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Physical activity, fitness, and gray matter volume

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Abstract

In this review we explore the association between physical activity, cardiorespiratory fitness, and exercise on gray matter volume in older adults. We conclude that higher cardiorespiratory fitness levels are routinely associated with greater gray matter volume in the prefrontal cortex and hippocampus, and less consistently in other regions. We also conclude that physical activity is associated with greater gray matter volume in the same regions that are associated with cardiorespiratory fitness including the prefrontal cortex and hippocampus. Some heterogeneity in the literature may be explained by effect moderation by age, stress, or other factors. Finally, we report promising results from randomized exercise interventions that suggest that the volume of the hippocampus and prefrontal cortex remain pliable and responsive to moderate intensity exercise for 6-months to 1-year. Physical activity appears to be a propitious method for influencing gray matter volume in late adulthood, but additional well-controlled studies are necessary to inform public policies about the potential protective or therapeutic effects of exercise on brain volume.

Keywords

Exercise; Physical activity; Grey matter volume; Aging; Cognition

1. Introduction

Memory loss and brain atrophy are often considered hallmarks of aging. But, not all forms of memory are equally affected by age (Fleischman et al., 2004; Hedden and Gabrieli, 2004); likewise, not all brain regions show age-related atrophy (Fjell and Walhovd, 2010). In fact, age-related losses in gray matter volume occur non-uniformly with the prefrontal cortex, caudate nucleus, and medial temporal lobes demonstrating the most significant losses (Fjell et al., 2013; Raz et al., 2005; Tamnes et al., 2013). Age-related reductions in volume are thought to precede and lead to more severe memory loss and cognitive impairment, but

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there is considerable individual variation in the rate, extent, and regions showing gray matter atrophy in late adulthood (Fjell and Walhovd, 2010; Groves et al., 2012). This recognition of individual variation in volumetric loss has paved the way for research to examine “successful aging”, a term sometimes used to distinguish individuals that have shown less cognitive loss, or fewer markers of brain pathology or dysfunction (e.g., volume loss), than their age-matched counterparts (Thielke and Diehr, 2012). The hope has been to identify lifestyle, behavioral, genetic, and/or biological factors that distinguish “successful aging” from more precipitous losses in function, or “accelerated aging”. If such factors could be identified that distinguish “successful aging” from “accelerated aging”, then these factors may inform treatments and preventions that could reduce age-related brain atrophy and lessen the risk for cognitive impairment.

Physical activity has garnered significant attention in recent years as a potentially effective method for elevating cognitive function and improving brain health throughout the lifespan. Hence, a physically active lifestyle may increase the likelihood for “successful brain aging” and attenuate the likelihood for “accelerated brain aging.” In fact, several recent reviews have supported the claim that physical activity has a potent effect on brain health, with the caveat that there remains much yet to learn about the ways in which physical activity could be an effective prevention for brain volume losses or an effective treatment for losses that have already accrued (Brown et al., 2013; Erickson et al., 2013b; Erickson and Kramer, 2009; Erickson et al., 2012; Guiney and Machado, 2013; Hillman et al., 2008; Scherder et al., 2013; Voss et al., 2011). We begin this review with research that explores whether physical activity, fitness, and exercise are associated with gray matter morphology in late adulthood, and the potential implications of these findings. We finish this review with a discussion of future research directions that could help better understand the meaning and importance of volumetric associations with physical activity and exercise.

2. Definition of terms and techniques

Before we begin a discussion of whether cardiorespiratory fitness, physical activity, and exercise are related to gray matter morphology in late adulthood, it is prudent to first define how this field has conceptualized these terms and used them within the context of cognitive aging. First, the term “physical activity” is often used as a general term to refer to activities that may be either aerobic or non-aerobic in nature including bicycling, walking, gardening, dancing, swimming, and other activities or hobbies. Cross-sectional and prospective longitudinal studies of cognitive aging have often asked participants to report their levels of physical activity with questions such as “How many city blocks do you walk on an average day” and “On average, how many hours per day do you spend walking?” The strength of this approach is that self-reported physical activity questionnaires can be easily administered across multiple time points (e.g., prospectively) on large cohorts and capture a range of different activities from hobbies to structured exercise (e.g., tennis). Self-report questionnaires are a low-cost means to capture activity levels, especially for studies that require sampling thousands of participants to assess variation in disease incidence or prevalence (e.g., Alzheimer's disease). However, self-report questionnaires may be inaccurate in capturing the type, intensity, and duration of the reported activity. That is, social desirability biases may influence reporting patterns, artificially escalating physical

activity levels or, they may underestimate activity by not reliably capturing lower intensity activities (e.g., walking while shopping or fidgeting throughout the day). Along these lines, some participants may misremember or forget about certain activities, which is an important potential confounder when memory performance is the outcome of interest in studies of cognitive aging or dementia.

More recently, objective assessments of physical activity include the use of devices equipped with pedometry, accelerometry, and other tools to determine the intensity of physical activity (e.g., energy expenditure) and the duration of the activity, without asking participants to self-report their activities. These sophisticated products are becoming more prevalent as they are becoming less expensive for researchers and provide participants with almost immediate feedback regarding their activity levels. As such, these devices eliminate several of the weaknesses associated with self-reported activity. However, these products also have their own challenges such as non-compliance, changes in behavior due to simply wearing the device, and the challenge of accurately summarizing large pools of data collected over several days or weeks. Nonetheless, these devices are being widely used as an alternative method to self-reported physical activity (Buchman et al., 2012; Erickson et al., 2013a).

