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Cognitive Aging and the Promise of Physical Activity

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Abstract

Is the field of cognitive aging irretrievably concerned with decline and deficits, or is it shifting to emphasize the hope of preservation and enhancement of cognitive function in late life? A fragment of an answer comes from research attempting to understand the reasons for individual variability in the extent and rate of cognitive decline. This body of work has created a sense of optimism based on evidence that there are some health behaviors that amplify cognitive performance or mitigate the rate of age-related cognitive decline. In this context, we discuss the role of physical activity on neurocognitive function in late adulthood and summarize how it can be conceptualized as a constructive approach both for the maintenance of cognitive function and as a therapeutic for enhancing or optimizing cognitive function in late life. In this way, physical activity research can be used to shape perceptions of cognitive aging.

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1. INTRODUCTION

Is cognitive decline an inevitable consequence of aging? Certainly, decades of cognitive aging research demonstrate downward trends in nearly all cognitive domains including episodic memory, executive function, processing speed, and fluid reasoning (Schaie 1993). Aging is also linked with an increased risk of various cognitive disorders and neurologic diseases (e.g., Alzheimer's disease). There is also unequivocal evidence for age-related brain atrophy, loss of white matter microstructure, and dysfunctional patterns of neural activity that all likely contribute to cognitive decline (Raz et al. 2010). Thus, there is overwhelming evidence that neurocognitive losses are indeed a ubiquitous consequence of aging. But is there any reason for hope and optimism in the face of this evidence of loss and decline?

The field of cognitive aging has progressed well beyond an emphasis on decline, deterioration, and decay and instead has shifted focus to (*a*) identifying factors that explain individual variability or moderate the trajectory of age-related neurocognitive decline, (*b*) identifying the mechanisms that lead to variation in cognitive aging, and (*c*) examining possible ways of intervening, mitigating, delaying, preventing, or reversing age-related cognitive decline. This shift reflects an awareness among investigators that a narrow view of cognitive aging as decline and deterioration is an exceptionally superficial outlook that masks the complexities, trajectories, and promises of neurocognitive aging.

The fact that there is significant individual variability in cognitive aging is irrefutable. It is quite clear that some older adults show very gradual or minimal cognitive decline while others show more rapid losses, regardless of a clinical diagnosis of cognitive impairment. A major theoretical and empirical focus of cognitive aging research has been to try to understand this individual variability. There have been many ways of conceptually framing variability in cognitive aging trajectories, including theories and terminology such as cognitive reserve, brain plasticity, compensation, reversibility, and many others (Stern et al. 2019). Despite subtleties and nuances with respect to each of these terms and concepts, they all share one defining feature: They all attempt to provide an explanation for individual variability in neurocognitive function during late life. And some of them go one step further to highlight possible approaches for reversing losses that have already begun to occur. Yet, despite the prevalence of these theories and terms in cognitive aging research,

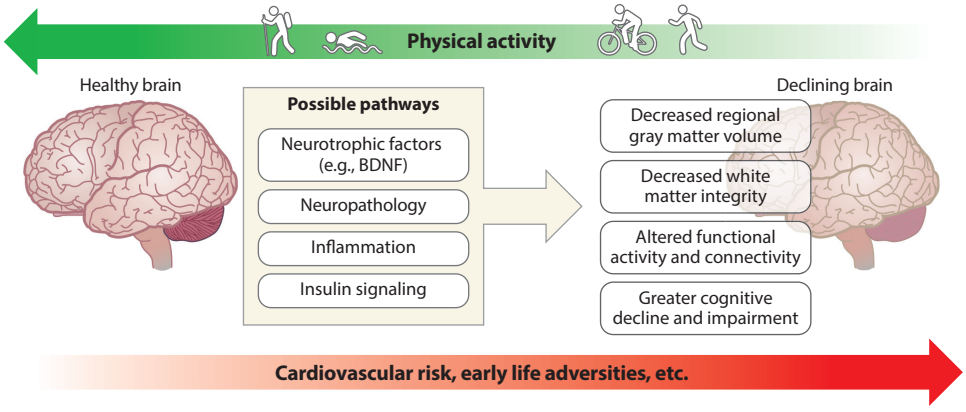

Figure 1

A conceptual diagram showing that cardiovascular risk and early life adversity increase risk for more accelerated declines in cognitive aging, while physical activity has the opposite pattern, possibly by reversing the same putative mechanisms. Biological mechanisms of physical activity might include increased production of some molecules (i.e., BDNF) or decreased expression or accumulation of other molecules (i.e., neuropathology). Abbreviation: BDNF, brain-derived neurotrophic factor.

they are often criticized as generating unfalsifiable hypotheses and are too frequently used as post hoc explanations for results that are otherwise difficult to interpret. But these criticisms, despite being justified in many circumstances, do not undermine the fundamental challenge and aim of trying to provide an explanation for the significant individual variation observed in cognitive aging.

One might ask, however, what lies beyond the horizon of understanding individual variation in cognitive aging? In other words, once we have identified factors that explain individual differences in neurocognitive aging, what should come under our research lens next? The answer to this question might lie in the bed of precision medicine; that is, once investigators have identified factors that explain individual variation in cognitive aging, be they genetic factors or life experiences and exposures, there might be clearer paths for prescribing individuals to partake in tailored behaviors to reduce their chances of showing cognitive losses and for maintaining higher levels of cognitive function for longer. An awareness of these factors may lead to more options for interventions and therapeutic approaches for addressing risks of cognitive decline or ways in which prescriptions and therapies could be tailored based on an individual's life experiences, exposures, or genetics. The aim of many investigators and clinicians is to someday provide a more definitive answer to the first question posed in this review: Is cognitive decline an inevitable consequence of aging?

In this review, we focus on several factors that explain individual variation in age-related cognitive decline. Then, we use physical activity as an example of an approach that not only appears to explain individual variation in neurocognitive aging but also is a highly accessible, unpatentable, cost-effective, and scalable intervention to improve neurocognitive function in late adulthood (**Figure 1**).

2. IMPACT OF PHYSICAL HEALTH ON NEUROCOGNITIVE AGING

Before embarking on a discussion of what is known and unknown about the impact of physical activity on cognitive aging, we might ask a more fundamental question: Why would the actions of the body influence the health and function of the brain? First, we should recognize that Western philosophical traditions have a tendency to erroneously divide the brain from the body and describe the

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functions of the brain as if they were independent processes. Even the language that we use when referring to our body or our brain creates an artificial and false distinction. Thus, conceptually dividing the brain from the other organ systems is a dualistic fallacy. But because we are tethered to the limitations of language, we will continue to use these terms to describe how the central nervous system (the brain) interacts with, affects, and is affected by other organ systems (the body).

Advances in the fields of human neuroscience and health psychology have reaffirmed that there is a dynamic reciprocal relationship between the brain and the body and that the health of one directly influences the health of the other. This observation has prompted the emergence of the field of health neuroscience (Erickson et al. 2014a, Stillman & Erickson 2018), which leverages the conceptual frameworks and methodologies of multiple disciplines (e.g., health psychology, cognitive neuroscience) to better understand how the brain affects and is affected by physical health. This field also emphasizes the role of contextual factors such as chronic stress, socioeconomic status, race and racism, and early life adversity in modulating the interplay between brain and body. One exciting implication of the conceptual framework adopted by health neuroscience is that behavioral interventions known to improve physical health outcomes may also be effective for promoting healthy brain aging. Here we provide an overview of evidence linking physical health to indicators of brain health and the ways in which contextual factors impact this relationship.

