional MRI studies implicating the hippocampus as an important brain region in exercise-induced benefits. The well-established coupling between the hippocampus and performance on tasks of episodic memory, and the subsequent associations with the development of AD, precipitates the question of whether PA interventions might help prevent or delay decline in cognitive functioning, specifically memory deficiencies commonly observed in amnestic cognitive impairment and AD. We review the extant literature within this field next, highlighting the critical studies providing preliminary support for the involvement of PA in neurodegenerative disorders.

EFFECTS OF PHYSICAL ACTIVITY ON NEUROLOGICAL AND PSYCHIATRIC DISEASES

In addition to the growing literature demonstrating positive effects of PA on cognition and brain function of healthy children and adults, there is also a growing foundation of positive results for a diverse range of clinical populations, including those diagnosed with attention-deficit/hyperactivity disorder (ADHD), schizophrenia, multiple sclerosis (MS), and major depression, as well as age-related neurodegenerative diseases such as AD and Parkinson's disease (PD). In addition to cross-sectional studies, of particular usefulness are prospective approaches that conduct baseline assessments in a period before onset of diagnosable clinical symptoms in order to assess whether individual differences in PA predict differential onset or presence of pathology (e.g., Buchman et al. 2012, Hamer & Chida 2009, Mittal et al. 2013). However, reverse causation is a significant concern. In many cases it is plausible that individual differences in PA may be caused by asymptomatic progression of pathology. Therefore, RCTs with well-chosen comparison groups are preferable for examining the impact of change in PA on biological markers of disease or cognitive and behavioral symptoms. We review the state of knowledge on clinical populations that have been responsive to PA interventions, with an emphasis on RCTs whenever possible.

Although most of the studies on ADHD have examined the acute effects of exercise (e.g., Pontifex et al. 2013), there are some promising results from longer-term intervention trials as well. For example, Smith et al. (2012) demonstrated improvement in response inhibition, fine and gross motor proficiency, and teacher ratings of ADHD symptoms in 17 children (grades K–3) who participated in an 8-week before-school program that included 26 minutes of continuous moderate-to-vigorous PA. With a similar weekly dose in 3 sessions/week for 10 weeks, Verret et al. (2012) demonstrated that for participants in the PA relative to a no-contact control group, there was an improvement in motor skills; neuropsychological measures of visual search speed; sustained auditory attention; and parent ratings on the Child Behavioral Checklist for social problems, thought problems, and attention problems. However, these results should be taken as

preliminary because Smith et al. (2012) did not have a control group, and Verret et al. (2012) did not have a randomized assignment to treatment and control groups.

Individuals with schizophrenia are another population that may benefit from increased PA. Observational data with either self-reported PA or objective PA monitoring have shown that schizophrenia patients tend to be more inactive and more sedentary than demographically matched control subjects (Lindamer et al. 2008, Vancampfort et al. 2011). Yet studies have demonstrated the feasibility of designing PA interventions for this population that are effective at attenuating positive and negative symptoms of schizophrenia (Beebe et al. 2005). Additionally, studies have shown that moderate-intensity aerobic exercise training can increase hippocampal volume in schizophrenia patients (Pajonk et al. 2010). Given that cross-sectional evidence demonstrates that individuals with schizophrenia (Pajonk et al. 2010) or at a high risk for schizophrenia (Mittal et al. 2013) have smaller hippocampal volumes compared to demographically matched healthy participants, these results provide preliminary support for exercise training to benefit the neurobiological substrates that are impacted in this disorder. Future studies are needed for replication and to understand the role of change in hippocampal volume or other brain systems in improved symptomology following exercise interventions (Vancampfort et al. 2014).

Moderate-intensity exercise interventions can improve symptoms for young and older adults with major depression (for a review, see Cooney et al. 2013). These benefits are proposed to include both psychological (self-efficacy, self-esteem) and neurobiological (improved regulation of the hypothalamic-pituitary-adrenal axis, neurotrophic or monoamine signaling) mechanisms (Erickson et al. 2012, Pickett et al. 2012). A smaller subset of studies has examined the effects of moderate-intensity exercise training on cognitive abilities in depressive populations. These studies had three- to four-month intervention periods, active control groups (stretching and toning), and young and middle-age participants (Foley et al. 2008, Hoffman et al. 2008, Krogh et al. 2009); however, none of the studies observed a selective benefit on cognitive performance for the aerobic exercise group. Thus, although the literature supports the notion that regular moderate-to-vigorous exercise could improve depressive symptoms as much as antidepressant treatment, there are still open questions for the benefits on cognitive function in this population.

