CHAPTER

10

Exercise, Cognition, and Health

Kirk I. Erickson[1] *and Teresa Liu-Ambrose*[2]

[1]Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA [2]Department of Physical Therapy, University of British Columbia, Vancouver, BC, Canada

OUTLINE

INTRODUCTION

The expected increase over the next several decades in the proportion of adults over the age of 65 may lead to a concomitant increase in the proportion of age-related diseases and disorders, including age-related cognitive decline, Alzheimer's disease (AD), and other types of dementia (Association, 2010). Age-related cognitive decline is relatively ubiquitous and may precede frank cognitive impairment and dementia later in life. In fact, brain pathology and brain atrophy are thought to precede the onset of age-related cognitive decline by several decades,

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indicating a growing need to identify factors earlier in life that either precipitate the onset of cognitive decline or protect against decline (Jack & Holtzman, 2013). Lending support to this idea, individual variability in both the extent and rate of decline in episodic memory, processing speed, and executive function suggests the presence of factors that influence the trajectory of cognitive losses (Salthouse, 2010). These results suggest some promising hypotheses that age-related cognitive decline may not be inevitable and that if the factors contributing to individual variation in cognitive decline could be identified we may be able to more effectively test interventions to prevent, delay, or even reverse accumulated losses (Erickson, Gildengers, & Butters, 2013).

Over the past several decades there has been an increase in the number of non-pharmaceutical products marketed as tools to potentially mitigate cognitive losses and dementia in late life. Some of these products, such as nutraceuticals and cognitive training video games, have become a major source of revenue for some organizations but are currently based on rather equivocal empirical support. Health behaviors, such as regular participation in physical activity, have also garnered attention as promising methods of reducing the risk for cognitive impairment and will be discussed in depth in this chapter.

One basic premise of this literature is that the brain, including its molecular, cellular, and structural architecture, retains the capacity to change in a favorable way in late adulthood. This premise is not as self-evident as is sometimes assumed. For example, an argument has long been made, with plentiful support from animal research, that the brain loses some of its capacity for plasticity with increasing age (Kolb & Teskey, 2012). Although animal research has not argued for a complete absence of brain plasticity in late life, a diminished capacity for plasticity may suggest that physical activity or cognitive training interventions could have limited effects in altering cognitive and brain outcomes in late adulthood. As will be seen in this chapter, it appears that the brain retains a natural capacity for plasticity in late adulthood and that physical activity has the capacity to take advantage of this natural characteristic of the brain.

Despite the many unanswered questions in this field, and the need for much more research to be conducted, we will conclude that there is considerable promise for non-pharmaceutical approaches that focus on health behaviors, and in particular physical activity, to positively influence neurocognitive function in late adulthood. We have organized this chapter by first defining important terminology and then describing epidemiological and observational results. We then discuss recent interventions and brain imaging studies that attempt to determine the neural correlates of cognitive improvements resulting from physical activity and finish by discussing the potential molecular mechanisms, other health behaviors, and take-home messages of this line of research.

DEFINITIONS

Before proceeding to a discussion of research findings it is important to first define the terminology that will be used throughout this chapter. First, the term "physical activity" is a general term often referring to any activity that may be aerobic or non-aerobic in nature and independent of the type, dose, or frequency of the activity. This may include moderate-to-vigorous forms of structured aerobic activities such as brisk walking, tennis, or swimming and hobbies such as gardening, carpentry, or dancing (Caspersen, Powell, & Christenson, 1985). Physical activity has historically been measured in cross-sectional and observational studies of cognitive aging by self-report questionnaires that ask participants to report their levels of physical activity by questions such as "On average, how many city blocks do you walk

per day" (Erickson et al., 2010). The strength of these approaches is that self-report questionnaires can be easily administered in studies with large sample sizes and do not take much time to score, but their weaknesses are that they may be prone to both social desirability biases and may not reliably capture non-structured activity throughout the day (Erickson, Weinstein, & Lopez, 2012). More recent studies have begun to successfully employ objective measures of physical activity using monitoring devices, such as accelerometers and pedometers (Gow et al., 2012). These studies tend to demonstrate a greater magnitude of benefit of physical activity on cognitive and brain outcomes than studies using self-report questionnaires (Middleton et al., 2011).