The American Heart Association has defined cardiovascular health as having ideal values for 7 of the top 10 most costly risk factors for cardiovascular disease: smoking, diet, physical activity, body composition, blood pressure, total cholesterol, and fasting plasma glucose (Folsom et al. 2015). Having and maintaining ideal cardiovascular health from young to middle adulthood has been prospectively associated with higher performance on tests of processing speed, executive functioning, and verbal memory compared to having intermediate or poor cardiovascular health (Reis et al. 2013). Moreover, a prospective longitudinal study of brain health indicated that older adults who had a greater number of cardiovascular health factors rated as ideal at baseline exhibited fewer white matter lesions and brain infarcts and larger overall brain volume at follow-up (Gardener et al. 2018), suggestive of healthier brain aging. Thus, maintaining cardiovascular health over the lifespan is associated with preservation of brain health and may prevent or slow the onset of age-related cognitive decline.

In contrast, indicators of poor cardiovascular and metabolic health such as hypertension, obesity, and type 2 diabetes (T2D) have been linked to negative brain health outcomes, especially in late life. Hypertension has been established as one of the leading risk factors for cognitive impairment and dementia in older adulthood due to hypertension-related damage to cerebral vasculature (Faraco & Iadecola 2013). Systolic blood pressure greater than 130 mm Hg in midlife has been prospectively associated with a 38% increased risk of developing dementia later in life, an association that persisted even after accounting for other dementia risk factors such as cardiovascular disease, age, and poor health behaviors (Abell et al. 2018). Further, the deleterious effects of hypertension on cognitive functioning continue to be evident after the development of dementia; one study demonstrated that hypertension was associated with more severe cognitive impairments among older adults with Alzheimer's disease (Moonga et al. 2017). Cognitive domains that appear to be most consistently associated with hypertension include memory and executive functions (Iadecola et al. 2016), which are cognitive domains that show the earliest and most precipitous declines with advancing age. As described in Section 6, they are also two of the domains showing the most improvement following adoption of regular physical activity (Erickson et al. 2019). Although there is some evidence that pharmacological treatment of hypertension may reduce risk for cognitive decline and dementia, results of clinical trials exploring the benefits of antihypertensive medication for brain health have been generally mixed (Iadecola et al. 2016).

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Obesity is also a leading modifiable risk factor for age-related cognitive decline and dementia. Although obesity is a risk factor for poor cardiovascular and metabolic health outcomes, excess adipose tissue is associated with risk for dementia independent of cardiovascular risk (Stillman et al. 2017b). Data from a sample of more than 6,000 adults followed prospectively for several decades demonstrated that having excess central adiposity in midlife was associated with significantly elevated risk for dementia in older adulthood, particularly among those individuals who exhibited both central adiposity and obesity (body mass index $\geq$30) (Whitmer et al. 2005, 2008). Even in the absence of overt neurological illness, midlife obesity is prospectively associated with lower performance on tests of overall cognition, memory, attention, and executive functioning (Hassing et al. 2010, Masi et al. 2018). Individuals with overweight and obesity also exhibit widespread alterations in structure and function of brain regions sensitive to age-related decline, including the hippocampus (Donofry et al. 2020, Yokum et al. 2012) and regions of the prefrontal cortex (PFC) such as the dorsolateral PFC (Brooks et al. 2013) and orbitofrontal cortex (Marques-Iturria et al. 2013). Fortunately, surgical and behavioral weight loss interventions have been shown to improve indices of neurocognitive function (Donofry et al. 2020, Peven et al. 2020, Veronese et al. 2017), providing evidence that the deleterious associations between obesity and accelerated cognitive aging may be reversible.

It is important to note that, while midlife obesity increases risk for cognitive decline and dementia, higher weight in older adulthood has frequently been associated with maintenance of neurocognitive health (Curtis et al. 2005). In fact, diagnosis of dementia is often preceded by unintentional weight loss (Buchman et al. 2005, Johnson et al. 2006). It remains unclear whether higher weight in older adulthood is indeed protective or whether late-life weight loss may be caused by an incipient neurological disease process that has yet to manifest in diagnosable illness (Brenowitz 2021). Nevertheless, these findings suggest that weight loss interventions may be most effective for preventing age-related cognitive impairment when delivered in early and mid-adulthood, well before the onset of neurological illness.

T2D has similarly been shown to accelerate cognitive aging and increase vulnerability for the development of neurological illness. Individuals diagnosed with T2D in midlife are estimated to be at 50% increased risk for dementia later in life (Moheet et al. 2015). T2D is also prospectively associated with impairments in memory, attention, and executive functioning relative to individuals free of T2D (Espeland et al. 2013, Kanaya et al. 2004). There is some evidence that declines in cognitive performance in T2D are accompanied by changes in brain structure and function, with these brain changes potentially accounting for T2D-related cognitive decline in late adulthood (Chen et al. 2014, Liu et al. 2018, Yu et al. 2019). Insulin resistance, a precursor to the development of T2D, has also been shown to affect cognitive performance (Umegaki et al. 2017), suggesting that impaired glycemic control is detrimental to brain health even when it does not meet clinical criteria for T2D and may predict the onset or progression of cognitive decline. Insulin is involved in the regulation of brain function and plasticity, including regions sensitive to age-related declines such as the hippocampus (Grillo et al. 2019, Spinelli et al. 2019). Animal models have demonstrated that reduced insulin sensitivity impairs adult hippocampal neurogenesis and synaptic plasticity (Spinelli et al. 2017). Thus, insulin dysregulation may represent a mechanistic link between cardiometabolic and age-related cognitive decline.

In sum, there is an irrefutable and massive body of prospective longitudinal evidence linking physical health in early and midlife to neurocognitive health outcomes in late life. This establishes several foundational assertions: (*a*) that cardiovascular and metabolic health explain significant individual variation in the trajectory of cognitive aging, (*b*) that age-related neurocognitive decline is not self-contained or independent from the health and function of peripheral organ systems, and (*c*) that experimental manipulations designed to improve physical health (e.g., blood pressure)

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are critical for determining the causal links between cardiovascular and metabolic health and age-related cognitive decline.

3. EARLY LIFE ADVERSITY AND NEUROCOGNITIVE AGING

We have established above that cardiovascular health in midlife explains individual variation in neurocognitive health in late life. However, are there other factors that explain individual variability in age-related cognitive decline, and could those factors include early childhood experiences? Is it possible that childhood experiences initiate and predict the trajectories of cognitive performance, risk and resilience, and plasticity that persist into late adulthood? Or could the consequences of early life adversity have more protracted effects on brain health such that the negative repercussions of early life adversity are not fully realized until other physiological processes emerge that accelerate age-related cognitive decline?