Although there are several ways of measuring physical activity, regular participation in physical activity influences physical fitness, which includes strength, balance, and aerobic capacity. Hence, measures of physical fitness are often used in studies of cognitive and brain aging as objective methods of assessing physical health and function. The most commonly used measure to assess cardiorespiratory fitness is a graded exercise test to determine VO_{2max} . Although considered to be an accurate and objective measure of aerobic fitness, VO_{2max} is sometimes difficult to administer to populations that have physical or cognitive limitations, can be costly, and often requires more staff time and commitment on the part of the participant than other methods of testing physical fitness (e.g., balance tests). Hence, this method is infrequently used in studies of impaired populations or in studies requiring large samples examining disease risk (Burns et al., 2008b); however, in the neuroimaging studies described here, VO_{2max} has been a widely used predictor of gray matter volume.

Exercise is a structured activity that improves physical fitness. Exercise interventions often assess changes in cardiorespiratory fitness (VO_{2max}) to test the effectiveness of the intervention to improve aerobic capacity (Erickson et al., 2011; Kramer et al., 1999). In these interventions, participants are usually randomized to receive greater amounts of monitored and structured activity for some period and then compared to a control group. In the context of the studies discussed in this review, brisk walking, or walking at a moderate intense pace to increase heart rate to approximately 65-75% of the maximal heart rate zone, is the most common exercise treatment in interventions. Although walking is the most common and safest type of activity for older adults, non-ambulatory individuals and people with balance or gait problems are usually excluded from participation in walking interventions. This not only reflects a limitation of these studies, but also suggests that research designs that employ exercises other than walking (e.g. strength training) may be used on non-ambulatory samples to determine whether the positive effects of exercise can be

extended to other populations and whether exercises other than walking show similar beneficial effects (Liu-Ambrose et al., 2012; Nagamatsu et al., 2012).

Magnetic Resonance Imaging (MRI) provides spatially accurate and high-resolution information that can be used to interrogate gray matter volume and is the tool of choice for most studies examining associations between the brain and physical activity, fitness, or exercise. To assess gray matter volume, high-resolution anatomical images are acquired at ~1 mm resolution, which allows for regionally specific assessments and demarcation of gray matter from white matter and cerebrospinal fluid. These anatomical images can be processed and analyzed in a variety of ways to determine regionally specific gray matter volume estimates. For example, voxel-based morphometry (VBM) and tensor-based morphometry (TBM) are voxel-based methods that examine whether gray matter volume varies on a point-by-point basis throughout the brain as a function of a variable of interest (e.g., fitness). In contrast, semi-automated methods for determining cortical thickness or regional volumetry of regions usually use *a priori* information about the size, relative location, and shape of regions to identify and determine the size of each region. Each of these analytical techniques has strengths and weaknesses that have been described in depth elsewhere (Bandettini, 2009; Kuhnt et al., 2013; Perlini et al., 2012) and will not be discussed in this review. Despite their strengths and limitations, these analytical techniques have resulted in an increased understanding of gray matter plasticity that will be discussed in the following sections.

In sum, understanding some of the terms and techniques used in this literature is important for understanding both the implications and limitations of physical activity, fitness, and exercise on brain morphology. Throughout the remainder of this review we will focus the discussion on studies examining associations between physical activity, fitness, and exercise with gray matter volume in older adults. We do this at the expense of reviewing studies that have used other neuroimaging modalities or techniques such as diffusion-weighted imaging, evoked potentials, task-evoked or resting state functional MRI, or other methods; however, we will not discuss the effects of physical activity, exercise, or fitness on brain volume in other populations (e.g., children). We chose this approach not only for the sake of brevity, but also to emphasize the theoretical and conceptual strengths and limitations of studies examining gray matter volume in older adults.

3. Cross-sectional associations between cardiorespiratory fitness and gray matter volume

Meta-analyses (Colcombe and Kramer, 2003; Smith et al., 2010) suggest that the effects of exercise on the brain might not be uniform across all regions and that some brain areas, specifically those areas supporting executive functions, might be more influenced by participation in exercise than areas not as critically involved in executive functions. A seminal meta-analysis of randomized aerobic exercise interventions in older adults revealed that the effects of exercise on cognitive function might be both general and specific (Colcombe and Kramer, 2003). The effects appear to be *general* in the sense that many different cognitive domains are improved after several months of aerobic exercise, but *specific* in the sense that executive functions are improved more than other cognitive

domains. This reasoning fits in line with evidence that the brain does not uniformly atrophy in late life and that some regions (i.e., prefrontal cortex) may be more sensitive to the effects of aging than other brain areas. In other words, the results from meta-analyses have suggested that the brain regions showing the most rapid age-related losses in volume might also be the regions most sensitive to a more physically active lifestyle.

