# Physical activity and cognition: A narrative review of the evidence for older adults

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Etnier, J.L., Drollette, E.S., Slutsky, A.B. (2019). Physical activity and cognition: A narrative review of the evidence for older adults. *Psychology of Sport and Exercise 42*, 156-166.

**Made available courtesy of Elsevier: https://doi.org/10.1016/j.psychsport.2018.12.006**



**Abstract:**

Researchers have long been interested in understanding the potential benefits of physical activity for cognitive performance. Given that advancing age is associated with cognitive decline and is predictive of a heightened risk of clinical cognitive impairment, older adults are a vulnerable population that may particularly benefit from physical activity participation. **Objectives:** The goal of this narrative review is to consider evidence relative to the beneficial effects of physical activity for cognitive performance, brain structure, and brain function in older adults. **Methods:** The current state of the literature is presented for studies incorporating behavioral and neuroimaging outcomes. We focus on the highest quality published evidence using the Oxford Centre for Evidence-Based Medicine (2009) evaluation scheme. Thus, we consider meta-analytic reviews followed by experimental, prospective, and cross-sectional empirical evidence. In the absence of meta-analytic evidence, we present a comprehensive review and discuss exemplars of studies to illustrate important points. **Results:** Findings from these studies have enhanced our understanding of the potential role of physical activity in the enhancement and/or maintenance of cognitive function into advancing age. In sum, prospective evidence provides level 2a evidence and a B+ recommendation that physical activity reduces the risk of cognitive decline and clinical cognitive impairment. Experimental evidence provides level 1a evidence and an A- recommendation for small-to-moderate benefits for behavioral outcomes. Evidence from neuroimaging studies is less well developed and generally did not merit grade recommendations, with the exception of A- evidence for a positive effect of exercise on hippocampal volume. With respect to brain function, there is level 1b evidence of benefits using fMRI data and level 3b evidence of benefits using ERP data. **Conclusions:** Further advancement in this area will be reliant on large-scale RCTs of sufficient duration to pursue questions related to the mediating roles of brain structure and function in the observed behavioral benefits of physical activity.

**Keywords:** physical activity | older adults | neuroimaging | cognitive performance

**Article:**

## 1. Introduction

Scientists have long been interested in understanding the link between the body and the mind as it relates to cognitive performance. The notion of a healthy mind in a healthy body suggests that physical health affects cognitive health. Research exploring the benefits of chronic physical activity for cognition has increased dramatically in recent decades and has focused largely on potential benefits for older adults. This focus is reflective of several factors including the growing population of older adults, their susceptibility to cognitive impairment, and the possibility that physical activity might be particularly beneficial for this population.

The population of older adults is increasing (Colby & Ortman, 2015), raising significant concerns regarding the societal-level health cost burden associated with age-related cognitive decline and clinical cognitive impairment (European Commission, 2015). Age-related cognitive decline is defined as typical performance decrements in a variety of domains including memory (Borella et al., 2017; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002) and speed of processing (Borella et al., 2017; Salthouse, 1996). Although this decline is normal, it has implications for problem-solving, accuracy, and speed of execution of everyday cognitive activities (Borella et al., 2017) and, furthermore, the rate of decline is predictive of clinical cognitive impairment (Backman, Jones, Berger, Laukka, & Small, 2005). Clinical cognitive impairment occurs when decrements in cognitive performance exceed that which would be expected based upon age and education level. Clinical cognitive impairment ranges from mild cognitive impairment (MCI) to dementia, with Alzheimer's disease (AD) being the most common form of dementia. Projections suggest that the global prevalence of AD will reach 131.5 million by 2050 (Prince, 2015). Although the increasing population of older adults and their expected cognitive challenges are of concern, we know that physical inactivity is a risk factor of AD with 21.0% of cases in the United States and 20.3% of cases in Europe being attributable to this factor (Mayer et al., 2018), and there is evidence that physical activity might ameliorate the negative cognitive and neurodegenerative effects typically observed in older adults. Hence there is great interest in understanding more about the potential benefits of physical activity for older adults, and several hypotheses guide our work in this area.

The cognitive reserve hypothesis posits that cognitive reserves are developed through lifestyle activities including education and physical activity, but that cognitive reserves decline with advancing age (Fratiglioni, Paillard-Borg, & Winblad, 2004; Scarmeas & Stern, 2003; Stern, 2002; Whalley, Deary, Appleton, & Starr, 2004). Cognitive reserves are thought to encompass brain volume, brain metabolic activity, and cerebral pathology (Stern, Alexander, Prohovnik, & Mayeux, 1992; Whalley et al., 2004). The frontal aging hypothesis (Stern et al., 1992; West, 1996) and the executive function hypothesis (Hall, Smith, & Keele, 2001) in combination suggest that age-related changes to frontal lobe structure and function result in decrements in performance on frontally-mediated tasks (i.e. executive function tasks). Based upon these hypotheses, it is expected that older adults have compromised cognitive reserves and frontal lobe functioning and, hence, have greater capacity, compared to younger adults, for improvement in response to physical activity.

## 1.1. Approach

The purpose of this narrative review is to consider the recent empirical evidence exploring the effects of chronic physical activity on cognition in older adults as assessed using behavioral and neuroimaging (e.g., structural and functional magnetic resonance imaging, MRI; event-related potential, ERP) measures. Although early narrative reviews of this literature considered behavioral measures of performance and assessments of brain structure or function simultaneously (e.g., Erickson & Kramer, 2009; Kramer, Erickson, & Colcombe, 2006), with the exception of Ballesteros, Kraft, Santana, and Tziraki (2015), Bherer, Erickson, and Liu-Ambrose (2013), Hotting and Roder (2013), and Voelcker-Rehage and Niemann (2013), recent reviews have focused exclusively on behavioral measures (e.g., Carvalho, Rea, Parimon, & Cusack, 2014; Law, Barnett, Yau, & Gray, 2014) and have not considered the developing body of evidence for changes in cognitive performance, brain structure, and brain function concurrently. Furthermore, we are not aware of any recent review that has included a consideration of studies that use functional MRI (fMRI) and studies that use ERP measures. Hence, this review is important because it provides an up-to-date, comprehensive consideration of cognitive outcomes, brain structure, and brain function as assessed using fMRI and ERPs.