MS is a neurodegenerative disease that has been shown to be responsive to moderate-intensity PA and exercise training. MS is an autoimmune disease resulting in widespread inflammation, degeneration of the myelin sheath surrounding axons, and gray matter atrophy. One RCT study has shown a positive effect of 8–10 weeks of moderate-intensity exercise training on verbal learning and memory and attention in MS patients, although there were no improvements from exercise training on tests of executive function and processing speed (Briken et al. 2014). These training benefits along with several cross-sectional studies that suggest a positive association between CRF and cognitive performance, brain structure, and brain function in individuals with MS (Prakash et al. 2007, 2008, 2010) support the feasibility and promise of aerobic exercise training for those with MS, but more RCTs are needed that include cognitive and brain function as clinical endpoints.

Finally, there is promising evidence that structured exercise interventions are feasible, and possibly effective at reducing symptoms, in those with cognitive impairment more generally as well as those with mild cognitive impairment (MCI), AD, and PD. Unfortunately, the criteria for establishing cognitive impairment, MCI, and dementia are far from consistent across studies, making it difficult to draw conclusions about differential effects of exercise across different diagnostic categories. Overall, there is evidence for a weak positive effect of aerobic exercise training on cognitive function in an MCI population that is either low in self-reported activity before the intervention (Baker et al. 2010, Gates et al. 2013, Nagamatsu et al. 2013) or relatively active at baseline (Lautenschlager et al. 2008, van Uffelen et al. 2008). A recent meta-analysis highlighted that across studies, the strongest effect is for moderate- to vigorous-intensity aerobic

exercise training on verbal fluency and indicated that there is stronger evidence for high-intensity resistance training to result in improved memory performance compared to aerobic exercise (Gates et al. 2013). However, overall, the review cautions that most studies have been underpowered and thus future research needs to increase the statistical power of RCT studies with cognitively impaired and MCI populations. Similarly, although there are promising results from exercise trials with cognitive outcomes in participants with diagnosed AD (Forbes et al. 2013, Kemoun et al. 2010, Yágüez et al. 2010) or PD (Cruise et al. 2010, Murray et al. 2014, Tanaka et al. 2009), more research is needed before we can conclude that exercise is protective for age-related neurological diseases (Ahlskog et al. 2011, Lautenschlager et al. 2012). In particular, it is unknown how different forms of exercise are neuroprotective and whether they modify disease or act on aging processes that improve the ability to compensate for disease progression (Lautenschlager & Cox 2013).

MOLECULAR AND CELLULAR BENEFITS OF PHYSICAL ACTIVITY: EVIDENCE FROM ANIMAL STUDIES

The reviewed literature demonstrates that PA and aerobic exercise training can have a positive effect on cognitive performance across the life span and on the symptomology of several psychiatric and neurological pathologies. Importantly, some of this evidence is from RCT studies that minimize threats to internal validity and suggest there is a causal relationship between moderate-intensity exercise and cognition. Although there is reason to be optimistic about this conclusion, the field still lacks a strong understanding of how exercise affects the brain. Understanding the mechanisms of PA on the brain can provide insight into whether and how exercise works against the very pathways involved in brain and cognitive aging and psychiatric and neurological diseases. As reviewed above, methods of human neuroscience provide one approach to examining mechanisms. However, the vast majority of human neuroscience methods are noninvasive and therefore do not allow direct measurement of exercise effects on the brain at the cellular and molecular level. Therefore, animal models of exercise training play a vital role in developing our knowledge of the mechanisms behind the benefits of PA and exercise on cognition in humans. Below we review the evidence for how exercise benefits the brain on multiple levels including the basic structural and functional properties of neurons and their capacity for resilience and plasticity, vascular remodeling, and cellular markers of biological aging. We also review translational studies that link cellular and molecular markers known from animal models and effects of exercise on human brain and cognition.

