Exercise counteracts declining hippocampal function in aging and Alzheimer's disease.
Review

Exercise counteracts declining hippocampal function in aging and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) affects more than 5.4 million Americans and ranks as the most common type of dementia (Thies and Bleiler, 2011), yet effective pharmacological treatments have not been identified. Substantial evidence indicates that physical activity enhances learning and memory for people of all ages, including individuals that suffer from cognitive impairment. The mechanisms that underlie these benefits have been explored using animal models, including transgenic models of AD. Accumulating research shows that physical activity reinstates hippocampal function by enhancing the expression of brain-derived neurotrophic factor (BDNF) and other growth factors that promote neurogenesis, angiogenesis, and synaptic plasticity. In addition, several studies have found that physical activity counteracts age- and AD-associated declines in mitochondrial and immune system function. A growing body of evidence also suggests that exercise interventions hold the potential to reduce the pathological features associated with AD. Taken together, animal and human studies indicate that exercise provides a powerful stimulus that can counteract the molecular changes that underlie the progressive loss of hippocampal function in advanced age and AD.

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Introduction

Alzheimer's disease (AD) affects more than one in eight Americans over the age of 65 and nearly half of those over the age of 85 (Thies and Bleiler, 2011). Current estimates of AD prevalence are 33.9 million worldwide, but surging rates of AD are anticipated as the number of elderly rises. By 2050, AD prevalence is anticipated to soar to over 100 million people (Barnes and Yaffe, 2011; Brookmeyer et al., 2007). Although research to address this looming crisis has generated several pharmaceutical candidates, current treatments are plagued by limited efficacy, the risk of substantial side effects, and generally do not significantly alter the course of AD (Mangialasche et al., 2010). While further work is warranted to identify effective pharmacological treatments, the growing AD prevalence and escalating health care costs argue for the accessible and potent strategy of physical activity (Ahlskog et al., 2011).
It is commonly understood that physical exercise is an effective strategy to enhance overall health, yet only recently have studies addressed how exercise improves learning and memory. Emerging data underscore the potential for physical activity to reverse age and AD-related hippocampal decline. Through the induction of growth factors and several other cellular adaptations, exercise promotes dynamic changes that facilitate brain function. This review will focus on recent evidence that extends the benefits of physical activity to aging humans and those with AD, and use findings from transgenic AD lines to highlight the therapeutic potential of exercise. We will also address the underlying molecular mechanisms that improve learning and memory, focusing on hippocampal function.

Exercise promotes brain health in advancing age and AD

Several lines of evidence give support to the idea that physical activity offsets the cognitive decline that occurs in late adulthood (Raz et al., 2005). For instance, the results of epidemiological studies are remarkably consistent in revealing that high physical activity is associated with improved cognitive functioning in older adults (Ahlskog et al., 2011; Colcombe and Kramer, 2003; Smith et al., 2010). This improvement may be correlated to structural changes in the brain because greater amounts of physical activity are predictive of larger hippocampal volumes in healthy elderly individuals (Erickson et al., 2009). Similarly, older adults that engage in regular physical activity have greater medial temporal lobe volumes, while this region shows significant age-related atrophy in sedentary individuals (Bugg and Head, 2011). These epidemiological findings suggest that gross structural changes reflect a biological basis for physical activity to alter the trajectory of cognitive decline. This notion is supported by randomized clinical trials in the elderly that show 6- or 12-month exercise interventions increase hippocampal volume up to 2% and improve performance on spatial (Erickson et al., 2011) and episodic memory tasks (Klussmann et al., 2010; Rucheweyh et al., 2011).

Exercise is strongly associated with preserved brain health among the elderly. For example, physical activity has been identified as a protective factor against cognitive impairment and dementia (Larson et al., 2006), and the most common form of dementia, AD (Scarmeas et al., 2009). Meta-analyses of epidemiological studies indicate that self-reported levels of physical activity are associated with a reduced risk of cognitive decline (Sofi et al., 2011), and this association has been confirmed using objective measures of activity energy expenditure (Middleton et al., 2011). Furthermore, the risk of incident AD is inversely correlated to levels of daily exercise as assessed by self-report (Hamer and Chida, 2009) and objective measures of total daily physical activity (Buchman et al., 2012). The risk reduction for AD is observed even with moderate levels of activity in the elderly, equivalent to walking about one mile per day (Erickson et al., 2010), or leisurely physical activity twice a week (Rovio et al., 2005). In line with these findings, the leading modifiable risk factor for AD in the United States is physical inactivity, which increases the relative risk of AD by almost two-fold (Barnes and Yaffe, 2011).