Adverse childhood experiences such as abuse, neglect, and extreme poverty exert profound negative effects on health and well-being that persist well into adulthood. Individuals who have been exposed to childhood adversity are at significantly greater risk of developing numerous chronic health conditions such as cardiovascular disease, T2D, and obesity (Friedman et al. 2015, Merrick et al. 2019, Su et al. 2015), and they exhibit accelerated brain aging relative to adults without a history of childhood adversity (Short & Baram 2019). Indeed, early life adversity has been related to the development of dementia many decades after initial exposure (Danese & McEwen 2012, Short & Baram 2019). Unfortunately, early life adversity is common, affecting 40–60% of individuals across the globe, in both economically distressed and wealthier countries (Merrick et al. 2018). Moreover, the burdens associated with early life adversity are not equally distributed in the population, with marginalized groups such as racial and ethnic minorities being at far greater risk of exposure to adverse events in childhood (Merrick et al. 2018). Thus, differential exposure to early life adversity is likely contributing to racial and ethnic disparities in rates of age-related cognitive decline and dementia in late life. Despite these grave and persistent effects of early life adversity, it remains unclear whether interventions delivered in adulthood are capable of reversing these effects.

4. GENETIC RISKS AND AGE-RELATED COGNITIVE DECLINE

In addition to early life adversity and cardiovascular health in midlife, individual differences in age-related cognitive performance can also be attributed to the possession of genetic variants that elicit molecular cascades that affect neurocognitive processes; that is, genetic factors influence the neurobiological processes (e.g., neurotransmitter expression, growth factors, synaptic plasticity) that support cognitive processes as well as neural resilience, plasticity, and neuropathology that explain individual differences in the trajectory of age-related cognitive decline.

Several genetic variants have been linked with cognitive function and decline. For example, the apolipoprotein E (*APOE*) ε4 allele is the most well-established genetic risk factor for Alzheimer's disease and is also associated with accelerated hippocampal atrophy and more rapid declines in executive function and episodic memory in normal cognitive aging (O'Donoghue et al. 2018). In addition to *APOE* ε4, many other genetic variants have been identified as predictors of cognitive aging, generally with small effect sizes, including the brain-derived neurotrophic factor (*BDNF*) Val66Met single nucleotide polymorphism (Erickson et al. 2012, Lim et al. 2014). Polygenic risk scores are an alternative approach for examining the effects of genetic variation on cognitive performance and are created by combining effects of various single nucleotide polymorphisms that by themselves often have relatively small effect sizes. Results from these studies indicate that this

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analytical approach might have more explanatory power than examining single nucleotide polymorphisms, although more research is needed to confirm or refute these patterns (Porter et al. 2018).

This review is not intended to be an exhaustive summary of the genetic variants associated with age-related cognitive function because many other reviews have thoroughly covered this (Seto et al. 2021). However, what is important in the context of this review is that individual variability in both the onset and rate of age-related cognitive decline is partially explained and predicted by genetic variation. This is essential to consider in the context of environmental exposures and health conditions that also predispose someone for accelerated age-related cognitive decline. These results lead to speculation that the presence of cardiovascular health conditions moderates genetic variation such that the combination of genetic risk and poor cardiovascular health exacerbates the risks for age-related cognitive decline. Similarly, we could speculate whether early life exposure to adversity exacerbates the effects of genetic variants on age-related cognitive decline. In contrast, the combination of low genetic risk and an absence of early life adversity might be a key feature for maintaining an elevated level of cognitive performance into late adulthood. Definitive evidence for these possible interacting associations remains a gap for future research to address.

5. FOUNDATIONS FOR PHYSICAL ACTIVITY

In contrast to health conditions (e.g., hypertension), environmental exposures (e.g., early life adversity), and genetic factors (e.g., *APOE*) that increase the risk for accelerated age-related cognitive decline, engagement in physical activity might be an effective approach for mitigating cognitive decline in late adulthood. In fact, physical activity unequivocally affects brain health throughout the lifespan, and there have been many review articles describing these effects (Erickson et al. 2019, Hillman et al. 2008). The aim here is not to recapitulate the wealth of information contained in prior reviews but to provide the reader with a summary of the effects, mechanisms, and several reasons that likely explain some of the remaining muddiness and confusion in the literature. In addition, we propose that physical activity can be used as a model for improving our conceptual understanding of cognitive aging and the promise of treatments to mitigate loss.

Physical activity is an umbrella term that refers to movement that increases energy expenditure regardless of its intent or intensity, whereas exercise is a structured form of physical activity for the sake of improving fitness. In this context, many observational studies measure physical activity while exercise interventions provide a structured regimen that is designed to improve fitness. Exercise interventions including randomized clinical trials of exercise often attempt to target moderate- to vigorous-intensity physical activity (MVPA), although there continues to be debate about how to define, measure, and describe light-, moderate-, and vigorous-intensity activities and their relative impact on health end points. Physical activity and exercise are behaviors that can be measured by self-report or through devices that measure position and acceleration (e.g., actigraphs). In contrast, cardiorespiratory fitness is not a behavior but a physiological construct that is correlated with the degree of physical activity and exercise one engages in and thus can be modified by participating in MVPA. These terms are important for distinguishing and considering the material described below.

Cross-sectional studies of physical activity or fitness are snapshots of current levels, whereas prospective observational studies provide information about engagement in activity over time or the extent to which physical activity earlier in life impacts health outcomes later in life. In contrast, randomized clinical trials of exercise are experimental manipulations in which individual differences among participants are randomly distributed across control and treatment groups. Thus, causality can be more easily inferred from randomized clinical trials.

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6. THE ROLE OF PHYSICAL ACTIVITY IN COGNITIVE AGING

Prospective longitudinal evidence unequivocally indicates that greater amounts of physical activity earlier in life are associated with better cognitive functioning later in life including a reduced risk of developing dementia. For example, Tan and colleagues (2017) followed 3,714 adults with a mean age of 70 for 10 years and found that individuals engaging in the least amount of activity at baseline had a 50% increased risk of developing dementia, an effect that has been replicated in quantitative reviews (Beckett et al. 2015, Sofi et al. 2011). However, observational studies have inherent weaknesses including potential confounding by unmeasured third variables and possibilities of reverse causality. For example, it is unclear from observational studies whether initial declines in cognitive function and signs of neurodegeneration or neuropathology could be influencing mobility, balance, motivation, and goals for engaging in physical activity. In such a scenario, reductions in physical activity would be a consequence, or an early marker, of declining cognition rather than a cause of declining cognition. As such, more definitive evidence for a causal relationship between physical activity and cognitive function comes from randomized clinical trials in which participant characteristics are randomly distributed across group assignments and volumes, types, and intensities of physical activity are systematically manipulated.