Participation in physical activity influences physical fitness, such as cardiovascular endurance, muscle strength, muscle endurance, flexibility, and body composition. One measure of cardiovascular endurance is maximal oxygen capacity (VO_{2max}) and it is often used to assess the efficacy of interventions to improve cardiovascular fitness. That is, aerobic exercise interventions in which participants are randomized to a condition that receives a structured form of aerobic exercise (i.e., brisk walking) or to a more non-aerobic control condition (i.e., stretching), often use VO_{2max} to test whether the intervention effectively improved cardiovascular endurance. Most randomized exercise interventions examining neurocognitive outcomes have used aerobic forms of activity such as brisk walking with older adults, but more non-aerobic forms of activity such as resistance training have also been conducted and will be described in this chapter. Resistance training studies often incorporate measures of muscular strength (e.g., 1-repetition maximum), power, or endurance. In sum, the term "physical activity" is general and includes many forms of exercise such as strength training or aerobic exercise while VO_{2max} is a measure of aerobic capacity that is modifiable by participation in aerobic activities.

EPIDEMIOLOGICAL STUDIES

Epidemiological studies are observational in nature and examine whether engagement in physical activity is associated with longitudinal changes in cognitive function or risk for dementia. With few exceptions, these studies have found that physical activity is associated with reduced cognitive decline and a lower incidence of dementia. For example, in a study by Larson et al. (2006) 1740 men and women over the age of 65 without cognitive impairment reported the number of times per week that they performed different physical activities for at least 15 min over the past year. After a follow-up period of 6.2 years, the incidence rate of AD was significantly higher for individuals that engaged in physical activity fewer than three times per week (19.7 per 1000 person years) as compared to those who engaged in physical activity more than three times per week (13.0 per 1000 person years). In another study, Podewils et al. (2005) reported that over a course of 5.4 years in 3375 men and women over 65 years of age, greater engagement in self-reported physical activity was associated with a reduced risk of AD. Retrospective studies have also found that self-reported physical activity during early to midlife is associated with a reduced risk of dementia (Dik, Deeg, Visser, & Jonker, 2003; Middleton, Barnes, Lui, & Yaffe, 2010; Rovio et al., 2005) and mild cognitive impairment (MCI) (Grande et al., 2014). Meta-analyses of prospective studies have confirmed these associations. For example, in a meta-analysis of 15 prospective longitudinal studies including more than 33,000 participants that were followed for 1–12 years, greater engagement in physical activity was associated with nearly a 40% reduced risk for cognitive decline (Sofi et al., 2011). In sum, these studies and many others (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) make a convincing case that greater engagement in physical activity is associated with a reduced risk of cognitive decline and AD. In fact, Barnes

and Yaffe (2011) suggest that physical activity may be the single most important modifiable risk factor for dementia in the United States.

Several recent studies have begun to use objective measures of physical activity and fitness in relation to risk for AD, and suggest that these instruments may be more sensitive to physical activity patterns throughout the day and less susceptible to biases associated with self-reports. For example, Barnes, Yaffe, Satariano, and Tager (2003) examined self-report measures of physical activity in addition to objective measures of cardiorespiratory fitness (VO_{2max}) in a 6-year study of 349 individuals over the age of 55. They found that only objective fitness measures were significantly associated with reduced cognitive decline. In another study, Buchman et al. (2012) reported that greater total daily physical activity as assessed by 10 days of continuously monitored actigraphy was associated with a twofold reduced risk of AD over a 4-year period in 716 older adults, even after controlling for self-reported physical activity. Indeed, correlations between self-reported physical activity and objective physical activity levels are often relatively low (Westerterp, 2009), which might explain why larger samples are often necessary to detect associations using self-report measures of activity while smaller samples are sufficient for detecting associations with objective measures.

Overall, the epidemiological literature has provided convincing evidence that engaging in physical activity is involved in the risk for AD, however these studies have many limitations including the use of a wide range of physical activity measures, inconsistent use of more comprehensive cognitive batteries, and the key challenge of interpreting the causal directions between physical activity and risk for AD. For example, it is possible that those individuals experiencing subtle losses in cognitive function may choose to avoid engagement in physical activity or that loss in physical functions is a prodromal marker for cognitive decline and dementia-related pathology. Randomized interventions in which physical activity is systematically increased for a period of several months is more capable of addressing this issue.