Given the relatively large body of literature, we limit this review to the strongest evidence available using the levels of scientific evidence and grades of recommendation (Daramola & Rhee, 2011) described by the Oxford Centre for Evidence-Based Medicine (2009). In brief, the levels of evidence range from 1 (RCTs, highest quality) to 5 (expert opinion, lowest quality) with sub-levels of a (systematic or meta-analytic reviews, higher quality), b (individual studies, lower quality), and c (individual studies with methodological limitations, lowest quality). With respect to the grades of the recommendations, the levels of evidence are matched with the grades such that levels 1a-1c provide grade A, levels 2a-3b provide grade B, level 4 provides grade C and level 5 provides grade D evidence. The final grade is determined based upon the quality, quantity, and consistency of the evidence allowing for the grade to be increased to a + or decreased to a – based upon these factors. In this narrative review, evidence for the behavioral measures comes from meta-analytic reviews of prospective (level 2) and experimental (level 1) studies with cognitively normal and clinically impaired participants. With neuroimaging measures, the body of research is relatively less mature. Hence, the highest quality evidence in this area comes primarily from cross-sectional (level 3) and experimental studies (level 1) and has largely focused on cognitively normal older adults. In all cases, the highest level of scientific evidence available is presented, followed by a discussion of empirical evidence supporting important points to consider including mechanisms, inconsistencies, and future direction in a given area of research.

In addition, although fitness is not equivalent to physical activity, fitness is often considered a proxy for physical activity. Researchers who choose to use fitness instead of physical activity recognize that the two are linked and elect to use fitness because it can be objectively and accurately measured. Because positive links between fitness and brain health would support interventions to promote physical activity, this evidence is included in this review.

## 2. Findings for behavioral measures

### 2.1. Prospective studies

Prospective studies in which baseline physical activity is used to predict future cognitive decline have generally supported a reduction in risk assessed with cognitive performance and with measures of clinical cognitive impairment. The literature focused on cognitive performance has been reviewed meta-analytically on several occasions (Blondell, Hammersley-Mather, & Veerman, 2014; Sofi et al., 2011) with summary statistics consistently showing that physical activity reduces the risk of cognitive decline by 35–38%. In the case of dementia, longitudinal prospective studies provide the only possible evidence because long-term experimental studies are not available (Beckett, Ardern, & Rotondi, 2015). When these studies are reviewed meta-analytically, summary statistics indicate that physical activity is associated with a 28–49% reduction in the risk of AD (Beckett et al., 2015; Daviglus et al., 2011; Hamer & Chida, 2009). This body of evidence provides level 2a, grade B+ evidence in support of physical activity protecting against cognitive decline and clinical cognitive impairment with advancing age. It is important to emphasize that with respect to the incidence of dementia, this level of evidence is all that is available because experimental trials do not extend to the initial diagnosis of clinical cognitive impairment. Thus, this evidence addresses the relative long-term effects of physical activity that cannot be obtained from RCTs.

Prospective evidence is judged as level 2 evidence that can only support a grade B recommendation because of its inherent limitations. However, it is important to point out that some of these limitations have been specifically addressed in individual studies on physical activity and cognition with evidence continuing to support beneficial effects. One limitation of the extant literature is that individuals who are physically active are also likely to participate in cognitive and social activities, and these activities are themselves related to a reduced risk of cognitive decline (Carlson et al., 2008; Landau et al., 2012; Valenzuela & Sachdev, 2009; Verghese et al., 2003; Wilson, Scherr, Schneider, Tang, & Bennett, 2007; Wirth, Haase, Villeneuve, Vogel, & Jagust, 2014). Thus, participation in these other activities might confound our ability to identify physical activity as the agent of change. However, in the Kungsholmen Project, Karp et al. (2006) tested the effects of mental, physical, and social activities on the relative risk of dementia in older adults (>75 years) followed for 7 years. Participation in each category of activity, as well as participation across categories, was associated with a reduced risk of dementia. Therefore, although there are clear benefits to participating in multiple types of leisure activity, the independent effect of physical activity was also demonstrated.

A second limitation is that participants are often older aged at the start of the study and relatively short follow-ups have been used. This makes these studies susceptible to a reverse causation bias such that preclinical cognitive decline may be influencing physical activity behavior rather than the other way around (Sabia et al., 2017). However, some studies supporting beneficial effects of PA on cognition have not suffered from these limitations. For example, Larson et al. (2006) only included older adults (>65 years) who scored in the top 25% on the Cognitive Ability Screening Instrument to ensure that the findings were not limited by the concern of reverse causation. They found that after 6.2 years, individuals who exercised 3 or more times per week had a significantly reduced risk of dementia (HR = 0.68) as compared to those who exercised fewer than 3 times per week. Other studies have addressed this limitation by assessing physical activity during midlife and following participants for a substantially longer period of time. For example, Chang et al. (2010) assessed PA in adults (M = 61 years) at baseline and then again 26 years later. Results showed that cognitive performance (speed of processing, memory, and executive function) was significantly better for those who exercised as compared to those who were sedentary at midlife. Furthermore, the odds of dementia were significantly lower for those who exercised ≤5 h/week as compared to those who were sedentary (OR = 0.60). Hence, again, there are studies in which appropriate steps have been taken to reduce the influence of the design limitations on the conclusions that can be drawn.

A third limitation unique to studies on behavior is that physical activity has typically been assessed by self-report. Self-report measures of physical activity tend to have reasonable reliability, but are not highly correlated with objective measures of physical activity (Sallis & Saelens, 2000). However, Zhu et al. (2017) conducted a study in which they used accelerometers to assess physical activity over a 7-day period at baseline and then followed older adults for approximately 3 years. They found that a higher percent of time spent in moderate-to-vigorous physical activity was associated with a 39–47% risk of cognitive impairment after adjusting for potential covariates.

In summary, prospective evidence consistently supports that physical activity reduces the risk of subsequent declines in cognitive performance and of clinical cognitive impairment providing grade B+ evidence. This body of evidence is critical because it specifically addresses the potential long-term effects of physical activity participation on future cognitive behavior and the risk of clinical cognitive impairment later in life. Also important is the fact that positive results are maintained even in the most tightly controlled prospective studies. In addition to the prospective evidence, there is also experimental (level 1) evidence obtained through randomized controlled trials (RCTs) that highlights short-term (but still chronic) effects of physical activity on cognition. This literature is considered separately for older adults who are cognitively normal and for those with clinical cognitive impairment or with a heighted risk for clinical cognitive impairment.