The cognitive benefits of physical activity may be attainable even among individuals with marked cognitive decline. For example, meta-analyses of randomized trials have revealed that among those with cognitive impairment, exercise significantly improves cognitive performance (Heyn et al., 2004), memory and attention (Valenzuela and Sachdev, 2009). In this population, randomized clinical trials have demonstrated that a six-month exercise intervention is sufficient to reduce the rate of cognitive decline (Baker et al., 2010; Lautenschlager et al., 2008). Finally, the mortality risk for cognitively impaired individuals shows a dose–response curve in response to exercise, such that the highest levels of physical activity are associated with highest survival rates (Middleton et al., 2010). This is similar to findings among those diagnosed with AD, as more physical activity is associated with prolonged survival (Scarmeas et al., 2011). Taken together, these data underscore the idea that exercise is a potent strategy to alter the trajectory of cognitive decline.

The benefits of long-term physical activity may accrue over the lifespan and yield favorable health outcomes even when the brain has developed neuropathology. This pathology can be measured following the recent development of PET ligands (e.g., PiB) that allow for the in vivo detection and quantification of amyloid-β (Aβ) (Klunk et al., 2004; VallabhaJosula, 2011). 11C-PiB PET has revealed that the quantity of cerebral Aβ is inversely correlated to the amount of exercise in which one regularly engages (Liang et al., 2010), suggesting that physical activity enhances Aβ clearance rates or reduces deposition. Imaging studies in AD patients show that higher levels of cardiorespiratory fitness are associated with decreased brain atrophy (Burns et al., 2008) and preserved parietal and medial temporal lobe volume (Honea et al., 2009), similar to findings in healthy elderly individuals mentioned previously. The preservation of brain mass may underlie the functional benefits observed in AD patients that participate in regular exercise; and some evidence indicates that even late-stage exercise may confer cognitive benefits. For example, AD patients that undergo 5 to 12 weeks of moderate exercise show enhanced memory and improved performance on neuropsychological tests (Palleschi et al., 1996; Rolland et al., 2000; Yagüez et al., 2011). Although further work is required to extend these findings, these studies suggest that physical activity supports brain health even when initiated after the appearance of AD pathology.

Exercise improves learning and memory in AD mouse models

Most AD patients have accrued Aβ pathology prior to diagnosis (Becker et al., 2011); therefore, it is of increasing relevance to use animal models of AD in order to investigate therapeutic strategies in the presence of progressive neuropathology. To this end, AD research has been advanced by transgenic mouse models that express human genes with mutations associated with early-onset AD. Models that express variants of amyloid precursor protein (APP), tau, presenilin (PS) 1, and PS2 develop pathological characteristics of AD and show progressive neurological impairment (Hsiao et al., 1996; Lewis et al., 2001). These models carry mutant variants of human genes often identified in the inherited forms AD, for example, Tg2576 mice carry the gene encoding the 695–amino acid mutant isoform of human APP. Table 1 provides a listing of common AD models used and defines the genes, mutation sites, and promoters that drive their expression. The use of these models has provided invaluable insights into mechanisms that underlie AD and factors that influence the rate of disease progression.

Reported findings that exercise benefits learning and memory in non-transgenic mice (van Praag et al., 1999a) have been extended to include AD transgenic lines. For example, TgCRND8 mice given access to a running wheel show improved performance in the Morris water maze compared to sedentary counterparts, indicative of enhanced spatial memory and hippocampal function (Adlard et al., 2005b). Running exercise improves memory task performance in several other transgenic lines, including Tg2576 (Yuede et al., 2009) and 3xTg-AD (Garcia-Mesa et al., 2011; Garcia-Mesa et al., 2012). With advancing age, transgenic AD models accrue neuropathological characteristics that interfere with cognition. It is notable that in aged AD models, exercise retains the ability to improve hippocampal function, as shown in Tg2576 (Um et al., 2008), PS2 (Um et al., 2011), and Tau22 transgenic lines (Belardi et al., 2011). Although the majority of these studies used several months of running, a relatively short exercise intervention of three weeks in aged Tg2576 mice has been shown to improve hippocampal-dependent memory compared to sedentary controls (Parachikova et al., 2008). Thus, despite variation in methodology, the vast majority of exercise studies in AD models result in significant improvements to memory. Table 1 provides a list of recent studies and summarizes their major findings.
Brain tau and Aβ pathology