Physical Activity and Fitness Associations with Cognition

The examination of fitness, physical activity, and cognition dates back to the 1970s when Spirduso and Clifford (1978) found that older adult athletes performed significantly better on a series of simple reaction time and choice reaction time tasks compared to their sedentary counterparts and performed similarly to that of younger (18–25-year-old) adults. The association between higher fitness levels, greater amounts of physical activity, and superior cognitive performance has now been replicated in dozens of studies (Bunce, Barrowclough, & Morris, 1996) and meta-analyses of cross-sectional studies have demonstrated that engaging in physical activity or having higher fitness levels is associated with significantly better cognitive performance (Etnier, Nowell, Landers, & Sibley, 2006).

Randomized Trials of Aerobic Exercise on Cognition

Although cross-sectional studies have conclusively shown associations between physical activity, fitness, and cognitive function, these studies are naturally limited in their ability to make causal inferences about participation in physical activity and cognitive outcomes. Thus, the positive associations described in the cross-sectional literature could reflect an inherent difference between higher fit and lower fit adults in response styles, personality, genetic, or other biological or psychosocial factors. In other words, cross-sectional studies are potentially confounded by unmeasured third variables that

covary with a propensity to engage in physical activity or to have higher fitness levels. To partially circumvent this issue, randomized controlled trials have been conducted that assign individuals to one of two conditions: (i) a treatment condition that receives moderate-intensity physical activity such as brisk walking or resistance training, or (ii) a control condition that receives light stretching or educational course materials. For example, in one intervention, Dustman et al. (1984) randomized 43 sedentary, but cognitively healthy, older adults to one of three groups for a 4-month period: an aerobic training group that received three 1-h walking and slow jogging sessions per week, a control group that received light strength and flexibility exercises, and a non-exercise control group. They found that the aerobic exercise condition showed improvements on measures of memory, processing speed, and inhibitory control while each of the control groups did not improve on any of these measures. Similar effects were found in a sample of 124 cognitively healthy, but low-fit older adults that were randomized to 6 months of either a brisk walking condition or to a stretching-and-toning control condition (Kramer et al., 1999). They found that the exercise group, compared with the control group, demonstrated improvements on measures that were more executive in nature including task-switching, response compatibility, and stopping tasks, while tasks and conditions less executive in nature did not show the same benefits from the exercise treatment.

The results from Kramer et al. (1999) suggested a degree of domain specificity with exercise such that executive functions may be affected more than other cognitive domains. This hypothesis was tested in a meta-analysis of 18 randomized exercise interventions that included both treatment and control groups (Colcombe & Kramer, 2003). The results suggested that the effects of exercise on cognitive function were both general and specific; general in the sense that nearly all cognitive domains improved after exercise, but specific in the sense that executive functions were affected more than other cognitive domains. Results from other meta-analyses of exercise interventions have shown relatively consistent patterns (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Hindin & Zelinski, 2012; Smith et al., 2010), but also suggest that the positive effects of exercise might be moderated by age such that older adults benefit more than younger participants (Etnier et al., 2006; Smith et al., 2010).

Resistance Training on Cognition

Although resistance, or strength, training has a broad range of systemic benefits (Borst, 2004; Layne & Nelson, 1999), very few studies to date have focused on the role of resistance training in promoting cognitive health. However, it is noteworthy that a meta-analysis (Colcombe & Kramer, 2003) of randomized controlled trials found that aerobic exercise programs that were combined with resistance training had a greater positive effect on cognitive function than aerobic exercise alone (effect size = 0.59 vs. 0.41, SE = 0.043, $P<0.05$). A key randomized controlled trial supporting the hypothesis that resistance training is beneficial for cognitive function was conducted by Cassilhas et al. (2007). They demonstrated that resistance training three times per week for 24 weeks significantly improved several measures of cognitive function among 62 community-dwelling senior men aged 65–75 years. Extending the work of Cassilhas and colleagues, Liu-Ambrose et al. (2010) found that resistance training improved selective attention and response inhibition in senior women. Specifically, 155 community-dwelling women participated in a 12-month trial that required them to engage in progressive resistance training either once or twice per week. Compared with a balance and tone control group, those in the resistance training groups performed significantly better on the Stroop Colour-Word Test at trial completion.