## 2.2. RCTs

### 2.2.1. Cognitively normal older adults

There is a substantial body of research that has used an RCT approach to explore the potential benefits of exercise for cognitively normal older adults. In these studies, cognition is examined pre- and post-intervention in previously sedentary individuals who are then randomly assigned to an exercise condition or a non-exercise control condition. RCTs on physical activity interventions have typically focused on moderate intensity aerobic activity or combinations of aerobic and strength training activities. Although two recent meta-analytic reviews failed to show significant benefits for physical activity (Kelly et al., 2014; Young, Angevaren, Rusted, & Tabet, 2015), this is most likely reflective of the authors' decision in both reviews to compute effect sizes by cognitive outcome and for each combination of control group type and exercise modality rather than reporting an average effect across studies and then testing these variables as potential moderators of the effects. The short-coming of this decision is that effect sizes were summarized across a relatively small number of studies (1–6 per cognitive outcome and exercise/control group combination) which counters the purpose of the meta-analysis because it limits statistical power resulting in even moderate effect sizes being judged as non-significant.

By contrast, when summarized across all studies exploring the effects of chronic exercise on cognitive performance, seven meta-analytic reviews report overall effects that are consistently shown to be significantly different from zero and small-to-moderate in size (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Colcombe & Kramer, 2003; Hindin & Zelinski, 2012; Netz, Wu, Becker, & Tenenbaum, 2005; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018; Rathore & Lom, 2017; Smith et al., 2010). These meta-analytic reviews provide level 1a evidence in support of physical activity benefiting cognitive performance but the overall body of evidence must be graded as A- because of the heterogeneity in findings and because of the variability in the quality of the RCTs that were reviewed (see Northey et al., 2018).

### 2.2.2. Older adults with clinical cognitive impairment or heightened risk

Researchers have also been interested in exploring the potential for physical activity to benefit individuals with clinical cognitive impairment (i.e., Alzheimer's disease, stroke) or with a heightened risk for clinical cognitive impairment due to genetic or biological risk factors. In this area of research, intervention studies and RCTs have been conducted.

When reviewed meta-analytically, Panza et al. (2018) identified 19 studies on adults at risk for AD (due to a genetic risk, experiencing MCI, or having biological parents diagnosed with AD) comparing an exercise only condition to a non-diet, non-exercise control condition. When comparing cognitive performance at the post-test, results showed that the exercise group outperformed the control group ($d = 0.47$), but that there was heterogeneity amongst the findings.

Groot et al. (2016) meta-analytically reviewed RCT's of physical activity interventions as compared to non-active control conditions conducted with individuals diagnosed with dementia. Results showed that physical activity resulted in improved cognitive function (standardized mean difference, SMD = 0.42; $n = 16$). When limited to studies focused on AD (i.e., excluding other forms of dementia), the average effect size was still significant (SMD = 0.38). This finding is supported by another meta-analytic review (Strohle et al., 2015) in which exercise interventions were found to have a significant benefit for patients with AD (standardized mean change score using raw score standardization, SMCR = 0.83, $p < .05$, $n = 4$) and for those with MCI (SMCR = 0.20, $p < .05$, $n = 6$). Importantly, these effects surpassed the small effects observed in response to a drug treatment for AD patients (SMCR = 0.23, $p < .05$, $n = 45$) and the negligible effect observed for patients with MCI (SMCR = 0.03, $p > .05$, $n = 5$).

Oberlin et al. (2017) statistically reviewed studies looking at the effects of exercise on cognitive performance for individuals who had suffered a stroke. Results from 14 studies showed that exercise had a small effect on cognition ($g = 0.30$) with larger effects observed for studies using combined aerobic and strength training protocols ($g = 0.43$).

In summary, there is a growing body of level 1a evidence in support of physical activity as a behavioral intervention that improves cognitive performance in populations with clinical cognitive impairment or with a heightened risk for clinical cognitive impairment. In particular, meta-analytic reviews indicate that there are small beneficial effects for participants with MCI and stroke, moderate beneficial effects for individuals at risk for AD, and moderate-to-large effects for individuals with AD. Given the small sample sizes that are typical of the studies included in the meta-analyses and the variability in the quality of the individual RCTs, this evidence supports a recommendation of grade A-.

## 2.3. Moderators

Importantly, the heterogeneity of the findings in experimental studies and meta-analytic reviews may be partially reflective of our lack of understanding of relevant moderators that influence the magnitude of observed effects. Thus, researchers have begun to direct their attention to the further exploration of moderators identified through meta-analytic reviews or deemed relevant for practical or theoretical reasons.

One moderator that has received attention in empirical studies is the particular nature of the exercise intervention. For example, there is some evidence, albeit limited, that programs that combine physical activity and cognitive activity result in larger effects than either in isolation (Benloucif et al., 2004; Fabre, Chamari, Mucci, Masse-Biron, & Prefaut, 2002; Small et al., 2006). This research is based upon evidence from animal studies showing that cognitively engaging forms of physical activity result in more comprehensive benefits to cognition than does physical activity in isolation (van Praag, Kempermann, & Gage, 2000). More recently, this notion of combining physical activity with cognitive activity has been implemented through exer-gaming interventions. This is in part reflective of the expectation that larger effects might be possible because of this combined intervention, but also because of practical considerations in that exer-gaming is accessible and enjoyable and hence, might have better adherence. Stanmore, Stubbs, Vancampfort, de Bruin, and Firth (2017) summarized results from 17 RCTs with clinical and non-clinical samples across the lifespan and reported a significant benefit of exer-gaming for cognitive functioning as compared to all control conditions ($g = 0.44$) and even as compared to physically-active controls ($g = 0.44$). Consistent with these findings, Howes, Charles, Marley, Pedlow, and McDonough (2017) conducted a meta-analytic review of RCTs testing the effects of exer-gaming on cognitive performance by older adults (>=65 yrs) and found that exer-gaming improved performance on cognitive tracking tasks ($ES = 0.48$; $n = 8$). These meta-analytic reviews provide level 1a evidence. However, because the samples sizes in the included studies are relatively small, the included studies were described as being of "low-to very low-quality" (Howes et al., 2017, p. 113), and there was significant heterogeneity across the findings (Stanmore et al.), this evidence is judged to support a grade A-recommendation for the benefits of exer-gaming on cognitive performance.