The first several studies utilizing MRI techniques in this field did not directly test the effects of exercise or physical activity on gray matter volume, but instead examined the cross-sectional association between cardiorespiratory fitness and volume (see Table 1). To test whether higher cardiorespiratory fitness levels would be associated with greater gray matter volume in regions supporting executive functions, Colcombe et al. (2003) obtained fitness levels (estimated VO_{2max}) and high-resolution anatomical MRI brain images on 55 older adults between 55 and 79 years of age without dementia (Mini-Mental Status Score > 24). Cardiorespiratory fitness levels ranged from low-fit (estimated VO_{2max} = 11.21 mL/kg³/min) to high-fit (estimated VO_{2max} = 49.90 mL/kg³/min), and VBM methods were used to explore which regional volumes were associated with fitness levels. Consistent with previous studies, older ages were associated with widespread losses in gray matter tissue, but most robustly in the prefrontal, temporal, and parietal cortices. Yet, higher fitness levels moderated the age-related loss in gray matter such that with increasing age, higher fitness levels attenuated the age-related loss in tissue. Thus, there were two important outcomes from this study. First, as suggested by Colcombe and Kramer (2003), the brain regions supporting executive functions (i.e., prefrontal cortex) were the same regions associated with higher fitness levels, indicating some degree of regional specificity of cardiorespiratory fitness. Second, the results emphasized the importance of examining the association between fitness and brain volume as a function of age. More specifically, the association between higher fitness levels and greater gray matter volume was only observed when examining the moderating effect of age. As will be discussed more below, this result led to speculation that any discernible protective effects of higher fitness levels may only be observed after a certain age when losses in tissue volume are more prevalent.

Several other cross-sectional studies have found similar associations between higher cardiorespiratory fitness levels and gray matter tissue volume, but the moderating effect of age has been less consistently examined. For example, Weinstein et al. (2012) examined gray matter volume using VBM in 139 adults between 59 and 80 years of age without dementia and reported that higher fitness levels (VO_{2max}) were associated with greater gray matter volume in the prefrontal, temporal, and parietal cortices even after controlling for several potentially confounding variables including age. Thus, unlike the results from Colcombe et al. (2003), there was a main effect of fitness level on gray matter volume independent of age. Similarly, Erickson et al. (2007) and Gordon et al. (2008) found that higher cardiorespiratory fitness levels (VO_{2max}) using VBM methods were associated with greater gray matter volume in frontal and temporal lobes in older adults, but independently from the effect of age (however, see discussion of Bugg et al., 2012 below). Hence, although Colcombe et al. (2003) only found associations between cardiorespiratory fitness and gray matter volume when examining age-related volume loss, other VBM studies have reported associations between cardiorespiratory fitness and gray matter volume when controlling for variation associated with age (also see discussion for Alosco et al., 2013 below).

Although meta-analyses have emphasized the enhancing effect of exercise on executive functions, epidemiological evidence suggests that physical activity and exercise may reduce the risk for Alzheimer's disease (Barnes and Yaffe, 2011; Podewils et al., 2005; Sofi et al., 2011), which is characterized by impaired memory function and volumetric loss of the hippocampus (Small et al., 2011; Teipel et al., 2013). In concert with this, decades of rodent research have unequivocally shown that exercise influences the morphology and function of the hippocampus (Cotman et al., 2007; Gomez-Pinilla and Hillman, 2013; Vaynman and Gomez-Pinilla, 2006). Thus, based on this evidence, it was hypothesized that higher cardiorespiratory fitness levels might be associated with a larger hippocampus and better memory function in older adults. To test this hypothesis, Erickson et al. (2009) examined cardiorespiratory fitness levels (VO_{2max}) on 165 older adults without dementia between 59 and 80 years of age. The size of the hippocampus was obtained from an automated segmentation algorithm from high-resolution anatomical MRI data. As predicted, higher cardiorespiratory fitness levels were associated with larger hippocampal volumes, and larger hippocampal volumes were, in turn, associated with better memory performance on a spatial memory task independent of age and education levels. Erickson and colleagues speculated that the positive association between higher fitness levels and hippocampal volume could be one path by which physical activity reduces the risk for Alzheimer's disease.

Other studies have now replicated the association between higher fitness levels, larger hippocampal volumes, and cognition. For example, Bugg et al. (2012) reported that in 19 obese older adults between 65 and 75 years of age, higher fitness levels (VO_{2max}) were associated with larger hippocampal volumes, better executive function, and faster processing speed. Furthermore, Szabo et al. (2011) reported that the association between higher fitness levels and hippocampal volume in older adults explained the variation in the frequency of self-reported forgetting episodes. These results suggest that higher cardiorespiratory fitness levels may be associated with larger hippocampal volume in late adulthood, and that larger hippocampal volume may, in turn, contribute to better memory function.

Although few studies have examined regions other than the hippocampus and prefrontal cortex, Verstynen and colleagues (2012) examined the association between cardiorespiratory fitness levels (VO_{2max}) and the size of the basal ganglia including the caudate nucleus. Like the hippocampus and prefrontal cortex, the caudate nucleus, a region of the basal ganglia critically involved in motor function, reward learning, and executive function, showed significant age-related atrophy. Fortunately, rodent studies have found that exercise improves dopamine balance and function in the basal ganglia, suggesting that an association between fitness levels and volume might be apparent in this region. In a sample of 179 adults between 59 and 81 years of age without dementia, Verstynen and colleagues (2012) found that higher fitness levels were associated with greater volume of the caudate nucleus and nucleus accumbens, and in turn, greater volumes were associated with better performance on a task-switching paradigm. These results clearly indicate that the associations between higher fitness levels and gray matter volume extend beyond the prefrontal cortex and hippocampus and that subcortical areas involved in motor control and executive function are also related to fitness levels in late adulthood.