Effects of Exercise on Impaired Populations

These promising results from cognitively healthy older adults have prompted researchers to examine whether participation in exercise could enhance cognitive function in adults with MCI or dementia. For example, one study randomized 33 older adults with MCI to either an aerobic exercise group or to a stretching control group for 4 days per week for 6 months (Baker et al., 2010a). They found sex-specific effects such that the women in the study showed improvements in cognitive function after the intervention while the men showed only marginal improvements. In another study, 86 women with MCI were randomized to receive 2 days per week of aerobic exercise, resistance training, or a balance and toning control condition (Nagamatsu, Handy, Hsu, Voss, & Liu-Ambrose, 2012). They reported that both aerobic exercise and resistance training improved memory performance compared to the control condition. More specifically, aerobic exercise improved verbal learning memory while resistance training improved associative memory. However, only resistance training improved executive functions. These, and other studies (Lautenschlager et al., 2008), suggest that modest amounts of exercise may be an effective and low-cost method of improving cognitive function in individuals with MCI or the early stages of dementia.

Cross-Sectional Associations Between Physical Activity and Gray Matter Volume

Since 2003 there has been a dramatic rise in the number of studies using neuroimaging methods to examine whether engaging in physical activity influences the integrity of the human brain—either in terms of volume, morphology, white matter tracts, or functional outcomes. As will be described below, these studies using magnetic resonance imaging (MRI) or positron emission tomography (PET), have provided persuasive evidence that the brain retains some degree of plasticity in late adulthood and that only modest amounts of physical activity are necessary to promote a healthy brain.

One way to examine brain integrity is through assessments of gray matter volume. Unfortunately, the brain atrophies in late adulthood, and does so non-uniformly, with the prefrontal cortex, caudate nucleus, and medial temporal lobes showing the most precipitous losses. In a study to test whether higher cardiorespiratory fitness levels would be associated with greater gray matter volume, Colcombe et al. (2003) recruited 55 cognitively healthy older adults between 55 and 79 years of age and used a semi-automated method of calculating regional gray matter volume throughout the brain. As predicted, older age was associated with reduced gray matter volume in the prefrontal cortex and medial temporal lobes, but higher cardiorespiratory fitness levels attenuated the age-related decline in gray matter volume in these same regions. Thus, these results suggested some regional specificity to the effects of fitness on the brain: those regions largely supporting higher-level cognitive functions and executive functions were more strongly associated with fitness than other regions.

In another cross-sectional study, Weinstein et al. (2012) examined gray matter volume as a function of cardiorespiratory fitness levels in 139 cognitively healthy older adults and found that higher fitness levels were associated with greater gray matter volume in the prefrontal and anterior cingulate cortex and that greater gray matter volume was associated with better performance on several different cognitive outcomes including attentional control and memory processes. In fact, this finding has now been replicated in studies across the lifespan (Chaddock, Erickson, Prakash, Kim et al., 2010; Chaddock, Erickson, Prakash VanPatter, et al., 2010; Chaddock, Pontifex, Hillman, & Kramer, 2011; Chaddock et al., 2012).

Consistent with cardiorespiratory fitness results, Floel et al. (2010) used self-reported measures of physical activity in 75 cognitively healthy older adults and found that greater engagement in physical activity was associated with greater volume of the prefrontal cortex even in those with low amounts of physical activity (also see Gow et al., 2012) indicating that only modest amounts of physical activity may be sufficient for altering gray matter volume. The links with cognitive performance suggest that greater volume is not simply a meaningless by-product of higher fitness and physical activity levels but contributes to elevated cognitive function in late adulthood.

In addition to the prefrontal cortex, several studies have examined associations with the volume of the hippocampus, a region that plays a critical role in memory formation and predicts conversion to AD. For example, Erickson et al. (2009) examined cardiorespiratory fitness levels in 165 cognitively healthy adults and found that higher fitness levels were associated with greater hippocampal volumes and that larger hippocampi were associated with better spatial memory performance. In addition, Bugg, Shah, Villareal, and Head (2012) and Szabo et al. (2011) have reported that higher fitness levels are associated with larger hippocampal volumes and better executive function and reduced rates of forgetting in cognitively healthy older adults. Overall, these results provide provocative evidence that there are positive associations between hippocampal volume and physical activity habits or fitness levels.