Another important consideration relates to the dose of the physical activity intervention. Reviewers using meta-analytic techniques have attempted to identify how exercise dose (duration, intensity, frequency, total volume) impacts observed effects, but these findings are not definitive for a couple of reasons. First, it is difficult to summarize across meta-analytic reviews because of differences in coding. For example, Northey et al. (2018) coded duration as short (≤45 min), medium (>45 and ≤ 60 min) or long (>60 min), while Colcombe and Kramer (2003) coded duration as short (15–30 min), moderate (31–45 min) and long (46–60 min). Both reviews concluded that moderate duration was best, but for Northey et al. moderate was defined as >45 and ≤ 60 min, while for Colcombe and Kramer it was 31–45 min. Second, meta-analytic reviews may be limited by third-order causation. That is, studies may differ from one another in variables other than the specific moderator being tested, and those variables may themselves be driving observed (or unobserved) differences between the levels of the moderator. As such, our understanding of dose-response questions related to how to best prescribe physical activity to benefit cognitive performance will likely not be dramatically advanced until we have a better understanding of underlying mechanisms which may then help us to develop theoretical rationale for particular dose-response decisions. Because the evidence from meta-analytic reviews is indirect, the literature does not support a grade recommendation relative to questions of dose-response.

An additional moderator that is of particular relevance in recent research is related to a person's genetic risk for AD. Apolipoprotein E (*APOE*) is a susceptibility gene for AD with a dose-response relationship between the number of copies of the epsilon 4 allele and the risk for AD. *APOE* epsilon 4 heterozygotes (those with one copy of the epsilon 4 allele) have a three times greater risk of AD and *APOE* epsilon 4 homozygotes (those with two copies of the epsilon 4 allele) have an eight times greater risk of AD as compared to *APOE* epsilon 4 non-carriers (Verghese, Castellano, & Holtzman, 2011). Intriguingly, there is evidence supporting that *APOE* genotype moderates the relationship between PA and cognitive performance. Cross-sectional and prospective studies have shown that larger cognitive benefits are typically (Deeny et al., 2008; Niti, Yap, Kua, Tan, & Ng, 2008; Rovio et al., 2005; Schuit, Feskens, Launer, & Kromhout, 2001), but not always (Podewils et al., 2005) reported for *APOE* epsilon 4 carriers as compared to *APOE* epsilon 4 non-carriers. This is a developing body of evidence providing level 2b evidence that is heterogeneous across trials resulting in a grade B- recommendation. Importantly, there are currently three clinical trials funded by the National Institutes of Health that include *APOE* as a moderator and that will provide a causal test (level 1 evidence) of its role in the effects of chronic physical activity on cognitive performance by cognitively normal adults (R01AG053952 Erickson; R01AG058919 Etnier; R01AG057552 Smith).

In summary, experimental studies testing the causal relationship between PA and cognitive performance generally support that exercise has small-to-moderate positive effects for cognitively normal and cognitively impaired older adults and older adults with a heightened risk of clinical cognitive impairment. Future research will continue to explore relevant moderators to better understand how to administer the exercise to get the largest benefits, in which cognitive areas we can expect to see the biggest effects, and for whom these effects might be most critical.

## 3. Findings for neuroimaging measures

Given the high quality (level 1a and level 2a) evidence to support physical activity yielding cognitive benefits in older adulthood using behavioral measures, researchers have turned their attention to putative mechanisms. Although the mechanistic support is still limited, promising mediating factors are brain structure and brain function. It is critical to advance our understanding of the potential impacts of physical activity on brain health that might then underlie observed benefits to cognitive performance because this might inform decisions about dose-response and about multi-component interventions. In this section, we specifically focus on brain structure and brain function speaking of cognitive outcomes only when they are relative to brain outcomes.

### 3.1. Brain structure

Magnetic resonance imaging (MRI) is a neuroimaging technique that uses strong magnetic fields to non-invasively collect high-resolution anatomical images. When using MRI to image the brain, high-resolution images can be processed and analyzed to quantify total brain volume, total gray and white matter volume, and regional brain volume. There are currently a variety of methods to analyze high-resolution brain images, all with strengths and limitations, that have been reviewed elsewhere (Bandettini, 2009). For the context of this section, we will discuss the outcomes from the MRI analyses resulting in volumetric measures, without specifically speaking to the methodology.

## 3.2. Physical activity and brain structure

Total brain and gray matter volume decline with increasing age and the declines in brain structure are associated with cognitive declines (see Raz & Rodrigue, 2006). Importantly, physical activity may affect the age-related trajectory of declines. For instance, in prospective studies, physical activity during middle age is predictive of total brain volume (Rovio et al., 2010), gray matter volume (Rovio et al., 2010), and regional brain volume in some areas, such as the prefrontal cortex and hippocampus (Erickson et al., 2010), that are vulnerable to age-related declines (Raz & Rodrigue, 2006). These prospective studies provide level 2b evidence supporting that physical activity is protective against age-related decrements in brain structure. There is also concurrent support of the associations between physical activity or fitness and total (Halloway, Arfanakis, Wilbur, Schoeny, & Pressler, 2018; Hamer, Sharma, & Batty, 2018) and regional brain volume (Benedict et al., 2013; Boots et al., 2015; Floel et al., 2010; Gordon et al., 2008; Varma, Chuang, Harris, Tan, & Carlson, 2015; Verstynen et al., 2012; Weinstein et al., 2012) in older adults. This level 3b evidence also supports that physical activity benefits brain structure.