Not all studies, however, have found results entirely consistent with those studies reported above (Bugg et al., 2012; Erickson et al., 2009; Szabo et al., 2011). In particular, using VBM methods to interrogate gray matter volume, Honea et al. (2009) found differing relationships between cardiorespiratory fitness levels (VO_{2max}) and hippocampal volume when comparing neurologically healthy older adults ($n = 56$) to older adults with early-stage Alzheimer's disease ($n = 61$). While the healthy older adults showed no relationship between fitness and hippocampal volume, higher cardiorespiratory fitness levels were associated with larger volumes of both the hippocampal and parahippocampal regions in Alzheimer's disease patients, independent of genetic susceptibility for Alzheimer's disease (APOE $\epsilon 4$ status). Overall, these results suggest the possibility that individuals with dementia may show different or stronger associations between cardiorespiratory fitness and hippocampal volume than their counterparts without dementia (also see Burns et al., 2008a). It is possible that individuals with dementia have more to gain from being physically fit than individuals without early signs of dementia. Whatever the explanation, further research is needed to explore the possible protective effect of higher fitness levels on hippocampal volume in adults with Alzheimer's disease.

In the preceding paragraphs we have discussed the association between cardiorespiratory fitness levels and gray matter volume in cross-sectional studies. As has been discussed, all eight studies (Alosco et al., 2013; Bugg et al., 2012; Colcombe and Kramer, 2003; Erickson et al., 2007; Erickson et al., 2009; Honea et al., 2009; Verstynen et al., 2012; Weinstein et al., 2012) have found that greater volume of the prefrontal cortex and temporal lobes, including the hippocampus, are associated with higher fitness levels in older adults, even when controlling for potentially confounding variables such as age. One slightly inconsistent study reported an association in individuals in the early stages of dementia but not in individuals without dementia (Honea et al., 2009) and one other study with a smaller sample ($N=19$) only found effects in the hippocampus and not in the prefrontal cortex (Bugg et al., 2012). Yet, in general, there appears to be some consistency among studies using VO_{2max} as a predictor of gray matter volume with some regionally specific associations.

So, why might cardiorespiratory fitness levels have regional associations with gray matter volume rather than widespread effects across the entire cortex? Is it coincidence that the areas most frequently associated with fitness levels are the same areas that are most commonly associated with age-related loss? If the trajectory of age-related volumetric losses were playing an important role in determining the regional specificity of these effects, then we might expect prior studies to be reporting more consistent moderation by age (i.e., age \times fitness interactions) such that the positive associations between fitness and gray matter volume would only be apparent at older ages. Unfortunately, it is difficult to discern the degree and consistency of age-related moderation in prior studies, so examining age \times fitness interactions in samples composed of a wider age range could help resolve this issue. Despite these outstanding questions, the promising association between fitness and gray matter volume begs the question of whether increased physical activity would show similar regionally specific associations with gray matter volume.

4. Cross-sectional associations between physical activity and gray matter volume

Cardiorespiratory fitness is an objective measure of aerobic capacity and is modifiable by participation in regular physical activity, but is not by itself a measure of physical activity. Hence, it is important to examine whether self-report or objective measures of physical activity are also associated with gray matter morphology. The association between higher cardiorespiratory fitness and greater gray matter volume in the hippocampus and prefrontal cortex led to the prediction that participation in greater amounts of physical activity might be associated with greater gray matter volume as well. To test this hypothesis, Floel et al. (2010) collected self-reported levels of physical activity in 75 adults without dementia (Mean Mini-Mental Status Score = 29.3) between 50 and 78 years of age. Importantly, all participants were rather sedentary, having reported partaking in fewer than two exercise bouts per week. Hence, any associations between brain volume and physical activity would suggest that even lower levels of physical activity could have an influence on brain morphology. Consistent with their predictions, these investigators reported that greater amounts of activity were associated with greater gray matter volume in the prefrontal cortex, cingulate cortex, temporal lobes, and cerebellum as assessed by VBM methods. There were several important points that emerged from this study. First, despite the limitations of self-reported physical activity, this investigative team demonstrated that this method could be used to reliably predict gray matter volume in late adulthood. Second, the correlation with gray matter volume was significant at lower ends of the physical activity spectrum suggesting that only modest levels of physical activity are necessary for detecting an effect (also see Gow et al., 2012).

This association between gray matter volume and self-reported physical activity has now been replicated in other studies. For example, Bugg and Head (2011) used a self-reported history of engagement in exercise over the past 10 years in a sample of 52 older adults aged 55-79 without dementia. Physical activity levels were measured by METs, or the “metabolic equivalent of task.” This quantifies the physiological measure of the energy cost of physical activities by calculating a ratio of metabolic rate during a physical activity to baseline resting metabolic rate. For instance, a MET of 1 indicates the intensity it takes to sit quietly, so a MET of 2 requires twice as much energy as sitting quietly. In this study, participants ranged from sedentary (average of 0 METs per week over the past 10 years) to active (average of 29.72 METs per week over the past 10 years). MRI brain images were interrogated using an automated labeling method (FreeSurfer) to identify the location and size of cortical and subcortical brain areas. Although a greater amount of physical activity was marginally associated with gray matter volume in the prefrontal cortex, the authors found a significant age \times physical activity interaction on the volume of the medial temporal lobe such that a greater amount of physical activity reduced an age-related decline in medial temporal lobe volume. The authors followed up this study with a sample of 88 older adults without dementia and found that self-reported physical activity only accounted for the variance in hippocampal volume when examining levels of lifetime stress (Head et al., 2012). That is, higher physical activity levels mitigated the detrimental effects of lifetime stress on the size of the hippocampus. Again, as with Colcombe et al. (2003) when

examining effects of cardiorespiratory fitness, the positive associations with physical activity only appeared when examining effect moderation, i.e., the negative influence of either age or stress on medial temporal lobe structures.