Despite some mixed evidence, the more rigorously controlled clinical trials with larger sample sizes tend to more clearly indicate that exercise is capable of improving cognitive and brain function. For example, in a 6-month aerobic exercise randomized clinical trial in 124 adults between 60 and 75 years of age, exercise selectively improved executive function, suggesting some specificity of exercise on brain and cognitive measures (Kramer et al. 1999). Meta-analyses and reviews have largely supported this result, albeit with some variability across studies. For example, a seminal meta-analysis demonstrated that in late adulthood, randomized clinical trials of exercise improved cognitive performance relative to control groups with a moderate effect size and with the greatest improvements for executive function (Colcombe & Kramer 2003). Other meta-analyses have concluded that supervised exercise interventions improved cognitive performance in adults over 50 years of age including for both cognitively normal and impaired individuals (Northey et al. 2018). In sum, exercise is capable of enhancing cognitive performance in late adulthood, with some qualifications. In particular, (*a*) both participant characteristics (i.e., age of the sample, sex distribution) and study features (e.g., duration of the intervention, level of supervision, cognitive domains assessed) moderate the effect of exercise on cognitive performance, and (*b*) effect sizes of exercise interventions on cognitive outcomes tend to be in the small-to-moderate range (Erickson et al. 2019). This indicates that larger sample sizes are generally required to detect significant effects and that many prior studies have been insufficiently powered. To complicate this issue, large sample sizes require higher levels of funding and resources and are more challenging for monitoring exercise adherence and compliance, an issue that researchers and funding agencies must take into account for future work in this area.

Despite this seemingly overwhelming body of evidence for the positive effects of exercise on cognitive performance in late adulthood, there are studies (Frost et al. 2021, Sink et al. 2015) and meta-analyses that have failed to find positive effects of exercise on cognition (Kelly et al. 2014, Young et al. 2015). What factors might explain this heterogeneity? One possibility is that meta-analyses often differ in their inclusion and exclusion criteria. For example, Northey et al. (2018) included all supervised exercise interventions regardless of quality, cognitive status of the sample, or exercise type. This contrasts with others that apply stricter inclusion criteria and focus on one mode of exercise, which results in fewer studies included, thereby reducing power (e.g., Young et al. 2015). Other meta-analyses vary in terms of whether they examine adherence, moderators of the intervention (e.g., age of the sample), features of the study (e.g., level of supervision), or

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types of control groups. In fact, Young et al. (2015) suggested that their null findings might be due to variability in the cognitive responses to exercise that they were unable to closely examine. In addition, although most meta-analyses perform a quality assessment of the studies included in the analysis, the quality assessment scales (e.g., PEDro) do not provide ratings for the quality of the cognitive instruments used or the quality of the delivery of the exercise intervention, two issues that could greatly influence the likelihood of detecting effects. As such, there are numerous reasons, often not fully transparent to readers, why some studies and meta-analyses fail to find effects.

Unfortunately, there are not yet clear public health guidelines for prescribing exercise to optimize its potentially cognitive enhancing effects in older adults. This limitation might be one of the primary sources for the heterogeneity across studies. Specifically, we have little clarity about the intensity of exercise, volume of activity per week, minimum duration of an intervention, frequency of the activity per week, whether the activities need to occur in at least 10-min bouts, and the type or mode of exercise that maximizes the effects. To make matters more complicated, the physiological pathways and mechanisms that mediate cognitive benefits might differ as a function of these experimental features of exercise prescription. For example, the physiological pathways induced by a longer intervention of light-intensity exercise might be quite different than the physiological pathways induced by a shorter but more intense intervention. These pathways and patterns might influence both the magnitude of the cognitive benefits and the particular cognitive processes affected (e.g., executive function versus episodic memory). As an example, there has been speculation that changes in cardiorespiratory fitness might be a prerequisite for showing cognitive effects from an intervention. If so, then studies of higher intensity, for at least several months in duration, might be needed for detecting changes to cognitive function. However, all these issues might also depend on the baseline activity levels of the sample, the participants' levels of cognitive impairment, or the cognitive and brain regions that are being targeted.

Exercise does not appear to influence all cognitive processes uniformly and is unlikely to shift performance on all cognitive tests; that is, physical activity appears to influence executive functions more than other cognitive domains. As such, studies that rely on measures of global cognitive function may be using insensitive measures for detecting subtle cognitive improvements especially in cognitively normal individuals. Thus, studies that fail to comprehensively examine cognition, do not utilize measures of executive function that are reliable and valid, limit cognitive testing to general tests (e.g., Mini-Mental State Exam), or use a composite measure of general cognitive function might not find patterns consistent with the rest of the literature.

Baseline participant characteristics likely contribute to the cognitive response to exercise interventions. For example, women show greater cognitive benefits from exercise compared to men (Barha et al. 2017), and this might be further modified by the age of the sample such that men might show greater exercise-induced cognitive benefits earlier in the lifespan, while women show greater benefits at later life stages (Ludyga et al. 2020). Participant age may also influence the cognitive response to exercise, with one meta-analysis concluding that adults 55–75 years of age may yield the greatest exercise-induced cognitive benefit, compared to older participants (Chen et al. 2020). These findings indicate that there may be a window of opportunity to engage in exercise to produce maximal cognitive benefits. Thus, implementing physical activity as a strategy for maintenance of brain health and cognitive function may be the most effective for cognitive aging, as opposed to implementing physical activity as a treatment among individuals that may have more comorbid conditions or limitations.

Genetic variation may also influence the efficacy of exercise to enhance cognitive function in late adulthood (Erickson et al. 2013). Several studies have reported that associations between physical activity and cognitive function are weakest in individuals carrying the *APOE* ε4 allele (Obisesan et al. 2012, Podewils et al. 2005), while other studies have found the opposite

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pattern—that the associations between physical activity and cognition are strongest in those with the greatest genetic risk for Alzheimer's disease. For example, a randomized clinical trial showed that exercise improved cognitive performance in *APOE* ε4 carriers only (Solomon et al. 2018). Similar patterns have been reported for other genetic polymorphisms that affect cognition such as *BDNF*. For example, carriers of the Met allele (*BDNF* Val66Met) have smaller hippocampal volume and poorer memory performance compared to Val homozygotes, but greater amounts of physical activity might mitigate the negative cognitive sequelae of the *BDNF* Met allele (Brown et al. 2014, Erickson et al. 2013). Overall, genetically inherited susceptibility for a decline in cognitive function may be mitigated by engaging in physical activity. However, small sample sizes, analytical limitations, and the lack of randomized clinical trials greatly limit the decisiveness of conclusions in this area.

In sum, the magnitude of exercise-induced cognitive benefits is likely influenced by sample size, approach to statistical analyses, and study quality; the type, duration, and intensity of exercise; sex, age, and other baseline lifestyle factors (activity levels); early life exposures (e.g., adversity); cardiovascular and metabolic health conditions (e.g., hypertension, obesity); and genetics (*APOE*, *BDNF*), among many other factors. Further examination of how these moderating factors influence the exercise-cognition link is crucial, as results may be used to inform the creation of an algorithm to predict the cognitive response to exercise to generate optimized precision medicine approaches (Brown et al. 2014).

7. PHYSICAL ACTIVITY AND DEMENTIA

Dementia is a cluster of symptoms that are characterized by significantly greater than expected deficits in several cognitive domains, usually including episodic memory as well as impairments in the ability to perform activities of daily living. Alzheimer's disease is the most common type of dementia with its primary neuropathological features of Aβ plaque accumulation and tau formation. Current pharmaceutical treatments for dementia provide temporary symptomatic relief; however, they do not alter disease course and often have undesirable side effects. Thus, behavioral and lifestyle interventions such as physical activity may be alternative therapeutic approaches. For example, randomized clinical trials in individuals diagnosed with dementia or mild cognitive impairment (MCI) have reported small but significant improvements in cognitive performance after several months of exercise (Groot et al. 2016, Heyn et al. 2004, Law et al. 2020). However, several exercise trials have failed to find cognitive improvements among individuals with dementia, despite improvements in physical fitness (Lamb et al. 2018, Sanders et al. 2020). This has generated debate about the possibility of a point of no return by which neurodegeneration and neuropathology become so advanced that exercise (or other treatments) has a limited impact on the course of the disease or the trajectory of cognitive decline.