In addition to improving spatial memory, running exercise reduces the accumulation of tau pathology in several transgenic lines. This may have important implications because the hyperphosphorylation of tau is a pathological feature of AD that disrupts neuronal functions, including axon transport and mitochondrial respiration (Eckert et al., 2010; Reddy, 2011). In studies of hPS2m mice, three months of exercise was sufficient to reduce levels of phosphorylated tau (pSer404, pSer202, pThr231) compared to sedentary controls (Um et al., 2011). Additionally, chronic exercise in Tau22 mice reduces levels of tau hyperphosphorylation in the CA3 hippocampal subregion, and increases the abundance and activity of several tau-regulating kinases (Leem et al., 2009). A recent study in Tau22 mice has revealed that long-term running reduces levels of pathological tau species (pSer212/ pThr214 and pSer422), and provides evidence that exercise increases the expression of genes required for tau clearance within hippocampal neurons (Belarbi et al., 2011). Additional studies are warranted to examine the mechanisms by which exercise may alleviate tau neuropathology.

Several reports have found that exercise reduces the brain Aβ load in TgCRND8 and Tg2576 mice (Adlard et al., 2005b; Yuede et al., 2009) and can decrease levels of soluble fibrillar Aβ oligomers (Nichol et al., 2008). Measurement of these soluble Aβ oligomers may have important implications for AD, as these are considered the primary toxic species because their abundance correlates with the severity of neurodegeneration and synaptic dysfunction in AD (Haass and Selkoe, 2007). Evaluating effects on Aβ pathology has been challenging because of the variability of findings. For example, a stable Aβ load has been observed in APP transgenic lines following exercise exposure that was sufficient to enhance spatial learning and memory (Arendash et al., 2004; Parachikova et al., 2008). Inconsistent effects on Aβ deposition have been observed in APP/PS1 transgenic lines given access to running wheels in enriched housing conditions. For example, some studies have found a decrease in Aβ abundance (Costa et al., 2007; Lazarov et al., 2005) but one reported an increase (Jankowsky et al., 2003). These inconsistent findings may be attributed to the amount of exercise allowed, because enriched housing generally features shared running wheel access among animals. Of note, enrichment without running has dissociable effects compared to running exercise alone (Ehninger and Kempermann, 2003; Gobbo and O’Mara, 2005), but both interventions enhance hippocampal BDNF and activate common intracellular signaling pathways (for review, see Bekinschtein et al., 2011; Olson et al., 2006; van Praag et al., 2000). Moreover, several studies have identified exercise as the central component that enables a full complement of enrichment-induced benefits in neural function (Fabel et al., 2009, Kobilo et al., 2011, Rodríguez et al., 2011). In addition to exercise differences, the sex of transgenic animals and activate common intracellular signaling pathways (for review, see Bekinschtein et al., 2011; Olson et al., 2006; van Praag et al., 2000).

Mechanisms

Exercise-induced Neutrotrophins and Growth Factors

One of the pivotal events that underlies cognitive enhancement in response to exercise is the rapid induction of brain-derived neurotrophic factor (BDNF) mRNA and protein, particularly in the hippocampus (Cotman and Berchtold, 2002; Neeper et al., 1995). Studies in rodents show that BDNF protein levels progressively increase with regular exercise for at least two months, and these elevated levels of BDNF can be re-induced after a sedentary period for up to two weeks (Berchtold et al., 2005). This enduring response reveals a molecular memory for BDNF in exercise-primed animals, and indicates that a reduced frequency of exercise may remain sufficient for the accrual of BDNF, which occurs most prominently within hippocampal...
subfields that are rich in the high-affinity BDNF receptor, TrkB. The activation of TrkB may be required for exercise-induced improvements to hippocampal function, because blocking BDNF action using a TrkB antibody abolishes gains in spatial learning (Vaynman et al., 2004). Although the TrkB receptor has high affinity for several neurotrophins, the central role of BDNF is indicated by our recent findings that inhibition of BDNF signaling in the hippocampus (via BDNF siRNA) prevents exercise-dependent spatial learning (Intlekofer and Cotman, 2012).