Although the relationship of physical activity, fitness, and brain structure is informative, both concurrently and across decades of life, adoption of a physical activity program during older adulthood can also provide protection against declines. Recently, Firth et al. (2018) used meta-analytic techniques to review the effect of physical activity interventions for healthy older adults on hippocampal brain volume. They found a positive effect of physical activity on left ($g = 0.36$) and right hippocampus ($g = 0.24$) volumes, however the effect was limited to a comparison with controls, rather than a within-subjects' comparison of change in volume. This provides level 1a evidence that physical activity benefits hippocampal volume in older adults by affording protection against expected declines observed in controls, rather than proliferation, per se, which would have been evidenced by changes compared to their own volumes prior to the intervention. Hence, the current evidence suggests that the structure of the brain is malleable throughout the lifespan, and physical activity during middle and older adulthood can affect expected declines in brain volume.

### 3.2.1. Physical activity, brain structure, and cognitive performance

Although this evidence serves as an important building block to investigate the relationship of physical activity and fitness with brain structure and cognition, these studies did not report brain structure outcomes relative to cognitive outcomes. There is merit in describing these studies because of the valuable insights they provide with respect to the potential role of brain structure in explaining the observed link between physical activity and cognition, however we now turn our attention to physical activity intervention studies that report brain outcomes relative to cognitive outcomes.

During the past two decades, numerous RCTs and physical activity interventions for older adults with a major focus on brain structure and cognition have been conducted. Jonasson et al. (2016) conducted a 6-month exercise intervention for older adults consisting of walking or jogging, three days a week, for 30–60 min each session. Following 6-months of aerobic exercise, older adults improved their cognitive score, a composite score of multiple cognitive domains, and the improvement was associated with dorsolateral prefrontal cortex thickness. Interestingly, change in fitness following the intervention was associated with change in hippocampal volume, but change in hippocampal volume was not associated with change in cognitive score. Age-related cognitive declines are consistently associated with declines in regional brain volume, rather than cortical thickness (Cox et al., 2018; Raz & Rodrigue, 2006), however these findings from a 6-month physical activity intervention suggest increased cortical thickness may be an important factor for the effects of physical activity on cognitive performance. Despite these positive findings, other 6-month intervention studies have failed to show a relationship between change in brain structure and cognitive performance in older adults (Anderson-Hanley et al., 2018; Ruscheweyh et al., 2011). These contradictory findings may be due to individual variability in the adaptations to physical activity interventions. To account for part of this variability, researchers have explored the overall quantity of physical activity achieved throughout the intervention to better understand the importance of study design and adherence relative to brain structure and cognitive changes. Ruscheweyh et al. (2011) reported that changes in activity level throughout the intervention were associated with changes in prefrontal and cingulate cortex volumes. Furthermore, they reported that volumetric changes were a partial mediator between changes in activity level and changes in memory following the intervention. Similarly, when Anderson-Hanley et al. looked at the quantity of physical activity completed in a cycling intervention (i.e. number of rides), they reported an association with prefrontal and cingulate cortex volume, and the change in prefrontal cortex volume was associated with change in memory (Anderson-Hanley et al., 2018). These follow-up analyses investigating the quantity of physical activity were needed to fully realize the effects of the interventions. It may be expected that a longer intervention would tease out the variability in brain and cognitive outcomes due to overall activity quantity. In support of this expectation, Erickson et al. (2011) found that after 12-months of physical activity, the volume of the hippocampus was increased, and the increase was directly associated with improved memory performance. However, change in fitness was also associated with increased hippocampal volume, which suggests inter-individual variability of adaptations to physical activity is still an important factor to consider in the relationship of physical activity, brain structure outcomes, and cognitive outcomes.

Although the previously described studies were focused on traditional aerobic physical activity (i.e. walking, jogging, cycling), there is also some support for non-traditional physical activity (e.g. dance, tai chi) affecting brain structure and cognition. For example, Mortimer et al. (2012) conducted a 40-week intervention for older adults which included tai chi, social interaction, or walking for about 1 h a day, three days per week. The results revealed that the tai chi and social interaction interventions were successful in improving cognitive performance and increasing whole brain volume, as compared to the no exercise control, whereas the walking intervention and control groups did not differ. Of importance, the walking intervention was not prescribed as a progressive program and only required older adults to walk at a self-selected brisk pace, which may have affected the efficacy of the intervention. Another style of non-traditional physical activity is coordination training. One-year of coordination training for older adults, through activities such as balancing on stability boards, was successful at improving cognitive performance and increasing the volume of the globus pallidus, a sub region of the basal ganglia, whereas one-year of aerobic training did not yield the same benefits (Niemann, Godde, Staudinger, & Voelcker-Rehage, 2014). These studies support the previously described premise that physical activity that is cognitively engaging will result in larger cognitive benefits. With this premise in mind, dancing, which has high cognitive and physical demands, has recently been investigated as an intervention for older adults to improve cognition and increase brain volume. Rehfeld et al. (2018) compared the effects of 6-months of dancing, with novel and challenging choreography, to the effects of traditional physical activity in older adults. Although both dancing and traditional physical activity resulted in improved cognition, the effects of the dancing yielded widespread increases in regional brain volume (anterior cingulate cortex, supplementary motor area, precentral gyrus, middle frontal gyrus, insula, superior temporal gyrus, and postcentral gyrus), whereas the effects of traditional physical activity was limited to the occipital and cerebellar regions [primary visual cortex, lingual gyrus, fusiform gyrus, temporal pole, and cerebellum (Rehfeld et al., 2018)]. However, when comparing similarly active older adults who either regularly participate in dance or traditional aerobic physical activity, they do not differ in cognitive performance or hippocampal brain volume (Niemann, Godde, & Voelcker-Rehage, 2016). Although these regional brain volume findings may seem conflicting, this may be due to analytical decisions such as limiting the analyses to specific regions of interest (Niemann et al., 2014; Niemann et al., 2016) versus choosing an exploratory whole brain analysis (Rehfeld et al., 2018). In addition, the non-traditional physical activity studies presented here either did not report cognitive outcomes (Niemann et al., 2014) or did not report a comparison of changes in brain structure with changes in cognition (Mortimer et al., 2012; Rehfeld et al., 2018). These omissions present a major limitation to this body of literature as compared to the findings reported in response to traditional aerobic physical activity interventions.