One argument in this debate is that the significant heterogeneity in studies of cognitively healthy individuals is amplified in studies of dementia patients. Specifically, there is substantial diversity in the etiology of various types of dementia and thus various underlying biological changes, which may be differentially influenced by exercise interventions. For example, the hallmark of Alzheimer's disease is the accumulation of tau and Aβ, which may be reduced by physical activity (Brown et al. 2019). However, frontotemporal dementia is primarily characterized by degeneration in the frontal and temporal lobes, and there is little research as to how physical activity may impact this etiology (Demurtas et al. 2020). Additionally, studies often do not distinguish between disease stage, except for a general distinction between MCI or dementia. The pathway from diagnosis to mortality in Alzheimer's disease is approximately 8.3 years, and thus individuals at different stages of this trajectory have varying degrees of neurodegeneration and may show different responses to

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exercise. Individuals with dementia are also more likely to suffer from comorbid conditions that can influence intervention efficacy and ability to complete the exercise as intended. Comorbidities may make it difficult to standardize exercise dosage across patients, as activities may need to be modified to suit individual needs and ensure safety, and exercise modalities may differentially impact cognitive health. Thus, physical activity may be effective as a treatment for MCI and dementia; however, targeting early phases of the disease course and a more individualized approach to treatment might be required for optimal cognitive benefit (Amieva et al. 2016).

In addition to being a possible therapeutic for cognitive decline in dementia, physical activity has been examined as a method for delaying or preventing the onset of the disease. Indeed, evidence from observational research indicates that physical activity can reduce the risk for cognitive decline and dementia over a 1- to 12-year period (Sofi et al. 2011). Additionally, greater midlife physical activity is associated with a reduction in later-life dementia risk (Engeroff et al. 2018, Palta et al. 2019), making midlife a prime target for implementation of preventive strategies. At this life stage, individuals may be in the presymptomatic stages of Alzheimer's disease, as accumulation of Alzheimer's disease biomarkers begins decades before the onset of clinical symptoms (i.e., clinically detectable cognitive change) (Villemagne et al. 2013).

Taken together, exercise might be effective as both a method for preventing conversion to dementia and a treatment to improve cognitive function in individuals diagnosed with dementia. This approach, however, likely requires individualized exercise prescription and might be more effective early on in the course of the disease before neurodegeneration and neuropathology are advanced and widespread.

8. HOW PHYSICAL ACTIVITY SHAPES THE AGING BRAIN

How does physical activity affect cognitive function in late adulthood? The answer to this seemingly simple question is rather complex and nuanced. We and others have written extensively (Stillman et al. 2016, 2020) about the conceptualization of the mechanisms of physical activity on brain health including molecular and cellular pathways, systems-level pathways, and psychosocial pathways (e.g., sleep). Of course, these different levels of analysis are not mutually exclusive of one another. For example, engaging in physical activity might increase the expression of growth factors that promote dendritic branching, which in turn results in volumetric changes that may mediate improvements to sleep quality, thus yielding cognitive improvements. In this example, exercise-induced improvements to sleep quality would be a mechanism by which cognitive improvements are realized, albeit through a cascade of molecular and cellular paths. Complicating the issue is that the mechanisms by which physical activity influences cognitive and brain health outcomes are likely to differ by the age of the sample (e.g., children versus elderly), population (e.g., dementia versus cognitively normal), brain region (e.g., hippocampus versus PFC), cognitive domain being targeted (e.g., episodic memory versus attentional control), and parameters of exercise (e.g., light intensity versus vigorous intensity).

Adding to this complexity is that physical activity influences hundreds or thousands of molecular pathways. As such, physical activity elicits many molecular and cellular cascades in parallel that are likely influencing the brain independently, additively, or multiplicatively. This is referred to as a sledgehammer effect—that is, engaging in physical activity is like a sledgehammer to the system, an imprecise but highly effective means of influencing nearly every organ system in the body (**Figure 2**). The sledgehammer effect has two main ancillaries: (*a*) it makes discussions about mechanisms more challenging because most effects will unlikely be driven by one primary pathway—thus, contributions from multiple systems have to be considered in models of mechanisms for exercise; and (*b*) it provides an explanation for why the effects of exercise are so robust

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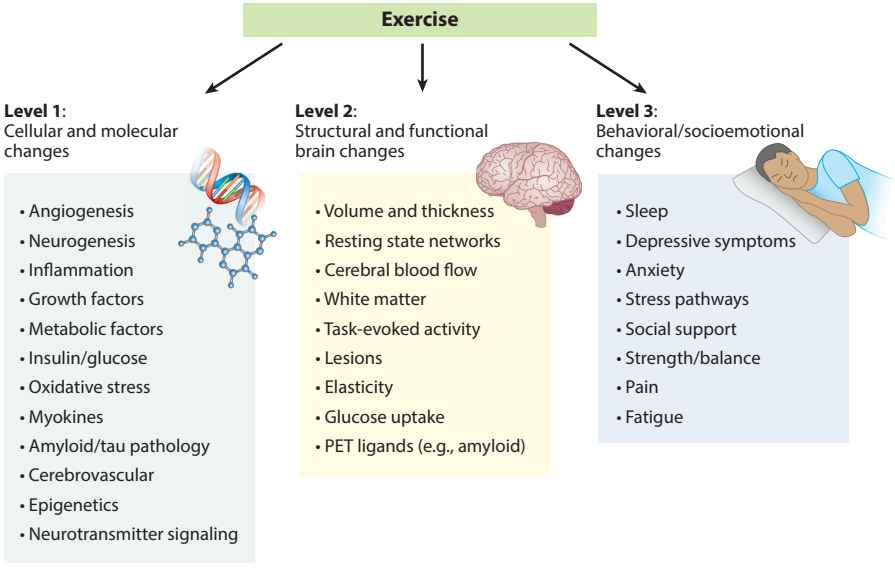

Figure 2

A conceptual diagram illustrating three levels of mechanisms by which exercise possibly influences cognitive outcomes. This list is far from comprehensive but shows that the effects of exercise are likely happening through a plethora of pathways, an effect referred to as the sledgehammer effect. Abbreviation: PET, positron emission tomography.

across populations, ages, and health conditions. There is more than one pathway to achieve the many health benefits of exercise. Despite these complexities, we outline here several pathways affected by physical activity that are likely contributing to cognitive enhancements in late adulthood.