BDNF plays an important role in synaptic plasticity by promoting long-term potentiation (LTP) (Patterson et al., 1996), a synaptic analog of learning and memory. Brief tetanic or theta burst stimulation in CA1 or dentate gyrus induces a long-lasting increase in synaptic response (Bliss and Lomo, 1973). The increased responsiveness relies on BDNF signaling, as suggested by the finding that LTP is impaired in transgenic lines devoid of hippocampal BDNF expression (Korte et al., 1995; Zakharenko et al., 2003), but can be rescued by transfection of CA1 cells with the BDNF gene (Korte et al., 1996) or incubating hippocampal slices in BDNF-containing medium (Patterson et al., 1996). Furthermore, BDNF facilitates LTP by activating signaling pathways (i.e. MAPK, Akt, PKMζ) (Mei et al., 2011), promoting cytoskeleton changes (Rex et al., 2007), and enhancing the synthesis of proteins required for vesicle trafficking and neurotransmitter release (Bekinschtein et al., 2007). Importantly, the results of many studies confirm that improved LTP and synaptic plasticity occurs in response to exercise (Liu et al., 2011; van Praag et al., 1999a). Physical activity has been shown to enhance neuronal morphology by increasing synaptic density and dendritic arborization in the hippocampus (Dietrich et al., 2008; Lin et al., 2012; Stranahan et al., 2009).

In addition to BDNF, exercise induces other growth factors that regulate overlapping responses, which together improve hippocampal function. Physical activity enhances neurogenesis in the dentate gyrus of the human and rodent hippocampus (Boehme et al., 2011; Pereira et al., 2007; van Praag et al., 1999b). Although BDNF has been implicated in neurogenesis, this survival of newly generated neurons specifically requires insulin-like growth factor 1 (IGF-1) (Trejo et al., 2001). Furthermore, IGF-1 is critical for the memory retention component of hippocampal function (Ding et al., 2006a). The neurogenic potential of exercise also relies on the induction of vascular endothelial growth factor (VEGF) (Cao et al., 2004; Fabel et al., 2003), and activation of the VEGF receptor may be a critical checkpoint upstream of BDNF signaling that regulates the robust increase in neural proliferation (Louissaint et al., 2002). Interestingly, human studies have found that levels of BDNF, IGF-1 and VEGF are attenuated in AD compared to healthy individuals (Laske et al., 2007; Phillips et al., 1991; Solerte et al., 2002; Solerte et al., 2005), indicating that exercise may exert trophic effects, in part, through reinstating levels of these select growth factors. In further support of this idea, neural cultures exposed to BDNF or IGF-1 are protected from Aβ-induced cell death (Kittyanjant et al., 2012), which may reflect that both activate survival-promoting signaling pathways such as PI3K/Akt (Yamada et al., 2001, Zheng and Irion, 2004).

Physical activity is especially important with advancing age because of its potential to offset several changes that contribute to age-related cognitive decline (Rosenzweig and Barnes, 2003). For example, the aged hippocampus may be less responsive to BDNF effects as the magnitude of BDNF-induced LTP is attenuated in aged animals (Gooney et al., 2004; Schimanski and Barnes, 2010). While the underlying mechanisms are unclear, recent work has identified age-dependent alterations in epigenetic regulation of BDNF exons that may impact BDNF signaling, resulting in impaired synaptic function (Zeng et al., 2011). Although exercise has been shown to increase BDNF protein levels in the hippocampus regardless of age, older animals maintained these elevated levels for a shorter duration (Adlard et al., 2005a). In humans, IGF-1 expression is diminished with age, and studies of elderly subjects show a strong association of IGF-1 levels with better physical function (Cappola et al., 2009; Onder et al., 2006). IGF-1 can be boosted by exercise (Baker et al., 2010), particularly in the form of strength training (Vale et al., 2009). Finally, animal studies show that exercise reverses the decline in neurogenesis that occurs with age and elicits favorable effects on neuroplasticity, albeit at lower levels than in young animals (Kannangara et al., 2011; Kronenberg et al., 2006; Kuhn et al., 1996; van Praag et al., 2005). Thus, mechanisms that promote hippocampal synaptic plasticity remain accessible throughout life and can be recruited with physical exercise.