Randomized Trials of Exercise on Gray Matter Volume

The results from the cross-sectional neuroimaging studies described above are compelling, but are limited in their capability to make causal inferences about physical activity and brain volume. To circumvent these challenges in interpretation, Colcombe et al. (2006) conducted a randomized clinical trial in 59 cognitively healthy older adults and found that 6 months of participation in moderate-intensity exercise 3 days per week resulted in an increase in gray matter volume in the prefrontal and anterior cingulate cortex compared to a stretching-toning control group. There is also evidence for plasticity of the hippocampus with exercise. For example, Erickson et al. (2011) randomized 120 cognitively healthy older adults to either a brisk walking exercise group or to a stretching-toning control group for 12 months. They found that the brisk walking condition increased the size of the hippocampus while the stretching control group showed a decline over the same period.

Associations Between Physical Activity, Fitness, and White Matter Integrity

White matter integrity also declines in late adulthood and has been linked to slower processing speed and poorer executive function. Fortunately, several studies have examined if physical activity is associated with elevated white matter integrity in late life. In one study, Tseng et al. (2013) using diffusion tensor imaging (DTI) examined white matter integrity in ten older adult athletes compared to ten sedentary controls. They found that the older adult athletes had greater white matter integrity and fewer white matter lesions compared to their sedentary peers. Similar effects were found when examining cardiorespiratory fitness levels in a sample of 26 cognitively healthy older adults (Johnson, Kim, Clasey, Bailey, & Gold, 2012) (also see Marks et al., 2007) and when using self-reported levels of physical activity. For example, in 276 older adults, Tian et al. (2014) found that greater self-reported physical activity levels were associated with greater white matter integrity in the medial temporal lobes and cingulate cortex. Although few randomized trials have as of yet examined effects of increasing physical activity on white matter

integrity, one randomized intervention of 70 cognitively healthy older adults found negligible group-wise effects of the intervention on white matter integrity, but found that those individuals showing a greater change in aerobic fitness levels from the aerobic exercise intervention showed an increase in white matter integrity after the completion of the intervention (Voss, Heo et al., 2013). These results are consistent with those reported for gray matter volume, but since there has only been one randomized intervention examining white matter integrity, it remains difficult to draw causal conclusions about whether an exercise intervention influences this tissue property.

Aerobic Exercise Effects on Functional MRI Patterns

In addition to volumetric studies, several functional MRI studies have examined whether exercise changes the dynamics of brain function. For example, Colcombe et al. (2004) found in cognitively healthy older adults that higher cardiorespiratory fitness levels were associated with greater brain activation during an attentionally demanding task in the prefrontal and parietal cortices and reduced activation in the anterior cingulate cortex. Similar effects were found in older adults randomized to receive either an exercise brisk walking condition compared to those randomized to a stretching-toning condition (Colcombe et al., 2004). Other functional MRI studies have found similar associations such that greater prefrontal cortex activation is associated with higher fitness levels (Prakash et al., 2011; Vidoni et al., 2013) or that maintenance of physical activity after the completion of an intervention resulted in greater prefrontal cortex activation (Rosano et al., 2010). Greater amounts of self-reported physical activity have also been associated with increased activity in the prefrontal cortex compared to sedentary peers (Smith, Nielson, Woodard, Seidenberg, Verber et al., 2011) and a 12-week randomized exercise intervention in individuals with MCI increased activation in the prefrontal cortex during a semantic memory task (Smith et al., 2013). In addition to task-evoked activation patterns, Voss et al. (2010) found that higher cardiorespiratory fitness levels were associated with greater functional connectivity in regions of the so-called default mode network, and these associations explained some of the link between cardiovascular fitness and cognitive function (also see Burdette et al., 2010).

Effects of Resistance Training on Cerebral Blood Flow and fMRI Patterns

In a cross-sectional study of 59 older adults, Xu et al. (2014) acquired MRI resting state cerebrovascular perfusion data. It is hypothesized that one mechanism by which physical activity maintains cognitive function in older adults is by augmenting cerebral perfusion. Xu et al. demonstrated that women who engaged in resistance training at least once per week exhibited greater cerebrovascular perfusion than women who did not. This interaction remained significant after controlling for other physical activity, demographics, and health variables.