8.1. Animal Evidence

Some of the research on physical activity and brain outcomes can be traced to animal (mostly rodent) models of environmental enrichment (EE). Initial studies on EE compared groups of young animals reared in standard cage conditions to those reared in cages enriched with a combination of cognitive, social, and physical stimulation (Hebb 1949). The animals housed in the enriched cages had signatures of enhanced brain health that persisted as the animals aged, including larger total brain volume and weight (e.g., Bennett et al. 1969), higher levels of neurotrophic factors, neurogenesis, and decreased cellular apoptosis (Kempermann et al. 1997, Walsh et al. 1969). Importantly, the changes induced by EE were not limited to brain morphology or biochemistry; behavioral differences between the groups were also observed. For instance, EE animals performed better on spatial learning and memory tasks compared to those from the standard rearing environment (Nilsson et al. 1999, Wright & Conrad 2008), suggesting that EE improves the functioning of the neural circuits that support these cognitive functions.

The observed benefits of EE on learning and memory spurred interest in applying EE to aging and models of neurodegenerative disease (Rosenzweig & Bennett 1996, Wright & Conrad 2008). Specifically, EE was tested as a potential therapeutic strategy to counteract age-associated declines in learning and memory. The conclusion that emerged was that EE can remediate some of the negative effects of normal and pathological aging on the brain. Further, this remediation may occur

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preferentially in regions sensitive to aging such as the hippocampus (Diamond 2001, Jankowsky et al. 2005, Nakamura et al. 1999).

Given that EE involves multiple aspects of environmental stimulation, a well-recognized limitation of the EE literature is that it is impossible to isolate the effects of any single component on brain health (e.g., Voss et al. 2013). However, numerous studies have now demonstrated that one component of EE, physical activity, is a particularly potent catalyst for brain plasticity (Kobilo et al. 2011, van Praag et al. 2000). This is because physical activity by itself can initiate many of the same molecular, cellular, and structural brain changes observed with EE. For instance, numerous studies have demonstrated that voluntary wheel running in mice housed in standard cages increases neurogenesis and dendritic arborization in the dentate gyrus subfield of the hippocampus and increases levels of neurotrophins (e.g., BDNF) that may promote neuronal survival (de Sousa Fernandes et al. 2020, Kobilo et al. 2011). Further, exercise-induced increases in circulating BDNF predict improvements in memory and executive functioning (Erickson et al. 2011, Leckie et al. 2014) as well as increased hippocampal volume (Erickson et al. 2011) among older adults. Running-induced neurogenesis has been demonstrated in young and normally aging animals, as well as in animal models of neurodegenerative disease. Crucially, hindering running-induced neurogenesis via the blockade of critical neurotrophic pathways (e.g., TrkB) also blocks improvements in learning and memory performance (Vivar et al. 2013). This latter finding constitutes some of the strongest evidence that neurotrophin-mediated neurogenesis is a causal mechanism underlying exercise-induced cognitive improvements in aging. The effects of physical activity on brain health indicators such as neurogenesis in aging animals suggest that physical activity can reverse some of the decline in neurogenesis that occurs as part of both normal and pathological aging (Vivar et al. 2013).

Aerobic exercise also increases cerebral blood flow (Stillman et al. 2021) and stimulates angiogenesis by enhancing cerebral expression of vascular endothelial growth factor and insulin-like growth factor 1 (Morland et al. 2017). Increased cerebral vascularization and blood flow allow for delivery of more oxygen, nutrients, and growth factors to maintain cellular health and to support the growth of new neurons in regions such as the hippocampus.

8.2. Human Neuroimaging Evidence

Animal research provides important insight regarding the molecular and cellular pathways contributing to the cognitive improvements resulting from physical activity. However, it is impossible with current technology to determine whether these same molecular and cellular pathways are affected by physical activity in humans. Instead, in humans there is a reliance on examining either peripheral blood markers or neuroimaging biomarkers to give us insight into the possible biological mechanisms of physical activity on cognition. Here, we provide a brief overview of the neuroimaging results from this literature over the past several decades.

The effect of physical activity on hippocampal volume has been extensively studied. This is partly related to the hippocampal-centric nature of the animal work on this topic and because the human hippocampus is particularly susceptible to both normal and pathological aging processes. In normal aging, for example, hippocampal gray matter volume declines at a rate of ~1% per year beginning in midlife, a faster rate than many other brain regions (Raz et al. 2005). Further, deterioration of the hippocampus precedes and leads to episodic memory decline in older adulthood (den Heijer et al. 2006, 2010), and accelerated hippocampal atrophy predicts conversion to MCI and dementia. These findings suggest that the structural integrity of the hippocampus may be an important biomarker for the trajectory of cognitive aging, at least in the context of relational and episodic memory performance.

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However, focus on the average age-related trajectories of regional brain volume change masks the marked individual variability observed in the rates of change (Raz et al. 2005). Largely mirroring the individual variation in cognitive function described above, it is clear that some individuals show more precipitous changes in regional brain volumes while others show minimal changes over time. Similar to cognitive performance, this heterogeneity in regional brain volumes can also be partly explained by engagement in physical activity and variation in cardiorespiratory fitness. Indeed, higher cardiorespiratory fitness levels and greater amounts of physical activity are consistently associated with larger hippocampal volumes in both cognitively normal older adults (e.g., Cole et al. 2020, Erickson et al. 2009) and aging populations at high risk for cognitive decline (Dougherty et al. 2017, Okonkwo et al. 2014). A meta-analysis of randomized clinical trials examining the effects of exercise on hippocampal volume found a modest yet significant net positive effect, and this effect was strongest in studies of adults 65 years or older (Wilckens et al. 2021).

Although the focus of the human volumetry work has largely been on the hippocampus, the volume of other brain regions, such as the PFC, has also been associated with cardiorespiratory fitness and physical activity (Erickson et al. 2014b). Metrics of brain volume, such as cortical thickness, also change following exercise interventions (Chen et al. 2020). However, the effects of exercise on volume of other brain regions are less consistent (and less often studied) than those reported in the hippocampus and PFC, and thus they require further research to more firmly establish.

Measures of brain function are also affected by participation in exercise. The bulk of the evidence can be separated into two categories: studies of resting-state connectivity and those of task-evoked activation. Resting-state connectivity within large-scale brain networks [e.g., the default mode network (DMN)] typically weakens with age (Damoiseaux et al. 2008), and the connectivity between distinct resting-state networks becomes dedifferentiated, suggesting that these networks become less specialized, and less efficient, in aging (Zonneveld et al. 2019). Supporting this interpretation, patterns of resting-state connectivity have been associated with worse cognitive performance on age-sensitive measures, such as episodic memory, in older adults (Zonneveld et al. 2019). Fortunately, higher cardiorespiratory fitness is associated with stronger connectivity within the DMN and better cognitive function (Voss et al. 2010a). Connectivity within large-scale brain networks, including the DMN, also increases following exercise interventions (Burdette et al. 2010, Voss et al. 2010b). Intervention-induced increases in connectivity were also associated with better cognitive performance in these studies, suggesting that exercise interventions can preserve and promote cognitive functioning in aging adults, via effects on the intrinsic connectivity between brain regions.