Several other studies have reported that physical activity is not significantly associated with either total brain volume (Rosano et al., 2010) or gray matter volume assessed on a voxel-basis using VBM methods (Smith et al., 2011) in older adults. Rosano et al., (2010) reported that 2-years after the completion of an exercise intervention (N = 30), those participants who maintained a greater amount of physical activity did not have larger brain volumes than those who did not maintain higher activity levels. These results, however, were not discussed in the paper and were only reported in a table. Furthermore, regional gray matter volume results were not reported. Similarly, Smith et al. (2011), using VBM methods and self-reported levels of physical activity (N=68), found that higher amounts of physical activity were not associated with greater gray matter volume and that physical activity did not moderate the effect of genetic susceptibility for Alzheimer's disease (APOE e4 allele) on gray matter volume. In line with these null results, Ho et al. (2011) examined the association between self-reported physical activity and gray matter volume on 226 adults between 73 and 84 years of age without dementia using TBM methods. This investigative team reported that a greater amount of physical activity was associated with greater brain volume, but this effect was eliminated when including Body Mass Index (BMI) as a covariate in the statistical model. Overall, these results, interpreted in the context of the studies by Bugg and Head (2011) and Head et al. (2012), suggest that the effects (or lack thereof) of self-reported physical activity on gray matter volume may be partially confounded by the age of the sample or other unmeasured risk factors (e.g., stress, BMI). Longitudinal and randomized interventions of physical activity are more capable of controlling for and assessing these possible confounding associations.

5. Longitudinal and randomized trials of physical activity on gray matter volume

As described previously, the cross-sectional associations between self-reported physical activity and gray matter volume vary, with some studies finding that greater amounts of activity are predictive of greater gray matter volume (Floel et al., 2010; Gow et al., 2012), others finding that the association between physical activity and gray matter volume are dependent on age, lifetime stress, and BMI (Bugg and Head, 2011; Head et al., 2012; Ho et al., 2011), and yet others finding no association between physical activity and gray matter volume (Rosano et al., 2010; Smith et al., 2011). Such heterogeneity of findings could indicate that cross-sectional assessments of physical activity are confounded by unmeasured third variables like that reported by Head and colleagues (2012). Further, it may be that the inaccuracies in self-reported assessments of physical activity are contributing noise and reducing the likelihood of finding reliable effects. Naturally, an alternative hypothesis is that physical activity has a negligible association with gray matter volume. In any case, longitudinal studies that follow individuals over an extended period, or randomized controlled trials that examine whether randomly assigning individuals to receive monitored and structured exercise for an extended period, have control over several of these potential

problems with cross-sectional investigations. That is, longitudinal and randomized designs have the power to be able to monitor, and sometimes control, changes in confounding factors (e.g., BMI) that may explain the associations between physical activity and gray matter volume.

In one such study, Erickson and colleagues (2010) followed a group of 299 adults over the age of 65 without dementia (determined by consensus conference) for a period of 9 years. Self-reported physical activity was obtained on all participants and the question “How many city blocks do you walk on average per week” was used as the primary measure of activity. High-resolution anatomical MRI data was obtained on all participants after the 9-year interval and VBM was used to assess gray matter volume. The investigators examined whether self-reported physical activity (i.e., blocks walked) was predictive of regional gray matter volume assessed 9-years after the physical activity assessment, even after controlling for potentially confounding factors including age, sex, education, white matter lesions, APOE genotype, BMI, and gait speed. Erickson and colleagues (2010) reported that greater amounts of physical activity was associated with greater gray matter volume 9-years later in the prefrontal cortex, anterior cingulate, parietal cortex, cerebellum, and hippocampus. Furthermore, they found that walking 72 blocks per week (~1 mile/day) was necessary to observe these effects and that greater tissue volume in these regions was predictive of subsequent cognitive impairment 4 years after the MRI assessment (also see Rovio et al., 2010 and Gow et al., 2012).

Despite the promising results from the study by Erickson and colleagues (2010), the causal nature of the association between activity and gray matter volume remained a matter of speculation. For example, the authors were not able to explore changes in physical activity or gray matter volume over the 9-year interval, so it remains unclear whether decline in gray matter volume preceded changes in physical activity or whether reductions in physical activity preceded losses in gray matter volume. Randomized controlled interventions are necessary to better address the causal relationship between physical activity and gray matter volume.

In one controlled intervention of physical activity, Colcombe and colleagues (2006) randomized 59 adults between 60 and 79 years without dementia to either a brisk walking exercise treatment group or to a stretching and toning control group for 6-months. Both groups were closely monitored by exercise physiologists and reported to the laboratory 3-days per week for a 1-hour period for the duration of the trial. The brisk walking group maintained the intensity at 60-75% of their maximal heart rate zone from week 7 through the remainder of the intervention. The exercise intervention successfully improved aerobic capacity (VO_{2max}) in the brisk walking treatment group. When examining the changes in gray matter volume using VBM methods on MRI data, the brisk walking group showed an increase in volume from pre-intervention to post-intervention in the prefrontal cortex, anterior cingulate cortex, and lateral temporal lobes. In contrast, the stretching and toning control group showed a slight decline in volume in these same regions. These results were the first to suggest that starting an exercise regimen in late life could be an effective method at increasing gray matter volume.