Early evidence for the effects of exercise training on the brain came from studies that examined regional neurotransmitter density and neurotrophins in rats. The first neurotransmitters examined were acetylcholine (ACh) in the hippocampus (Fordyce & Farrar 1991) and dopamine (DA) receptor expression in the striatum (Gilliam et al. 1984, MacRae et al. 1987). Although chronic exercise training increased ACh and DA receptor density, only DA function was improved in older rats. These data present a possible mechanism for the role of moderate-intensity exercise in maintaining movement speed and possibly processing speed as seen in several meta-analyses of human RCTs (Colcombe & Kramer 2003, Smith et al. 2010). Neurotrophins are growth factors known to promote the survival, development, and function of neurons, and they therefore aid in recovery of function following neuronal injury. Cotman and colleagues' studies first demonstrated that even two days of wheel running resulted in increased mRNA expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and caudal and retrosplenial cortex that persisted up to seven days (Neeper et al. 1995, 1996). These studies are significant because they demonstrate that physical exercise can be a stimulus for increased expression of molecules in a brain region known to be important for memory and many aspects of cognition (Shohamy & Turk-Browne 2013). Studies that followed have continued to demonstrate the positive effects of moderate-intensity wheel

running on the hippocampus in young, middle-aged, and old-age groups in rodents (for a review, see Voss et al. 2013a).

Specifically, animal studies have now shown that rodents randomized to a wheel running condition for several weeks to months have increased neurogenesis (van Praag et al. 1999a, 2005), dendritic complexity (Eadie et al. 2005, Stranahan et al. 2007), synaptic plasticity (Farmer et al. 2004, van Praag et al. 1999b), and bioenergetic improvements such as reduced inflammation, oxidative stress, and improved mitochondrial function (Kohman et al. 2011, Marques-Aleixo et al. 2012, Steiner et al. 2011) in the hippocampus. These benefits have been shown to be in large part due to running-induced increases in the expression of BDNF (Gómez-Pinilla & Hillman 2013). New studies also show that just one week of wheel running increases BDNF transcription in the hippocampus via epigenetic changes (Abel & Rissman 2013). Importantly, many of these exercise-induced structural and functional changes in the hippocampus are associated with improved spatial learning and memory (Clark et al. 2008; Pietrelli et al. 2012; van Praag et al. 1999b, 2005; Vaynman et al. 2004) and pattern separation (Creer et al. 2010).

In addition to BDNF, other growth factors observed as important mechanisms for exercise-induced benefits on the hippocampus are insulin-like growth factor type 1 (IGF-1) and vascular endothelial growth factor (VEGF). Running induces uptake of liver-derived IGF-1, with greater IGF-1 found after one hour of running in the hippocampus, striatum, septum, thalamus, hypothalamus, cerebellum, red nucleus, and several brain stem nuclei (Carro et al. 2000). Blocking entry of circulating IGF-1 into the brain during exercise has also been shown to block exercise-induced increases in c-Fos expression throughout the brain (Carro et al. 2000) and neurogenesis in the hippocampus (Trejo et al. 2001). In contrast, blocking IGF-1 receptors in the hippocampus during exercise blocked exercise-induced increases in BDNF expression in the hippocampus (Ding et al. 2006). Blocking entry of peripheral VEGF into the brain has also been shown to block exercise-induced neurogenesis in the hippocampus (Fabel et al. 2003). However, the same study did not observe exercise-induced increases in VEGF mRNA in the hippocampus.