Task-evoked activation studies in aging populations have often reported that older adults show greater activation in task-related brain regions compared to younger adults to support the same level of performance (Cabeza et al. 2004). In comparison to resting-state connectivity, the effects of physical activity on task-evoked brain activation have been less often examined, particularly in the context of randomized exercise interventions in older adults (Chen et al. 2020). Of the handful of existing interventions examining task-evoked activation, virtually all have reported task-evoked activation changes in the exercise group following the intervention. However, there is inconsistency as to the direction of these activation changes compared to the control group, with some reporting decreased activation (Nocera et al. 2017) and others reporting increased activation (Wu et al. 2018). Sometimes the direction of intervention-induced activation changes differs across brain regions within the same study. For example, Colcombe and colleagues (2004) reported increased activation in several frontal and parietal brain regions during a modified flanker task but decreases in anterior cingulate cortex activation in the exercise compared to the control group.

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While exercise training has led to better cognitive performance in all of the studies summarized above, the pattern of brain activation changes supporting such improvements differs across studies. It is likely that the effects of exercise on task-evoked activation vary by cognitive task (and perhaps the degree of difficulty). One major limitation in interpreting these results is that increased task-evoked activation is often interpreted as evidence that exercise increases the brain's capacity for compensation, while decreases in activation are often interpreted as evidence for improved brain efficiency. Thus, the interpretations of results always favor the exercise group. Without anchoring differences in brain activity to behavioral outcomes, it is difficult to determine the importance and relevance of the activation patterns to age-related cognitive performance.

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8.3. Amyloid Mechanisms

As described above, physical activity reduces risk for dementia and could act as a therapeutic strategy to improve cognitive symptoms in adults diagnosed with dementia. One possible mechanism for these benefits is that physical activity modifies either the accumulation or clearance of Aβ, the protein that comprises the neurotoxic plaques that are a hallmark pathology of Alzheimer's disease. Evidence from animal models of Alzheimer's disease suggests that physical activity reduces the accumulation of Aβ (Khodadadi et al. 2018, Koo et al. 2017). The effect of physical activity on Aβ deposition appears to be dose dependent and may operate through the upregulation of proteins involved in clearance of Aβ (Di Loreto et al. 2014, Moore et al. 2016) and reduction of systemic inflammation (Nichol et al. 2008). Importantly, physical activity–induced reductions of Aβ mediate improvements in cognitive functioning in aged animals (Di Loreto et al. 2014, Moore et al. 2016, Nichol et al. 2008).

Research in humans has been less conclusive regarding the effect of physical activity on Aβ. Several cross-sectional studies have documented an inverse association between physical activity and Aβ among cognitively healthy mid- and late-life adults (Brown et al. 2013, 2017), those at high genetic risk for AD who remain asymptomatic (Brown et al. 2017, Law et al. 2020), and individuals with MCI (Baker et al. 2010). Physical activity moderates the impact of the *APOE* ε4 genotype on Aβ deposition (Head et al. 2012). Further, a prospective observational study found that the cognitive benefits of physical activity are mediated by reductions in Aβ (Stillman et al. 2017a). However, other studies have failed to find an association between physical activity and Aβ (Daniele et al. 2018). Given the discrepant findings in humans, additional research from randomized clinical trials is necessary to determine whether exercise slows the progression of cognitive decline by altering the accumulation and clearance of Aβ pathology (Brown et al. 2019).

8.4. Cardiovascular and Cardiometabolic Health

Could exercise-induced modifications to cardiovascular and metabolic health mediate the exercise-induced improvements to neurocognitive function? The bulk of evidence suggests that physical activity has beneficial effects on a range of proximal mediators and markers of cardiovascular disease risk. These include blood pressure, cardiac autonomic control, systemic inflammation, glucose regulation, adiposity, and lipid levels. For example, several meta-analyses of randomized clinical trials of exercise have demonstrated significant improvements in blood pressure (Cornelissen & Smart 2013, Whelton et al. 2002). Just as physical activity promotes angiogenesis in the brain, physical activity stimulates the proliferation and growth of endothelial cells in the periphery, increasing the density and diameter of vasculature (Winzer et al. 2018). Thus, it seems a natural and intuitive hypothesis that exercise-induced improvements in blood pressure and cardiovascular health partly mediate the cognitive benefits elicited by engaging in

exercise behaviors. Yet, despite its intuitive appeal, there have been surprisingly few studies that have provided convincing evidence for this (Guadagni et al. 2020). However, in this instance it would be useful to remember that the absence of evidence is not evidence of absence; that is, the dearth of supporting data by itself does not nullify the hypothesis. Because of the sledgehammer effect described above, it remains highly likely that exercise-induced improvements in blood pressure or other markers of cardiovascular health partly mediate the cognitive benefits of exercise but that the sensitivity and specificity of the cardiovascular and cognitive measurements, population studied, and parameters of exercise prescription influence the associations.

In addition to blood pressure, there has been speculation that physical activity might benefit brain function through its effects on body composition. Physical activity may initiate cellular and metabolic changes that promote improvements in brain health outcomes independently of the degree of weight loss achieved. For example, a 12-month randomized clinical trial demonstrated that participants engaging in greater amounts of exercise exhibited greater improvements in reward-related decision-making compared to dietary restriction only and dietary restriction plus moderate exercise groups (Peven et al. 2020). Together, these findings indicate that physical activity may attenuate the negative effects of obesity on brain health by modifying adipocyte metabolism, an effect that may be independent of or in addition to physical activity–induced weight loss.

Physical activity also improves glucose and insulin regulation, among both healthy individuals and those who are diagnosed with T2D. A meta-analysis of randomized clinical trials of aerobic exercise demonstrated that increasing physical activity reduced circulating glucose levels and improved HbA1c, a marker of glucose regulation, with effects being most pronounced among individuals with prediabetes or T2D (Boniol et al. 2017). Engagement in physical activity improves insulin sensitivity throughout the body, including in the brain (Bird & Hawley 2016). Indeed, insulin receptors are distributed throughout the brain, and central action of insulin appears to be involved in the regulation of peripheral metabolism as well as neuronal maintenance and neurogenesis (Kleinridders et al. 2014). Further, the observed benefits of physical activity on cognitive function may be mediated by improvements in insulin and glucose regulation (Zhao et al. 2018). However, relatively few studies examining the effect of physical activity on brain health outcomes have explored whether these effects are dependent upon changes in insulin or glucose regulation.

Inflammatory pathways have also been implicated in neurocognitive aging (Oberlin et al. 2021), and these pathways are modulated by physical activity. Several cross-sectional studies have demonstrated that physical activity (Draganidis et al. 2018, Nilsson et al. 2018) is associated with lower levels of proinflammatory molecules, even when accounting for other factors known to promote inflammation such as adiposity (Hamer et al. 2012, Vella et al. 2017). Similar effects of physical activity have been observed in prospective longitudinal studies, with higher physical activity being related to lower concentrations of inflammatory markers years later (Braskie et al. 2014, Hamer et al. 2012, Martinez-Gomez et al. 2019). As further evidence that physical activity is causally related to improved immune profiles, data from several randomized clinical trials have demonstrated that circulating levels of proinflammatory molecules decline among individuals randomized to exercise conditions (Sardeli et al. 2018). Although there is some evidence that exercise-induced reductions in inflammation may mediate maintenance of brain health (Shih et al. 2019), other studies have not observed this (van Vulpen et al. 2018).