In a 12-month randomized controlled trial of resistance training with 155 older women aged 65–75 years old, Liu-Ambrose, Nagamatsu, Voss, Khan, and Handy (2012) showed that twice-weekly resistance training increased neural activation in the anterior portion of the left middle temporal gyrus and the left anterior insula extending into lateral occipital frontal cortex. Among older women with MCI, Nagamatsu et al. (2012) demonstrated that twice-weekly resistance training improved associative memory performance (i.e., the ability to remember items that were previously presented simultaneously). In conjunction, regional

patterns of functional plasticity were found in the resistance training group. Specifically, three key regions in cortex showed greater functional activation during the associative memory task after 6 months of training—the right lingual gyrus, the right occipital-fusiform gyrus, and the right frontal pole.

Mediators and Moderators

Animal studies have been influential in our understanding of the molecular pathways that explain how exercise affects the brain. These studies have shown that exercise is capable of increasing the rate of angiogenesis, or the production of new capillary beds, in several brain areas including the cerebellum, striatum, and cortex (Voss, Vivar, Kramer, & van Praag, 2013). A greater number of capillary beds in the brain allows more nutrients and oxygen to enrich the tissue, thereby providing a healthier environment for existing cells. Exercise also increases the proliferation and survival of new neurons in the dentate gyrus of the hippocampus, which are involved in enhanced learning and memory associated with exercise (Erickson, Miller, & Roecklein, 2012). These cellular changes are likely occurring through a cascade of several different molecules including increased BDNF and IGF-1 expression, decreases in pro-inflammatory cytokines, and changes in several different neurotransmitter systems including dopamine and serotonin (Hillman, Erickson, & Kramer, 2008). Because of the limitations in studying these molecular pathways in human brain tissue, research has examined the extent to which blood-based changes in these molecules may be linked to improvements in either cognitive or brain function. For example, Erickson et al. (2011) found that increases in hippocampal volume after a 12-month aerobic exercise intervention were positively correlated with increased serum BDNF levels. Voss, Erickson et al. (2013) also reported that aerobic exercise-related changes in functional connectivity were correlated with increases in serum BDNF and IGF-1 levels while IGF-1 was associated with cognitive improvements after resistance training (Cassilhas et al., 2012). Exercise-induced changes in insulin sensitivity and pharmacokinetics may also play a role in mediating the improvements in cognitive performance (Baker et al., 2010b; Tarumi et al., 2013). Nonetheless, despite this promising research we still have a poor understanding in humans of how the different molecular pathways are related to brain and memory functions that improve with exercise and how the different molecular systems may differ between resistance and aerobic exercise (Cassilhas et al., 2012).

Exercise does not influence neurocognitive function equally for all people. That is, some individuals benefit more than others and understanding the factors that may be attenuating or magnifying the effects may encourage the development of tailored interventions. There is some evidence that exercise may be able to attenuate the genetic susceptibility associated with risk for dementia. For example, Smith, Nielson, Woodard, Seidenberg, Durgerian, et al. (2011) has shown that the positive effect of physical activity on functional MRI activation is moderated by the APOE genotype such that APOE ε4 carriers benefited more than non-carriers from physical activity. In support of this result, Head et al. (2012) using PET reported that APOE ε4 carriers showed reduced amyloid levels when they engaged in greater amounts of physical activity relative to APOE ε4 carriers that did not engage in physical activity. Although not all studies have shown the same effects (Podewils et al., 2005), there is growing evidence that genetic susceptibility for cognitive or brain decay may be an important moderator of physical activity with those carrying the risk allele demonstrating the greatest benefits of physical activity (Erickson, Banducci et al., 2013).

Other Health Factors Related to Cognition

In this chapter we have focused on the effects of physical activity and exercise as an important health behavior that influences cognitive and brain function in late adulthood. This emphasis on physical activity, however, does not mean that other health behaviors and health factors are not important in influencing cognitive and brain function in late adulthood. In fact, there is considerable evidence that high blood pressure is associated with both impaired cognitive function, an increase in white matter lesions, increased risk for dementia, and reduced gray matter volume (Bender & Raz, 2012; Goldstein, Bartzokis, Guthrie, & Shapiro, 2002; Kivipelto et al., 2001; Leritz et al., 2010; Tzourio, Dufouil, Ducimetiere, & Alperovitch, 1999; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). In fact, the association between high blood pressure and poorer cognitive function may be exacerbated by genetic susceptibility for dementia (de Leeuw et al., 2004; Peila et al., 2001; Zade et al., 2010), indicating moderating effects between genetic and health-related variables. Obesity is also an important health factor that has been found to increase the risk for dementia (Raji et al., 2010) and is related to impaired white matter integrity (Verstynen et al., 2013) throughout the brain and reduced activation in prefrontal brain circuits (McFadden, Cornier, Melanson, Bechtell, & Tregellas, 2013). Unfortunately there is limited evidence for weight loss interventions to have any lasting impact on cognitive performance in late life (Siervo et al., 2011).