Overall, there is level 1a support for increases specifically in hippocampal volume in response to physical activity, resulting in a grade A recommendation for this effect. There is also a growing body of level 1b evidence supporting traditional and non-traditional physical activity programs benefiting cognitive performance and other measures of brain structure. A small body of level 1b evidence has assessed the extent to which changes in brain structure in response to physical activity interventions mediate changes in cognitive performance. However, the variability in study outcomes based on individual differences and the overall activity dose means that the variable shown to be critical for predicting changes in brain structure and cognitive performance has not been randomly assigned in the study. Hence, this evidence is not ready for a grade level recommendation and additional high quality RCT's are mandated to better understand the key mechanisms in the physical activity or fitness, brain structure, and cognitive performance relationship of older adults.

### 3.3. Brain function

### 3.3.1. Functional MRI

The blood-oxygen level dependent (BOLD) signal is a proxy measure for neural activation when using fMRI to assess brain function (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). During cognitive tasks, neural activation increases in relevant brain regions creating a percent change of the BOLD signal from resting level. A reduction in the percentage of change in the BOLD signal, with preserved or improved cognitive performance, is interpreted as neural efficiency (Kleemeyer et al., 2017). Aging is associated with a greater percent change in the BOLD signal, suggesting inefficiency, however this is not always paired with changes in cognitive function (Reuter-Lorenz & Cappell, 2008). When behavior is preserved despite a greater use of resources, demonstrated by a greater percent change in BOLD signal, this is referred to as compensation (Reuter-Lorenz & Cappell, 2008). Therefore, the amount of resources available, otherwise described as level of cognitive reserves (Stern, 2002, 2012), may impact adaptations to physical activity or in relation to fitness such that individuals would experience more efficient processing (i.e. reduced percent change from rest) or improved compensation (i.e. greater percent change from rest) with preserved or improved cognitive performance.

Consistently in the literature, during executive-based tasks, higher fit older adults have greater activation in frontal regions and better cognitive performance compared to lower fit older adults (Colcombe et al., 2004; Prakash et al., 2011). The frontal lobe is one of the primary regions affected by age (Raz & Rodrigue, 2006; West, 1996), so perhaps the increase in activation in frontal regions is to compensate for significant losses in brain structure. Following a physical activity intervention, older adults show reduced activation in the cingulate cortex and improved cognitive performance (Colcombe et al., 2004; Voelcker-Rehage, Godde, & Staudinger, 2011). Although the cingulate cortex is also affected by aging (Pardo et al., 2007), reduced activation is suggestive of improved efficiency, and, therefore, the declines in structure may not be as prominent as other frontal regions. Others have found no effect from physical activity interventions. Maffei et al. (2017) randomized 113 older adults with mild cognitive impairment to a 7-month multidomain intervention that included physical activity, music, and cognitive training or a usual care control. Interestingly, from pre-to-post intervention, there was no change in brain function for the training group during a visuospatial attention task, but the control group increased medial-temporal cortex activity. Further, task performance was similar from pre-to-post intervention for both groups. Given that the control group maintained performance, but had increased brain activity, and the training group maintained performance without changes in brain function, these findings suggest a training-induced preservation of reserves with improved neural efficiency. This evidence then is very mixed and too limited to allow for an overall grade recommendation. Clearly, future well-designed RCTs are needed to provide level 1b evidence relative to the relationship between physical activity and cognitive function as assessed using BOLD signals from fMRI.

In addition to neural activation, measures of functional connectivity have been shown to be associated with physical activity, fitness, and cognition. Functional connectivity can be assessed in the resting-state or during task performance and refers to the level of co-activation, or similar BOLD signal time series, between spatially distinct, but functionally-related brain regions. Networks of brain regions with a high level of functional connectivity have been described (van den Heuvel & Hulshoff Pol, 2010), and inter-network connectivity (i.e. connectivity between well-defined networks) and intra-network connectivity (i.e. connectivity within well-defined networks) are affected by aging and important for cognitive function (Tsvetanov et al., 2016).

In older adults, inter-network connectivity, rather than intra-network connectivity, appears to be preserved with fitness and is associated with better executive function (Kawagoe, Onoda, & Yamaguchi, 2017). However, baseline intra-network connectivity is predictive of gains in executive function in response to a physical activity intervention (Baniqued et al., 2017) and change in intra-network connectivity in response to a physical activity intervention is associated with improved executive function performance (Voss et al., 2010). Although inter-network and intra-network connectivity are important for cognitive function (Tsvetanov et al., 2016), the limited evidence suggests there may be specific effects of level of fitness versus physical activity, thus suggesting an importance for a goal of improved fitness during physical activity interventions for older adults. At present, the evidence relative to functional connectivity is too limited to allow for a grade recommendation.

That being said, taken together, both neural activation and functional connectivity are affected by aging and have been shown to be positively influenced by physical activity and fitness. Whether the benefits are achieved through improving or preserving brain function or through neural efficiency or neural compensation is unclear, however each potential outcome is positive and important and may be critical in the face of age-related decline. Although utilizing fMRI to assess neural activation provides valuable information regarding brain function with impressive spatial resolution, it is not without limits. A major limitation of fMRI during cognitive tasks is the poor temporal resolution due to the hemodynamic response function. The BOLD signal is much slower than the underlying neural processes with the peak occurring around 6 s after the stimulus onset. It is suggested that this level of temporal resolution is sufficient to distinguish between trials, thus making it feasible for cognitive testing, but insufficient to establish activation patterns associated with the processing of the stimuli. Thus, in addition to fMRI, methods such as electroencephalography (EEG) are critical to our understanding of brain function by vastly improving the temporal resolution down to approximately a millisecond (Glover, 2011). To further understand the relationship of physical activity, fitness, and brain function, we turn now to brain function as assessed by event-related potentials.

### 3.3.2. Event-related potentials (ERPs)

Recent advances in neuroimaging have rapidly developed our understanding of physical activity effects on brain and behavior in older adults. One such technique, known as EEG, assesses electrical potentials produced by the cerebral cortex and subcortical regions of the brain recorded with metal sensors placed at the surface of the scalp. A class of EEG activity known as event-related potentials, or ERPs, allows for additional evaluation of neurocognitive processing that is time-locked to an event such as a stimulus or behavior response. ERPs are voltage fluctuations (i.e., summation of postsynaptic potentials) characterized by positive (P) and negative (N) components identified according to the time of occurrence relative to the stimulus or behavior (Hruby & Marsalek, 2003; Luck, 2014). Unlike overt behavior, ERPs provide a continuous millisecond-by-millisecond measure of cognitive processing prior to and following an event and thus provide high-temporal resolution of cognitive operations as they occur. The benefit of utilizing ERPs in the study of aging is the ability to observe neurocognitive processing at the time of the event when overt behavior may not be possible or may be biased by slowing of motor responses that are typical of aging. As such, evaluating underlying cognitive processing associated with stimulus evaluation provides an additional level of understanding when investigating the effects of physical activity behavior on the aging brain.