Oxidative capacity and energy metabolism

There is ample support for the hypothesis that the continuous oxidative stress inherent in exercise promotes neuroprotective adaptations that bolster the metabolic capacity of the brain. Increased bioenergetic demands induce vascular plasticity through the actions of VEGF and IGF-1 (Black et al., 1990; Dunn, 2000), and enhanced angiogenesis allows for greater exchange of nutrients, wastes and respiratory gases. Indeed, animal studies have shown that metabolic adaptations elicited by exercise include an increase in hippocampal glucose utilization (Vissing et al., 1996) and endothelial cell proliferation (Elstrand et al., 2008), suggesting a neurovascular adaptation to increased metabolic load. Further, one month of exercise increases hippocampal capillary density and branching, and reverses trends in gene expression that contribute to deficits in angiogenic potential observed in aged animals (Murugesan et al., 2011). This is consistent with human studies that show an association between physical activity and increased dentate gyrus blood volume (Pereira et al., 2007) and greater numbers of small blood vessels in the elderly brain (Bullitt et al., 2008). Such adaptations are likely to counter age- and AD-associated hippocampal impairment, an idea supported by evidence that greater hippocampal blood flow correlates to increased memory performance in aged individuals (Heo et al., 2010).

Exercise-induced neural activation in the hippocampus requires enhanced mitochondrial capacity to produce ATP from the oxidative phosphorylation of glucose. A consequence of these oxidative events is the accumulation of reactive oxygen species (ROS) that can damage neurons; however, exercise activates a series of counteractive mechanisms that enhance mitochondrial function and mitigate ROS-induced neurotoxicity. A protective effect of exercise against ROS is important because the hippocampus is a brain region particularly sensitive to oxidative stress (Candelario-Jalil et al., 2001). With advancing age and AD, hippocampal neurons accumulate ROS that promote the oxidation of nucleic acids, lipids, and proteins, and these modifications are associated with hippocampal impairment (Butterfield et al., 2006; Liu et al., 2002; Perlui et al., 2010). Accordingly, the inhibition of age-related oxidative damage improves performance on hippocampal-dependent tasks in animal studies (Carney et al., 1991; Pieta Dias et al., 2007).

Accumulating evidence suggests that exercise boosts neural defenses to oxidative stress, but the exact mechanisms require further clarification. Animal studies have shown that exercise enhances the activity of antioxidant enzymes that scavenge ROS (Navarro et al., 2004; Somani and Husain, 1996), particularly within the hippocampus (Brocardo et al., 2012; Devi and Kiran, 2004). Others did not detect alterations to enzyme activities, but did report that exercise attenuated age-related accumulation of reactive carbonyl derivatives, a marker of protein oxidative stress (Ogonovszky et al., 2005; Radak et al., 2001). This promising finding may have important implications for AD because it is associated with increased levels of carbonyl derivatives within the hippocampus (Hensley et al., 1995). In adults, aerobic fitness is associated with increased antioxidant defenses (Falone et al., 2009; Fratsoni et al., 2004), but further studies are warranted to define the role of exercise on antioxidant capacity in aging and AD.

Animal studies have shown that ROS accumulation increases the expression of uncoupling protein-2 (UCP2) in the inner mitochondrial membrane (Giardina et al., 2008), which has a protective function of
limiting ROS production (Degasperi et al., 2008; Lee et al., 2009). UCP2 is induced by physical activity in the hippocampus (Vaynman et al., 2006), and the use of UCP2 knockout mice suggests that UCP2 is required for increased spine synapse density in the dentate gyrus and CA1 (Dietrich et al., 2008). Interestingly, UCP2 also appears to be required for exercise-induced enhancement of mitochondrial proliferation and respiration (Dietrich et al., 2008). Mitochondrial biogenesis greatly enhances metabolic capacity and involves the coordinated expression of both nuclear and mitochondrial genes (reviewed by (Scarpulla, 2008)). Among the genes associated with mitochondrial biogenesis are SIRT1 and nuclear co-activator peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α), and exercise induces both in the hippocampus (Bayod et al., 2011; Steiner et al., 2011). This is especially important because SIRT1 and PGC-1α expression are diminished by aging and AD, and both are involved in Aβ processing (Donmez et al., 2010; Qin et al., 2009). In addition to UCP2, SIRT, and PGC-1α, exercise induces hippocampal genes involved in glycolysis, ATP synthesis, and synaptic plasticity (Ding et al., 2006b; Molteni et al., 2002; Tong et al., 2001). Thus, the bioenergetic demands of physical activity stimulate compensatory changes that benefit hippocampal function and offset the risk of neuronal damage.