Despite the provocative results reported by Colcombe and colleagues (2006), the sample size of 59 participants was rather small and the analyses focused primarily on the prefrontal cortex. Since prior studies of cardiorespiratory fitness (VO_{2max}) and physical activity have reported localized effects in the hippocampus, Erickson and colleagues (2011) examined whether an exercise intervention could increase the size of the hippocampus. To examine this hypothesis, they conducted a similar intervention to that of Colcombe et al. (2006) except that the intervention lasted for 1-year and included 120 neurologically healthy adults between 55 and 80 years of age. Instead of using a VBM approach to examine hippocampal volume, Erickson and colleagues (2011) used an automated segmentation algorithm to identify the location and size of the hippocampus both before and after the intervention. Then, the investigators further divided the region into anterior and posterior sections. First, like Colcombe et al. (2006), the brisk walking exercise intervention reliably improved cardiorespiratory fitness levels (VO_{2max}) compared to the stretching and toning control group, indicating that the intervention was effective at elevating fitness levels. Second, and consistent with their predictions, the stretching and toning control group showed a significant ($\sim 1.5\%$) decrease in the size of the hippocampus over the 1-year interval, while the brisk walking exercise group showed a significant ($\sim 2\%$) increase over the same interval. The significant time \times group interaction revealed that a moderate intensity exercise intervention could be effective at increasing the size of the hippocampus in an older adult sample without dementia. In addition, Erickson and colleagues (2011) reported that the effects of the intervention were specific to the anterior portion of the hippocampus, improvements in aerobic fitness were correlated with changes in hippocampal volume, higher fitness levels at baseline were associated with less decline in hippocampal volume for the stretching and toning control group, a serum-based biomarker (brain derived neurotrophic factor) was correlated with changes in hippocampal volume, and changes in hippocampal volume for the exercise group were correlated with improvements on a spatial memory task. That being said, the relationship with spatial memory performance was tenuous since the stretching and toning control group also showed improvements in memory performance despite decreases in hippocampal volume. Yet, overall, these results indicate that the brain remains modifiable well into late adulthood and that only a modest amount of exercise for 1-year is sufficient for altering the size of the hippocampus, a brain structure that typically deteriorates in late life and which is predictive of a conversion to dementia.

In another study, Ruscheweyh and colleagues (2011) conducted a Nordic walking (medium intensity exercise) versus a gymnastics (low intensity exercise) intervention. In this study, 62 adults between 50 and 78 years without dementia were randomized to one of two physical activity groups or to a no contact control group for 6-months. Participants engaged in the activities for 50 minutes, 3 days per week, with the Nordic training group maintaining intensity levels of 50-60% of their maximal heart rate zone and the gymnastics group maintaining 30-40% of their maximal heart rate zone. Similar to Floel et al. (2010), participants were excluded if they reported partaking in more than 2 exercise bouts per week in the last 6 months and were further excluded if they missed more than 20% of the exercise sessions. Although the investigators did not report group differences in changes in gray matter volume using VBM methods, they did report that changes in physical activity levels

over the 6-month period (independent of the group assignment) were associated with increases in gray matter volume in the prefrontal, parietal, and cingulate cortices.

Overall, despite the limited number of published longitudinal and interventional studies examining gray matter volume and physical activity, the effects that have been reported are promising. All longitudinal studies (Erickson et al., 2010; Rovio et al., 2010; Gow et al. 2012) have shown that greater amounts of physical activity are associated with the sparing of gray matter volume over a long-term interval, and three intervention studies (Colcombe et al., 2006; Erickson et al., 2011; Ruscheweyh et al., 2011) indicate that change in physical activity levels over a 6-month to 1-year period is sufficient for increasing gray matter volume in a regionally-specific manner. Although there is variation in the design, measurement, analysis, and samples in these studies, the convergence of findings suggest that only modest increases in physical activity may be an effective method for increasing gray matter volume in late adulthood.

6. Discussion

In this review, we summarized the existing literature examining the associations between cardiorespiratory fitness, physical activity, and exercise interventions on gray matter volume in late adulthood. Despite the relative infancy of this field, there have been more than twenty empirical studies conducted on this topic over a 10-year span (since 2003). Overall, a summary of these results suggest that physical activity might be a potent method to increase gray matter volume in late adulthood, and therefore, may be an effective prevention for cognitive impairment and other behavioral problems associated with brain atrophy.

We began this review discussing cross-sectional studies that have examined the association between cardiorespiratory fitness levels and gray matter volume in older adults. Our summary suggests that the majority of publications examining this association have found positive effects, i.e., higher fitness levels are associated with greater volume. However, the effects do not appear to be uniform throughout all areas of cortex, but instead are regionally specific to areas that tend to decline earlier in adulthood and that support executive and memory functions (i.e., the prefrontal cortex and hippocampus). The reason for the regional specificity is interesting to consider and may be related to the age-related deterioration in these regions, their sensitivity to molecular changes resulting from physical activity, or some combination of these factors.