Notably, the majority of the literature from animal models on neuronal structure and function has focused on the hippocampus. The exception tends to be animal models of neurodegenerative disorders that affect other brain regions such as the striatum in PD (Real et al. 2013) and Huntington's disease (Pang et al. 2006, Potter et al. 2010) models. Although we cannot yet measure BDNF receptor density in the human brain noninvasively, one approach for mapping change in growth factors to regional change in structure and function of the human brain from exercise treatment is to examine if acute and chronic exercise-induced change in systemic growth factors is associated with specific change in cognitive performance or brain function measures. For instance, studies have now shown that circulating BDNF is increased following an acute bout of moderate-intensity exercise (Knaepen et al. 2010) and that this acute response increases with training (Griffin et al. 2011); one study suggested that a large proportion of exercise-induced increase in circulating BDNF was due to BDNF from the brain (Rasmussen et al. 2009). Fewer studies have shown a change in basal BDNF serum levels following chronic exercise training (Knaepen et al. 2010). However, one study did observe a positive correlation between changes in circulating serum BDNF, IGF-1, and VEGF and increases in functional brain connectivity of the hippocampus with the lateral temporal lobes following a one-year moderate-intensity walking program, despite no group-level changes for the walking group compared to a control group (Voss et al. 2013b). Thus, although the animal literature has focused on the hippocampus, future research may incorporate more translational research methods to examine the molecular mechanisms of exercise effects throughout the human brain. This will likely involve the use of additional neuroimaging methods such as MRI spectroscopy and positron emission tomography in conjunction with animal models (Voss et al. 2013a).

Finally, moderate-intensity aerobic exercise improves vascular function including cerebrovascular health. Several studies have shown that wheel-running exercise increases angiogenesis in the motor cortex (Kleim et al. 2002), cerebellum (Black et al. 1990), and the hippocampus (Creer et al. 2010, van Praag et al. 2005) in rodents. These studies are consistent with studies in humans that have shown an association between CRF and participation in moderate-intensity PA with greater cerebral blood flow (Burdette et al. 2010, Pereira et al. 2007). Given that moderate-intensity cardiorespiratory PA is a direct stimulus on the vascular system, more research is needed linking molecular mechanisms of exercise-induced change in systemic vascular function with cerebrovascular health and cognitive function (e.g., Davenport et al. 2012).

INTERACTIONS BETWEEN PHYSICAL ACTIVITY AND GENE POLYMORPHISMS

Despite the modest but relatively consistent results from cross-sectional, epidemiological, and intervention studies showing that PA is associated with superior cognitive and brain functioning, many of these same studies have also documented significant unexplained variance in behavioral, structural, and functional changes observed as a function of participation in PA. Such individual differences may be partly explained by genetic variation that potentially modifies the efficacy of PA effects. Such an interaction may occur in at least two different ways. First, the presence of a risk allele that increases the risk for psychiatric, neurologic, or cognitive dysfunction or decline may attenuate the extent to which PA positively influences brain or cognitive phenotypes. In this scenario, the risk allele may be associated with a reduced capacity for brain plasticity, thereby mitigating the beneficial effect that PA has on brain, cognitive, or other (e.g., disease) outcomes. This interaction would be demonstrated by a result showing that PA improves brain or cognitive outcomes, but more so for those individuals who do not carry the risk allele. In contrast, a second way in which an interaction may occur is that the cognitive, brain, or disease risk associated with a risk allele is mitigated by participation in PA. In this scenario, participation in PA would attenuate the deficits associated with the risk allele and reduce or eliminate the differences between the genetic variants. This interaction would be demonstrated by a result showing that PA improves brain or cognitive outcomes, but more so for those individuals who carry the risk allele. As discussed below, these different hypotheses have been tested for several candidate genes that are known to have a role in the biological pathways involved in cognitive or brain phenotypes.

One of the most frequently studied gene variants in this field is the *apolipoprotein ε4* (*APOE ε4*) allele, which confers increased risk for accelerated cognitive decline and AD, probably through its effects on amyloid clearance and neuronal repair. Several studies have found that greater amounts of PA or higher fitness levels attenuate cognitive deficits or risk for AD more for carriers than noncarriers of the *APOE ε4* risk allele (Etnier et al. 2007, Rovio et al. 2005, Schuit et al. 2001, Woodard et al. 2012). Consistent with these studies, Head et al. (2012) reported that levels of brain amyloid as measured by positron emission tomography were highest in physically inactive carriers of the *APOE ε4* allele. However, most importantly, they found that physically active *ε4* carriers had reduced levels of amyloid that were equivalent to those of noncarriers of the risk allele. Similarly, other neuroimaging studies have reported that the effects of fitness or PA on glucose uptake and semantic memory activation were modified by *APOE ε4* status such that the positive effects of PA were greater in *ε4* carriers than in noncarriers (Deeny et al. 2012, Smith et al. 2011). Although several studies have failed to find interactions between *APOE* genotype and PA on cognitive performance or risk for AD (e.g., Lindsay et al. 2002), overall these results suggest that PA may have its most profound effects on individuals with the greatest genetic susceptibility for cognitive decline and AD.