Unfortunately, ERP investigations in this research domain are limited with the extant literature mainly reflecting cross-sectional methods (level 3b evidence). Regardless, the overall findings generally support the conclusion that greater physical activity participation by older adults is associated with greater neural efficiency and maintenance of neuroelectrical integrity. These interpretations stem from patterns observed across a variety of ERP outcomes with most studies evaluating the P3 component and relatively few investigations evaluating other components including measures of conflict monitoring (N2; error-related negativity or ERN) and motor initiation/response (contingent negative variance or CNV; movement-related cortical potential or MRCP). Hence, we will primarily focus on the relation of physical activity to P3 with a brief discussion highlighting other novel ERP investigations.

The P3 is arguably the most widely studied ERP component and represents a robust neuroelectric response observed across a variety of cognitive tasks. Specifically, the P3 is a positive voltage deflection occurring approximately 300–800 ms after the presentation of a stimulus. Amplitude is thought to reflect the degree of attentional resource allocation, and latency is theorized to represent timing of stimulus evaluation, independent of response selection and action (Conroy & Polich, 2007; Donchin, 1981; Duncan-Johnson, 1981; Fabiani, Karis, & Donchin, 1986). Aging studies consistently reveal smaller amplitude (Friedman, Nessler, Johnson, Ritter, & Bersick, 2007), prolonged latency (Brown, Marsh, & LaRue, 1983; Polich, 1996), and greater frontal (compared to the typical parietal) topography (Luck & Kappenman, 2011) for older compared to younger adults, suggesting greater decline in processing speed and alterations of cortical underpinnings responsible for mental operations necessary to meet specific task demands. Concerning physical activity, cross-sectional investigations utilizing typical oddball (Hatta et al., 2005; McDowell, Kerick, Santa Maria, & Hatfield, 2003; Pontifex, Hillman, & Polich, 2009; Tsai, Wang, Pan, & Chen, 2015), switch (Dai, Chang, Huang, & Hung, 2013; Hillman, Kramer, Belopolsky, & Smith, 2006), go/no-go (Taddei, Bultrini, Spinelli, & Di Russo, 2012), and flanker tasks (Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004) demonstrate that older adults with greater physical activity levels, higher-fitness, or greater sport-related participation revealed larger amplitude and shorter P3 latency compared to age matched inactive, lower-fit, or low-active peers (Dai et al., 2013; Hatta et al., 2005; Hillman et al., 2004; Hillman et al., 2006; McDowell et al., 2003; Taddei et al., 2012). Given the functional significance of the P3 and accounting for previously mentioned age effects, these data may suggest that physical activity participation delays the deleterious effects of age such that active older adults maintain underlying neurocognitive processing to a greater degree compared to inactive cohorts. However, a major limitation is the cross-sectional design of these investigations providing only level 3b evidence with additional RCT evidence necessary to demonstrate causal effects of chronic physical activity on the P3.

There are only two unique RCT studies that have tested this question, and they both fail to support a causal link between physical activity and changes in P3. Gajewski and Falkenstein

(2018) evaluated the P3 in older adults (65–88 years old) following 4-months of either physical training, cognitive training, social control group, or a no-contact control group. The physical training group received cardiovascular exercise training twice per week for 90 min per session. Results for the physical training group revealed no changes in behavior or P3 amplitude and latency following the intervention. A separate study by Tsai et al. (2015) randomized healthy older males (65–79 years old) to either a high-intensity resistance exercise training intervention (60 min for 3 sessions per week for 12 months) or a non-specific exercise intervention that served as the control condition. Results revealed a reduction in P3 amplitude for the control group and no change for the exercise group following the 12-month program. Together, it is difficult to infer collective interpretations from these findings given the divergent methodology including duration of the exercise program (4-months vs 12-months), the type of exercise (cardiovascular vs resistance), and the population (all males vs mixed sex). One possible interpretation of these null findings is that cross-sectional differences in P3 reflect more long-term differences that can only be observed after more time has passed so that age-related declines are evident relative to physical-activity related benefits. That is, the RCTs may require an intervention of sufficient duration to capture typical age effects on ERPs in the control condition (e.g., reduction in P3 amplitude or prolonged latency). Future research may benefit by considering this factor.

Only four investigations have evaluated the relation of physical activity and conflict monitoring in older adults utilizing the N2 (Gajewski & Falkenstein, 2015a, 2015b; Taddei et al., 2012) and ERN (Themanson, Hillman, & Curtin, 2006) components. These negative frontocentral deflections are derived from separate reduction methods such that the N2 is stimulus locked to correct trials (250–350 ms after stimulus presentation) and the ERN is response locked to commission errors (0–100 ms following an error). Although distinct, they represent similar cognitive operations regarding adjustments in cognitive control associated with behavior and environmental conflict (Clayson & Larson, 2011). The major difference is that the ERN represents continued mental processing associated with error salience with the target stimulus (Larson, Clayson, & Clawson, 2014) or degree of competition between correct and incorrect response options (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Cohen, Yeung, & Botvinick, 2004), and the N2 represents mental evaluation of conflicting task-irrelevant information prior to a behavior response (Yeung & Cohen, 2006). Although aging studies consistently demonstrate smaller N2 amplitude (Daffner, Alperin, Mott, Tusch, & Holcomb, 2015) with age, results for the ERN are not so clear with evidence demonstrating larger and smaller amplitude for older adults compared to younger cohorts (Clawson, Clayson, Keith, Catron, & Larson, 2017). As a result, researchers suggest that interpretation of changes in ERN amplitude may depend more on behavior performance level (Larson et al., 2014) irrespective of age.