Consistent with the cardiorespiratory fitness associations, the cross-sectional studies examining the association between physical activity and gray matter volume have found similar effects, albeit less consistently. For example, five of the cross-sectional studies have found an association between physical activity and gray matter volume (Bugg and Head, 2011; Floel et al., 2010; Gow et al., 2012; Head et al., 2012; Ho et al., 2011) whereas two have failed to find an association (Rosano et al., 2010; Smith et al., 2011). Importantly, three of the five studies reporting an association found that the effect was moderated by risk factors for brain atrophy including age (Bugg and Head, 2011), lifetime stress (Head et al., 2012), or were eliminated after accounting for BMI (Ho et al., 2011). Although Smith et al. (2011) examined whether volumetric effects of physical activity were moderated by genetic

susceptibility (APOE e4), including APOE into the model did not change their null effects (also see Honea et al., 2009). Thus, overall, the results from cross-sectional studies of physical activity on gray matter volume are less consistent than studies of cardiorespiratory fitness, and appear to be moderated by other risk factors for brain deterioration (e.g., age, lifetime stress). Yet, studies examining associations between cardiorespiratory fitness and gray matter volume have also reported interactions with age (Colcombe et al., 2003), hormone therapy in postmenopausal women (Erickson et al., 2007), obesity (Bugg et al., 2012), and cognitive status (Honea et al., 2009) indicating that heterogeneity across these studies could be explained by confounding or effect moderation by unstudied and/or unmeasured third variables. Interactions between dietary factors (Leckie et al., 2012), genetic risk factors (Erickson et al., 2013b), or other lifestyle variables could also explain some of the unexplained variation in prior studies.

Nonetheless, when examining the fitness and physical activity literatures together, the regions that are reported in all of these studies are highly overlapping, suggesting that both physical activity and fitness have regionally specific associations with the same brain areas and, thus, may be tapping into similar mechanisms to influence brain health and integrity. Nearly every study discussed here has reported effects of fitness or physical activity on the volume of the prefrontal cortex and/or the hippocampus. This consistency was found across studies that use different metrics (aerobic fitness versus self-reported blocks walked), different designs (cross-sectional versus interventional), different analytical approaches (VBM versus automated segmentation), and different exclusionary criteria (frequent participation in activity versus infrequent participation in physical activity). Such convergence in findings, despite these differences, is striking and speaks to the robustness of the associations and the consistency of the effects. These patterns are strengthened by the longitudinal interventional approaches that show that starting an exercise regimen influences the same brain areas (e.g., hippocampus and prefrontal cortex) that are so often reported in cross-sectional studies of fitness and activity.

Despite these promising conclusions about the associations between fitness, physical activity and gray matter volume, there remain many unanswered questions. For example, several studies have reported interactions with age (Bugg and Head, 2011; Colcombe et al., 2003) such that the effects of fitness and physical activity on prefrontal and hippocampal volume are greater at older ages. Such an effect is consistent with other neuroimaging research showing similar effects that are dependent on age (Erickson et al., 2012), but implies that there may be an age at which the positive effects of physical activity are magnified or attenuated. In other words, the positive effects of physical activity on gray matter volume may be most apparent in an age range that is showing precipitous losses in volume, or the period in which the brain might have the most potential to be influenced by these factors. Along these lines, Honea et al. (2009) reported that associations between hippocampal volume and fitness were only significant for those in the early stages of dementia, or those individuals putatively showing the most hippocampal atrophy. For public policy reasons it is important to determine the age range when it might be the most important to prescribe physical activity to prevent brain atrophy. Along these lines, these results suggest that it may also be important to tailor treatments based on individual differences in other lifestyle and genetic factors.

Another set of important questions relates to the duration or intensity of activity. That is, several studies have suggested that only modest amounts of activity are sufficient for detecting effects with gray matter volume (Erickson et al., 2010; Erickson et al., 2011; Floel et al., 2010; Gow et al., 2012; Ruscheweyh et al., 2011), yet the amount necessary to detect long-term and persistent changes in gray matter volume remains unknown, as does the dose necessary to significantly reduce the risk for cognitive impairment. Although Erickson et al., 2010 suggested that ~1 mile per day was sufficient to observe long-term effects on gray matter volume, this study was not interventional in nature and did not systematically manipulate activity intensity or duration. In short, answers to these questions are necessary to change public policy on using physical activity as a method of influencing brain health.

Finally, we have still much to learn about the link between gray matter volume and cognitive functions, with only a few studies reviewed here reporting associations between fitness, activity, gray matter volume, and cognitive function (Erickson et al., 2007; Erickson et al., 2009; Erickson et al., 2010; Erickson et al., 2011; Verstynen et al., 2012; Weinstein et al., 2012). Thus, the impact that greater gray matter volume has on cognitive function remains largely speculative. This and other important questions about the timing and type of activity (i.e., walking versus swimming) remains a matter of speculation as does the cellular and molecular pathways contributing to these measures of gray matter volume. Future studies are needed to answer these questions and provide greater insight into the implications of greater prefrontal cortex volume and hippocampal volume with fitness and activity.

In summary, we have reviewed the studies examining associations between fitness, physical activity, and gray matter volume. We chose to focus this review on gray matter volume in older adults at the expense of other ages or populations (e.g., children) and other imaging modalities (e.g., white matter imaging) in order to discuss more comprehensively the studies focusing on gray matter volume. Based on this review, we can conclude that there is a consistent association between higher fitness levels and physical activity with greater volume of the prefrontal cortex and hippocampus in older adults. The few randomized interventions published thus far have found results highly overlapping with the cross-sectional studies and suggest that the prefrontal cortex and hippocampus remain pliable in late life and that moderate intensity exercise for 6-months to 1-year is sufficient for changing the size of these areas. Although there is a need for additional interventions, we can conclude that physical activity reflects a promising approach to increase gray matter volume in late life when the risk for dementia and gray matter atrophy are highest.

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Table 1

A description of studies examining the association between physical activity, fitness, and exercise on gray matter volume in late adulthood.