Other genes have also been examined as possible moderators of the effect of PA on cognitive and brain phenotypes. For example, a gene encoding *BDNF* has a single-nucleotide polymorphism with a *valine* (*Val*) to *methionine* (*Met*) substitution at codon 66. In this case, the *Met* allele may confer an increased risk for *both* poorer cognitive performance and depression relative to *Val* homozygotes. However, meta-analyses have suggested that there is considerable inconsistency in the strength of the association between the *BDNF* polymorphism and cognitive function and depression phenotypes, a result that may indicate moderation by other factors such as PA. Because increased BDNF expression is considered a putative pathway by which PA influences brain function (see Molecular and Cellular Benefits section), several studies have examined whether the *BDNF* polymorphism modifies the association between PA and cognitive or depression outcomes. In one study with more than 1,000 mid-life participants (Erickson et al. 2013), the *Met* allele was associated with poorer working memory performance compared to the more common *Val* homozygotes, but this effect was apparent only in less physically active individuals. In contrast, more highly active individuals failed to show genotype-dependent effects on working memory. These results suggest that those carrying the *Met* risk allele may benefit more from PA than their *Val* homozygous counterparts and that increasing PA in *Met* carriers may be an effective method of reducing *BDNF*-dependent differences in working memory function. Interestingly, this interaction between PA and the *BDNF* gene has not emerged with respect to depression outcomes. Despite one study in adolescent girls showing that PA was associated with fewer depressive symptoms for *Met* carriers (Mata et al. 2010), more recent larger-scale studies ($N > 1{,}000$) of depressive symptoms in both adolescents and adults have failed to replicate this effect (Gujral et al. 2014, Stavrakakis et al. 2013). These results suggest that the interaction between *BDNF* (or other genes) and PA may depend on the phenotype of interest, with cognitive outcomes showing different patterns than mood outcomes.

Relatively speaking, few published studies have examined the moderating influence of genetic variants on PA-related associations with cognitive or brain outcomes. The studies discussed in this section show some promising patterns, but they are not without their limitations. Challenges facing this field include the following: (*a*) except for one small study examining a gene involved in dopaminergic function (Stroth et al. 2010), none of the studies discussed above examined gene × PA interactions in an RCT. Thus, all of the associations are drawn from cross-sectional or epidemiological data. This limitation leads directly to the second challenge facing this field: (*b*) small effect sizes require larger sample sizes. Most candidate gene studies have relatively small effect sizes when examining cognitive or brain phenotypes. Because of this, it becomes logistically and financially challenging to conduct a PA intervention with the large sample size needed to detect genetic differences. One way around this limitation is to screen and exclude participants on the basis of particular genotypes so that only those with a particular polymorphism are enrolled in the intervention or to identify more proximal biological markers of the effects (i.e., imaging markers) that can be considered endophenotypes with larger effect size. Finally, (*c*) all of the studies discussed in this section used a candidate gene approach based on biological theories of cognitive function or PA. Although this approach has its strengths, one weakness is that it sacrifices the capacity to examine genetic variation more broadly. More advanced genetic approaches using genome-wide associations and/or genetic risk scores might be able to provide a more comprehensive assessment of the degree to which PA interacts with many different genetic variants. These approaches, however, have their own limitations, and increasing the number of multiple comparisons would necessitate an even larger sample size. In short, it is very likely that genetic variation contributes to the individual differences observed across studies examining the efficacy of PA to improve cognitive, brain, and mood outcomes. However, there remain significant hurdles to overcome before PA interventions can be tailored on the basis of genetic make-up. In any case, a broad view

of both the *APOE* and *BDNF* findings described above suggests a strikingly similar effect: PA may have the capacity to mitigate genetic susceptibility for cognitive deficits.