Insulin resistance and leptin resistance are often both correlated with obesity and high blood pressure and both play an important role in cognitive function and brain health. Along these lines, more studies have been examining the impact of the metabolic syndrome (MetS) on cognitive function throughout the lifespan. MetS is a cluster of metabolic factors that increase risk for cardiovascular diseases and often includes the presence of Type II diabetes or insulin resistance. Using the MetS criteria, several studies have reported associations with both brain volume (Onyewuenyi, Muldoon, Christie, Erickson, & Gianaros, 2014) and impaired cognitive function (Yates, Sweat, Yau, Turchiano, & Convit, 2012) in mid to late life. These studies, and many others, have suggested an important role of cardiovascular and metabolic risk factors in cognitive and brain health and risk for dementia in late life. In fact, improvements in cardiovascular health may be an important pathway by which increased physical activity has long-term positive effects on the brain.

CONCLUSION

It is clear that cross-sectional research has shown that higher fitness levels and greater engagement in physical activity are almost uniformly associated with elevated cognitive function, greater prefrontal cortex and hippocampal volume, greater white matter integrity, increased prefrontal activation during challenging cognitive tasks, and increased resting state connectivity between the hippocampus and prefrontal cortex. Although there have been fewer randomized trials of exercise, those that have been conducted have supported the cross-sectional research and demonstrate that interventions are capable of improving cognitive function—especially executive and memory function, increasing gray matter volume, improving resting state connectivity, and increasing the efficiency of task-evoked activation. Finally, the cognitive and neuroimaging studies are supported by a large body of epidemiological studies that have clearly demonstrated that engaging in greater amounts of physical activity is associated with a reduced risk of experiencing cognitive decline or dementia. In short, epidemiological, cognitive, and neuroimaging studies have provided

a body of convincing research on the positive effects of exercise on brain health and function.

Despite these promising results there are several outstanding issues that have yet to be resolved. First, although there is growing evidence from cross-sectional and intervention research that both aerobic and resistance exercise influence brain and cognitive outcomes in MCI and dementia, more studies are needed to characterize and understand these effects. For example, we have a poor understanding of the potential for physical activity to act as a primary or secondary prevention of dementia or as a treatment for existing impairments. Along these lines, there is currently no evidence that an exercise intervention will have long-term consequences on slowing the incidence rates of dementia. Answers to these issues could have far-reaching public health implications for both dementia and other neurologic and psychiatric conditions.

There is also a paucity of research on the most appropriate dose of exercise, the frequency or duration, or the type of exercise most effective for enhancing memory and cognitive function. In addition, we still know very little about whether the exercise prescription would differ depending on the baseline cognitive status of the individual. Although most intervention studies have reported that 3 days per week is sufficient for detecting significant improvements in brain and cognitive outcomes, we have little evidence for whether greater frequencies or intensities of activity would be more beneficial or whether lower frequencies would show equivalent effects (Nagamatsu et al., 2012). Before physical activity can be widely prescribed as a method of improving cognitive function there is a need to identify the doses in which activity would prove to be most beneficial for the widest range of adults.

Finally, although we have a growing understanding of the possible mechanisms for how exercise influences the brain along with clear associations between other cardiovascular and cardiometabolic health factors and brain function, we have a poor understanding of the primary pathways involved and the ways in which cardiovascular, metabolic, and physical activity behaviors and predictors influence brain health and function together. Since these factors are correlated with one another, it will be important to determine the extent to which associations between obesity and brain health can be independently explained by physical inactivity, hypertension, or other cardiovascular risk variables.

In sum, we have highlighted some of the most recent and compelling research on physical activity and cognitive function and argue that this research demonstrates not only a hope that physical activity could be a promising method for improving brain function but that it also demonstrates a clear capacity for brain plasticity in late adulthood.

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