First Author (Year)	Design	Variable of Interest	MRI Technique	N	Mean Age (SD) in years unless otherwise noted	Findings
Alosco (2013)	cross-sectional	fitness and brain volume	Freesurfer	69	68.07 (8.02)	Increased fitness is associated with increased gray matter volume
Bugg (2011)	cross-sectional	fitness and brain volume	Freesurfer	52	69.0 (6.7)	Increased fitness is associated with increased frontal volume; exercise engagement moderated age-related medial temporal lobe atrophy
Bugg (2012)	cross-sectional	Fitness, brain volume and cognition	Freesurfer	19	68.4 (2.7)	Increased fitness is associated with increased processing speed, executive function, and hippocampal volume
Burns (2008)	cross-sectional	fitness, brain volume, and cognition	FAST	121	73.5 (6.5)	Increased fitness is associated with increased whole brain volume in AD patients, but not in a non-demented sample. Increased fitness is associated with better cognitive performance in both AD and non-demented samples.
Colcombe (2003)	cross-sectional	fitness and brain volume	VBM	55	66.5 (5.3)	Increased fitness is associated with decreased age-related losses in cortical volume
Colcombe (2006)	randomized clinical trial	fitness and brain volume	VBM	59	Age range: 60 - 79	Fitness intervention significantly increased gray and white matter volume in sedentary older adults
Erickson (2007)	cross-sectional	fitness, brain volume, and cognition	VBM	54	Age range: 58 - 80	Increased fitness is associated with decreased hormone treatment-related cortical volume loss and increased cognitive function
Erickson (2009)	cross-sectional	fitness, brain volume, and cognition	FIRST	165	66.55 (5.6)	Increased fitness is associated with increased hippocampal volume which mediates spatial memory performance
Erickson (2010)	cross-sectional	physical activity and brain volume	VBM	299	78 (3.65)	Increased physical activity (walking 72 blocks/week) is associated with increased grey matter
Erickson (2011)	randomized controlled trial	fitness and brain volume	FIRST	120	Aerobic exercise: 67.6 (5.81) Stretching control: 65.5 (5.44)	Fitness intervention increased hippocampal volume in exercise group
Floel (2010)	cross-sectional	fitness, brain volume, and cognition	VBM	75	60.5 (6.9)	Physical activity is associated with increased gray matter volume in frontal cortex and better memory encoding
Gordon (2008)	cross-sectional	fitness, brain volume, and cognition	VBM	60	Old group: 71.5 (4.7) Young group: 22.5 (2.1)	Both increased fitness and education level is associated with increased grey and white matter volume

First Author (Year)	Design	Variable of Interest	MRI Technique	N	Mean Age (SD) in years unless otherwise noted	Findings
Gow (2012)	longitudinal	physical activity and brain volume	FSL and in-house semiautomated algorithm	691	72.7 (0.7)	Increased physical activity is associated with increased grey and white matter, as well as decreased atrophy and white matter lesions
Head (2012)	cross-sectional	physical activity and brain volume	Freesurfer	91	Low exercise group: 74 (9) High exercise group: 71 (7)	Increased physical activity moderates the negative effect of stress on hippocampal volume
Ho (2011)	cross-sectional	physical activity and brain volume	TBM	226	77.9 (3.6)	Increased physical activity is associated with increased brain volume, controlling for education and age. Effect was eliminated when including Body Mass Index in the model.
Honea (2009)	cross-sectional	fitness and brain volume	VBM	117	73.8 (6.3)	Increased fitness is associated with increased parietal and temporal gray matter volume in early-stage AD subjects, but not in non-demented subjects. No relationship between volume, fitness and apoE genotype was found
Rosano (2010)	cross-sectional	physical activity and brain function	fully deformable automatic algorithm	27	Successful aging group: 81.45 (2.77) Physical activity group: 80.8 (3.95)	Physical activity was not associated with total brain volume or atrophy. Increased physical activity is associated with increased cognitive performance and related brain function as measured by fMRI
Rovio (2010)	cross-sectional	physical activity and brain volume	VBM	75	Active: 73.0 (3.5) Sedentary: 72.1 (4.4)	Increased physical activity in mid-life is associated with increased gray matter volume in late-life
Ruscheweyh (2011)	randomized controlled trial	physical activity, brain volume, and cognition	VBM	62	60.2 (6.6)	Increased physical activity is associated with increased memory performance, gray matter volume, and BDNF levels, regardless of intensity manipulation.
Smith (2011)	cross-sectional	physical activity and cognition	VBM	68	Age range: 65 - 85	Physical activity was not associated with gray matter volume. Increased physical activity is associated with increased semantic memory performance and brain function in those at risk for AD (apoE-4 carriers), as measured by fMRI
Szabo (2011)	cross-sectional	fitness, brain volume, and cognition	FIRST	158	66.49 (5.59)	Increased fitness is associated with better spatial working memory performance and increased hippocampal volume
Verstynen (2012)	cross-sectional	fitness, brain volume, and cognition	FIRST	179	66.6 (5.6)	Increased fitness is associated with increased volume in striatum and better task-switching performance. Caudate nucleus volume mediates performance on task-switching task.
Weinstein (2012)	cross-sectional	fitness, brain volume, and cognition	VBM	142	66.6 (5.6)	Increased fitness is associated with increased volume in dorsolateral prefrontal cortex and better performance on Stroop task. Gray matter volume mediates performance on cognitive tasks.

*AD = Alzheimer's Disease

*FIRST = FMRI's Integrated Registration & Segmentation Tool

*FAST = FMRI's Automated Segmentation Tool

*VBM = Voxel Based Morphometry

*TBM = Tensor Based Morphometry