The mitochondrial genome has a high mutation rate and limited repair mechanisms can prevent their accumulation. Remarkably, physical activity has been shown to attenuate mitochondrial DNA (mtDNA) deletions and point mutations that correlate with declining mitochondrial function in aging and AD (Coskun et al., 2004; Mecocci et al., 1993, 1994). An intriguing mechanism has been suggested by findings in muscle, a tissue that also undergoes exercise-induced enhancements to mitochondrial biogenesis and cellular proliferation. Physical activity that stimulates muscle progenitor cell proliferation reduces the mtDNA mutation load, because progenitor cells carry fewer mtDNA mutations than do mature cells (Tarnopolsky, 2009). It is tempting to speculate that a reduction in mtDNA mutation load could occur in the brain as in muscle, but this possibility remains untested. Nonetheless, several brain-specific mechanisms have been identified that augment energy metabolism, including the finding that exercise improves mitochondrial respiratory coupling through BDNF-dependent increases in complex I efficiency (Markham et al., 2004; Navarro et al., 2004). This is significant because it is well-established that complex I activity wanes with advancing age (Lenaz et al., 1997) and AD (Manzak et al., 2004). Consequently, the tuning of mitochondrial function may be an example of a central mechanism by which exercise protects against cognitive decline.

**Immune system modulation**

An increase in brain inflammation is recognized as one of the risk factors of cognitive dysfunction. Epidemiological studies support that regular moderate exercise is associated with reduced systemic inflammation (Gleeson, 2007). For example, cross-sectional data in men aged 65–74 years show a dose–response to exercise where the most physically fit individuals have the most anti-inflammatory profiles (Jankord and Jemiolo, 2004). Exercise intervention studies in the elderly have found that immune system function is boosted, suggesting that physical activity may alleviate the pro-inflammatory immune responses that characterize aging (Woods et al., 2009). Although the underlying mechanisms are not well understood, there is evidence in humans that physical activity reduces immune-cell reactivity by decreasing toll-like receptor expression, thereby diminishing cytokine release and chronic inflammation (Gleeson et al., 2006). Additionally, exercise interventions in the elderly have shown evidence of increased antibody responses to vaccination and T cell function (Grant et al., 2008; Kohut et al., 2004), indicating that physical activity may confer enhanced protection from infection. In advanced age, inflammatory markers such as C-reactive protein (CRP) are also associated with poorer cognitive performance (Dik et al., 2007) and reduced medial temporal lobe volume (Bettcher et al., 2012), but physical activity interventions reliably decrease C-reactive protein levels (Martins et al., 2010; Muscari et al., 2010). These findings reinforce the notion that inflammation is tightly associated with memory deficits in the elderly (Trollor et al., 2011; Yaffe et al., 2003), and demonstrate that exercise may shift the immune profile to allow for greater memory performance.

AD encompasses a broad range of immunological alterations, such as increased levels of inflammatory cytokines IL-1β (Griffin, 2011; Griffin et al., 1989) and TNF-α (Alvarez et al., 2007; Tarkowski et al., 1999). These alterations are likely to impair hippocampal function, as shown by rodent studies that have found that elevated levels of IL-1β and TNF-α disrupt LTP, resulting in impaired performance on hippocampal-dependent tasks (Barrientos et al., 2002; Cunningham et al., 1996; Ren et al., 2011). The maintenance of LTP requires a narrow range of IL-1β concentrations, above which IL-1β impairs synaptic plasticity (Ross et al., 2003). Elevated IL-1β levels impair BDNF-mediated signal transduction and the formation of filamentous actin spines (Tong et al., in press), which are required for the stabilization of BDNF-dependent LTP (Rex et al., 2007). Tg2576 mice develop elevated levels of IL-1β and TNF-α, but remarkably, this increase can be prevented by three weeks of wheel running (Nichol et al., 2008). One mechanism likely to contribute to this finding is that exercise causes the release of an anti-inflammatory cytokine, IL6, from muscle and brain (Nyo et al., 2002; Steensberg et al., 2000). IL6 suppresses the release of proinflammatory cytokines such as TNF-α (Starkie et al., 2003) and is associated with the induction of other anti-inflammatory cytokines (e.g. IL-1ra, IL-10) (Nieman et al., 2006), thus, exercise may quell exaggerated proinflammatory cytokine responses.