FUTURE DIRECTIONS AND CONCLUSIONS

We have made considerable progress in our understanding of whether and how PA is associated with cognitive and neural plasticity across the life span and in cases of compromised mental health. The literature reviewed above also points to critical directions for future research, which will likely contribute to our growing theoretical understanding of the effects of PA, as well as inform future public health recommendations.

For example, although epidemiological and cross-sectional studies often include total energy expenditure across different types and intensities of PA as the main criterion variable, many of the RCTs have examined the effect of moderate-intensity aerobic exercise on cognitive and neural functioning, with some recent evidence supporting the role of resistance training in conferring benefits for cognitive and neural functioning as well (Liu-Ambrose et al. 2010, 2012). It will be important for future research to examine the differential contributions of aerobic exercise training and resistance training, as well as the additive effects of these two interventions in incurring benefits across the life span. Inclusion of neuroimaging outcomes in these studies will further contribute to our understanding of the neural correlates of exercise-induced benefits. Along the same lines, it will be advantageous to systematically examine the dose-response relationship between the intensity of aerobic exercise training and the gains incurred as a function of increasing doses of intensity. A more systematic understanding of this dose-response relationship, especially using RCTs, and their moderation as a function of development will help guide the public health recommendations that usually involve a combination of moderate-intensity and vigorous-intensity exercises.

Another interesting direction for future research would be to examine the synergistic effects of PA with other cognitive training interventions. Much of the interest in PA and other cognitive training paradigms can be traced back to animal work on environmental enrichment (Rosenzweig 1966), in which access to a running wheel and the capability to interact with novel stimuli were found to be key ingredients responsible for enhanced spatial learning and memory. There have been recent reports of the feasibility of multimodal training programs in humans, such as the Experience Corps (Carlson et al. 2008), the Senior Odyssey program (Stine-Morrow et al. 2008), and the Synapse project (Park et al. 2014) in older adults. A more systematic incorporation of various elements of these training programs, such as cognitive stimulation, social stimulation, and creative thinking, can contribute to the ability to design and implement ecologically valid training programs with efficacy for both cognitive and neural health.

The range of cognitive tasks used in this literature, as well as the domains examined both cross-sectionally and through RCTs, have been critical for exploring the generality versus the specificity of PA associations. However, to the extent possible, future research would benefit from the use of a comprehensive battery of neuropsychological assessments that could be compared across research studies. For example, the National Institutes of Health Cognitive Toolbox (Weintraub et al. 2013) is one attempt to identify theoretically driven cognitive measures that could be used to facilitate comparisons across studies. In addition, the employment of neuroimaging tools to complement behavioral findings has significantly contributed to the understanding of how changes in neural circuitry as a function of PA training might be associated with accompanying behavioral change (for examples of studies employing brain-behavior associations, see Erickson et al. 2011, Voss et al. 2010). The continued use of behavioral and neuroimaging techniques, as well as complementary neuroimaging techniques, such as ERP and fMRI, has the potential to provide a clearer

understanding of how changes in various neural correlates influence one another and subsequently influence behavior.

To conclude, notable strides have been made in our understanding of the PA–cognition link both during normal development and in various psychiatric and neurological populations. Epidemiological studies provide promising support for PA to be associated with late-life cognitive functioning, as well as the onset of Alzheimer's and similar diseases. Additionally, although there is modest support for the role of moderate-intensity aerobic exercise in reducing age-related cognitive decline, much needs to be learned about the causal role of PA in enhancing and maintaining cognition through the life span. In the same vein, emerging evidence indicates that PA is involved in several neurological and psychiatric diseases, but more well-powered RCTs within this area are needed to rule out reverse causation, as well as other alternate explanations. Researchers have just begun to explore the moderating role played by genetic factors in the PA–cognition link, and although some candidate genes offer promising support, genome-wide association studies would significantly contribute to the understanding of how the genetic make-up interacts with this lifestyle factor in yielding benefits. Given the relative ease of implementation as well as the low cost that the PA intervention offers, the systematic study of different types and intensities of PA is critically needed to enhance the understanding of the science behind this lifestyle factor, as well as to inform public health recommendations.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Annual Review of Psychology

Volume 66, 2015

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