It is also important to keep in mind one of the tenets of health neuroscience—that there are reciprocal relationships between the body and brain. Hence, conceptualizing the relationship between cardiovascular and metabolic health and brain health as unidirectional is likely naïve and unrealistic. It is likely that exercise has a direct and immediate impact on gene expression and brain processes that in turn influence peripheral physiological functions, including markers of

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cardiovascular and metabolic risk. There are solid theoretical reasons for this hypothesis because many of the same brain regions affected by exercise, including the hippocampus, PFC, anterior cingulate cortex, and insula, are also involved in regulating visceral control. For example, the hippocampus, a region described above that is involved in supporting episodic memory function and is responsive to exercise, also plays a role in regulating neuroendocrine (glucocorticoid) and autonomic nervous system functions that are implicated in cardiovascular disease risk (McEwen & Gianaros 2011). In one study, Bar et al. (2016) found that a 6-week exercise regimen altered resting connectivity between the anterior hippocampus and the dorsal vagal complex, which in turn was associated with increases in vagal modulation as measured by changes in heart rate variability. This suggests that exercise-induced changes in the hippocampus might be involved in mediating exercise-induced changes in autonomic cardiac control. In sum, instead of conceptualizing the brain as a passive receptacle for peripheral physiological functions, we should also consider the possibility that exercise could influence peripheral physiological functions and cardiovascular disease risk by inducing molecular cascades that initiate in the brain.

9. CONCLUDING REMARKS

For decades the field of cognitive aging has focused on factors related to decline in cognitive function. Research into individual differences in the trajectory of decline, conceptual models of cognitive reserve, plasticity, and reversibility has provided hope for identifying demographic or modifiable lifestyle factors that could indicate ways of intervening and altering the trajectory of neurocognitive decline. Physical activity has become one of the most promising modifiable behaviors as it explains individual variation in cognitive performance, and randomized clinical trials demonstrate causal links between moderate-intensity exercise and improvements in cognitive and brain outcomes in late life.

The scientific literature examining individual differences has irrefutably demonstrated that cardiovascular and metabolic markers are associated with an increased risk of cognitive decline. Yet, risks for age-related cognitive decline might also be influenced by early life experiences. In fact, many of the health, cognitive, mood, and neural processes affected by early life adversity are the same ones that are positively affected by engaging in physical activity. In addition, although there are clear genetic risk factors for cognitive impairment, several studies have indicated that engaging in a physically active lifestyle might mitigate those genetic risks. Overall, the main message from this avenue of thought is that even under conditions in which there is a sense of little to no personal control (e.g., genetic risks or early life adversity), engaging in physical activity and other health behaviors is likely to substantially improve health outcomes and mitigate the risks associated with genetic polymorphisms or early life adversities.

What can we conclude from this review, and what comes next? First, as described in the preceding sections, we can conclude that physical activity unequivocally affects brain health outcomes. We make the argument here that this conclusion influences perceptions of cognitive aging—instead of conceptualizing cognitive aging as an immutable and progressive slope downward, the evidence from physical activity studies indicates that the brain remains more malleable in late life than what has been previously believed. In other words, the aging brain retains some of its natural capacity for plasticity, and physical activity may be able to take advantage of this property of the brain. Second, despite this confident assertion, there are many qualifying factors including the concepts, theories, and measurement of moderators and mediators of physical activity, the principles and parameters of exercise that are needed to optimize its benefits, and understanding ways of better promoting adoption of physical activity.

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Why is exercise or physical activity not more commonly adopted by scientists and health practitioners? There are at least four main reasons scientists and public health officials show reluctance in emphasizing physical activity for targeting neurocognitive health. First, physical activity is often described as a nonpharmacological intervention. This unfortunate terminology is negating rather than defining (i.e., it attempts to describe what physical activity is not rather than what it is) and carries with it a connotation that the molecular and cellular mechanisms of the effects are either enigmatic or surreptitious. As such, this terminology might diminish perspectives about the robustness and effectiveness of physical activity. We argue that physical activity (and several other health behaviors) should be considered a vehicle for modifying the endogenous pharmacology in contrast to medications that are inherently an exogenous method of pharmacology. Thus, altering the messaging and terminology around physical activity might influence the perceptions of exercise as medicine. Second, health and exercise neuroscientists continue to fight a battle that hinges on a perception that the best way of exercising the brain is through intellectual pursuits. In fact, there are common stereotypes that physical activity takes time away from engaging in scholarly activities. Educational policies that attempt to remove physical education and recess activities from the school curriculum in order to give more time to traditional academics (e.g., mathematics) perpetuate this stereotype despite evidence to the contrary—that academic achievement scores are often higher in schools that retain physical education classes (Hillman et al. 2008). Third, some arguments are dismissive of physical activity because of the claim that long-term adherence is poor. We contend that this argument conflates two separate issues, with one pertaining to the effectiveness of physical activity to modify brain health and the other pertaining to the promotion of adherence and behavior change. Most interventions, including pharmaceutical treatments, are plagued by poor adherence to treatment. Improving adherence is certainly a challenge to overcome, but poor adherence does not nullify the effectiveness of the treatment or the goal of prescription. Finally, a common argument is that the scientific literature about the effects of physical activity on brain health outcomes is too muddy with insufficient consensus about its possible positive effects. This argument has at its foundation a philosophical issue about the amount, consistency, and robustness of the data necessary for a consensus to be reached (and who composes the consensus body is another question). We have described in preceding sections that the overall claim about physical activity and cognition is irrefutable, and instead the more important questions are to unravel the issues around factors that moderate the effects.

Exercise is not a magic bullet cure for all cognitive aging ailments, but it is one of the most promising, highly accessible, cost-effective, and scalable approaches identified to date for preventing and treating cognitive decline. Yet, the lack of dose-response information greatly prohibits widespread prescription of physical activity for attenuating cognitive decline. As an analogy, imagine the creation of a medication developed to prevent or treat neurocognitive aging but neither physicians nor patients knew how much to prescribe, for how long or how frequently it should be taken, the mechanisms by which it works, whether it would work equally well for all patients, or in what form the medication should be taken. This is precisely the absurd scenario in which we currently find the field of exercise. Without answers to many critical questions, we will be unable to provide accurate or useful prescriptive information, leaving the potentially profound brain health benefits untapped.

In summary, what we have learned from the impact of physical activity on cognitive aging provides a hopeful perspective about the potential for maintaining higher levels of cognitive function well into late adulthood. Although cognitive decline might be a ubiquitous and some may argue inevitable consequence of aging, there is evidence that the rate and magnitude of decline might be manageable through health behaviors such as physical activity.

SUMMARY POINTS

1. The field of cognitive aging has progressed beyond an emphasis on decline and instead is focusing on factors that explain individual variability in cognitive performance, identifying mechanisms that lead to variation in cognitive aging, and examining ways of intervening to improve cognition or prevent decline.
2. Cardiovascular and metabolic health explain significant individual variation in the trajectory of cognitive aging.
3. Physical activity unequivocally affects cognitive and brain outcomes, and this influences perceptions of cognitive aging; that is, the rate and magnitude of decline might be manageable by engaging in health behaviors such as physical activity.
4. The magnitude of exercise-induced cognitive benefits is likely influenced by sample size, approach to statistical analyses, and study quality; duration and intensity of the exercise; sex, age, and other baseline lifestyle factors; early life exposures; cardiovascular and metabolic health conditions; and genetics.

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