In the AD brain, the accrual of Aβ plaques is a pathological hallmark of AD and is a major contributor to neuroinflammation (Ambree et al., 2006). Although the abundance of Aβ plaques can elicit an inflammatory response, disrupting neuronal homeostasis (Salminen et al., 2009). Aβ plaques can be removed via phagocytosis by microglia, but these cells also express inflammatory mediators that can promote prolonged neuroinflammation (Rogers et al., 2002). It may be possible to evoke phagocytotic microglia responses preferential to inflammatory consequences, as supported by findings in transgenic AD lines. For example, exposing TgCRDNI8 mice to enriched environments that feature running wheels reduces amyloid burden, and increases microglia number, activation, and phagocytotic activity without enhanced inflammatory cytokine responses. (e.g. IL-1β, IL-10) (Niemann et al., 2006), and demonstrate that exercise promotes cognitive benefits, at least in part, by reducing excessive inflammatory events by modulating microglia activity.

**APOE ε4**

There are three major Apolipoprotein E (APOE) alleles in humans, ε2, ε3 and ε4, but only ε4 is associated with increased risk for AD (Corder et al., 1993) and greater Aβ deposition (Morris et al., 2010). The identification of APOE ε4 as a susceptibility locus has prompted the development of transgenic models in order to elucidate the effects of exercise in the APOE genotype. A comparison of homozygote mice expressing the human ε4 or ε3 alleles has shown that only the ε3 mice show enhanced hippocampal function upon exposure to enriched environments (Levi and Michaelson, 2007). This finding indicates that innate differences in hippocampal plasticity, as a result of APOE genotype, could underlie susceptibility to AD. Although differences between ε4 and ε3 mice may have severe consequences for hippocampal function, there is some evidence that exercise interventions yield hippocampal improvements. For example, sedentary ε4 mice have impaired performance on hippocampal-dependent tasks relative to ε3 mice, however; running wheel access improves performance of ε4 mice to comparable levels of ε3 mice for some measures of hippocampal function (Nichol et al., 2009). Thus, at least some of
the neural consequences of carrying the ε4 isoform may be overcome by physical exercise.

In accordance with findings in transgenic lines, studies of human ε4 carriers show that physical activity is associated with a broad array of cognitive advantages, and exercise may offer a higher degree of benefit for ε4 carriers than for non-carriers (Etnier et al., 2007; Schuit et al., 2001; see however Lautenschlager et al., 2008). For example, in older adults with poor cardiorespiratory fitness, ε4 carriers show a deficit in temporal lobe activation relative to non-carriers, but among those with high fitness, only ε4 carriers show enhanced cortical processing speed (Deeny et al., 2008) and frontal network activity (Deeny et al., 2011). An interpretation of these findings is that sedentary ε4 carriers may be more sensitive to age-related cognitive decline relative to non-carriers, in accordance with findings from longitudinal studies (Schiepers et al., 2012). Exposure to exercise may also be sufficient to overcome the ε4-associated increase in Aβ deposition, because PET studies in ε4 carriers show that elevated 11 C-PiB binding levels are correlated to a sedentary lifestyle (Head et al., 2012). Taken together, these findings suggest that those with genetic susceptibility to AD stand to gain the most from physical activity. While the interaction of exercise and APOE status on cognition is not rigorously established, current research indicates that exercise may be able to offset at least some of the effects of ε4 on brain function.

Concluding remarks

The impending shift of demographics towards a more elderly population demonstrates a critical need to address neurodegenerative processes, and AD in particular. Even though research continues to make progress in understanding the etiology of AD, effective medications have not yet been identified, and no prescriptive approaches are employed to delay the cognitive decline associated with aging. Exercise is an emerging therapeutic strategy that improves the function of mitochondria, immune system, and can mitigate the neurodegeneration inherent in AD and advancing age. By inducing neurotrophins and growth factors that enhance neuroplasticity, physical activity can significantly improve hippocampal function to a degree even with advancing age and disease. Through enhancing multiple domains of brain health, exercise has emerged as an efficacious therapeutic strategy that yields broad benefits to cognitive function.

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