Regarding relations with physical activity, one study evaluated the ERN comparing higher- and lower-active young and older adults. Results revealed decreased ERN amplitude for higher-active adults, regardless of age, suggesting reductions in error-salient conflict encompassing behavior evaluation (Themanson et al., 2006). N2 investigations revealed larger amplitude (Gajewski & Falkenstein, 2015a, 2015b; Taddei et al., 2012) and shorter latency (Taddei et al., 2012) for higher active older adults including those with greater sport participation suggesting greater awareness of task-related conflict (Forster, Carter, Cohen, & Cho, 2011).

Lastly, three studies evaluated motor response preparation utilizing MRCPs (Berchicci, Lucci, & Di Russo, 2013) and CNV (Gajewski & Falkenstein, 2015a; Hillman, Weiss, Hagberg, & Hatfield, 2002). These components are negative deflections over frontal electrode sites and represent prefrontal motor preparation prior to an expected target stimulus. Amplitude is measured between the warning and target stimulus only for trials with a motor response (i.e., button press). Research suggests a U-shaped relationship between behavior performance and amplitude suggesting attentional resource optimization for superior behavior performance (Churchland, Byron, Ryu, Santhanam, & Shenoy, 2006; He & Zempel, 2013). Results from these separate investigations revealed smaller amplitude in active older adults compared to sedentary counterparts suggesting greater motor task preparation efficiency associated with greater physical activity participation (Berchicci et al., 2013; Gajewski & Falkenstein, 2015a; Hillman et al., 2002). Additionally, one study suggests that during speeded task conditions lower-active individuals appear to allocate greater neural resources while higher-active individuals demonstrate greater neural efficiency regardless of cognitive demand (Gajewski & Falkenstein, 2015a).

In summary, the overall ERP findings suggest that greater physical activity participation may be associated with greater neural efficiency and maintenance of cortical integrity in older adults. However, the limited supporting evidence is at the 3b level, the two RCTs conducted to test a causal relationship did not support an effect, and, overall, the literature is too limited to allow for a grade of recommendation. These findings do reveal possible factors that warrant consideration in future work to better elucidate physical activity effects on ERP outcomes in older adults. First, shifts in topographic distribution of ERP components are typically observed in aging studies and may provide additional understanding for physical activity effects on ERPs. One study, for example, reported differences in topography for maximal P3 amplitude between active and non-active groups such that active groups demonstrate a more youth-like distribution compared to low-active older adults (Hillman et al., 2006). Hence, evaluating shifts in topography, along with measures of amplitude and latency, should be considered in future research (for further discussion on this topic see Gomez-Pinilla & Hillman, 2013). Second, some studies reported in this review noted differences in ERP's between active groups regardless of age. Taken together with prior work across the aging spectrum (Gomez-Pinilla & Hillman, 2013), it appears that a lifestyle of physical activity is efficacious for positive neurocognitive outcomes with further implications suggesting that children and older adults may have the most to gain as exercise-induced neurocognitive benefits may be effective at promoting cognitive development and delaying age-related cognitive decline. However, the execution of high-quality, large-scale RCTs is necessary to test these relationships in a way that would allow for higher level evidence and more confident conclusions regarding a cause-and-effect relationship. Lastly, utilizing multiple neuroimaging modalities may provide greater understanding regarding brain mechanism outcomes associated with physical activity behavior in older adults. That is, incorporating multiple techniques may further enhance our understanding of the collective but distinct associations of underlying cognitive operations and highlight similar structural and psychophysiological outcomes that will assist with future work aimed at physical activity behavior effects on neurocognitive and brain health in older adults.

## 4. Discussion

Based upon this narrative review of the evidence, research exploring the effects of physical activity on cognition in older adults has demonstrated beneficial effects using behavioral and neuroimaging measures. The prospective behavioral evidence consistently demonstrates that physical activity reduces the risk of clinical cognitive impairment. Furthermore, evidence from RCTs supports that this relationship is causal. However, this evidence is graded as B+ and A-, and this line of research would benefit from larger, tightly controlled RCTs to confirm the causality of this relationship and to allow for an examination of potentially relevant moderators.

Fortunately, there are several on-going large-scale trials that will add importantly to our understanding of the potential of physical activity to improve cognitive performance by older adults. As examples of studies with cognitively normal older adults, at least two RCTs (IGNITE, PAAD-2) are currently being conducted to test the causal effects of a 1-year exercise intervention on cognitive performance while also considering the potential role of APOE as a moderator of the effects. As an example of a study looking at the potential benefits for participants with MCI, the Synergic trial is a multi-site study examining the potential benefits of 20-weeks of exercise, cognitive training, and vitamin D supplementation (Montero-Odasso et al., 2018). The Intense Physical Activity and Cognition (IPAC) study will address our interest in understanding more about dose-response effects of chronic exercise by testing the effects of the intensity level of a 6-month exercise intervention for 60–80 year adults by comparing high intensity, moderate intensity, and a no-exercise control group (Brown et al., 2017). The eMIND study is another RCT that is focused on examining PA as part of a multi-component intervention (Pothier et al., 2018). This is an important direction for research as we seek to explore ways to further enhance benefits to cognition in behavioral interventions through the use of multi-modal approaches. In this study, older adults (>65) with memory complaints will be randomly assigned to the intervention (a web-based intervention with nutritional counseling and physical and cognitive training) or a control condition for a 6-month period. As a result of the numerous on-going RCTs, it is anticipated that future research will dramatically strengthen our understanding of the causal link between physical activity and cognition and will expand our appreciation for questions related to dose-response and to moderators of the effect.

With respect to the neuroimaging studies, there is promising evidence of a link between physical activity and cerebral structure and function that comes from studies using MRI and ERP measures. The current state of the literature suggests that exercise can successfully alter brain structure in brain regions that have been implicated in age-related cognitive decline. Furthermore, the findings suggest that greater physical activity participation is associated with greater neural efficiency and maintenance of cortical integrity. Although there is grade A evidence supporting that physical activity increases hippocampal volume, a primary limitation of this line of research is that the majority of the evidence is at level 2b and 3b. This supports the need for large-scale RCTs of sufficient duration to test causal relationships between physical activity, brain structure, and brain function and to allow for tests of the mediating role of these measures in the link between physical activity and cognitive performance. This short-coming will also be addressed in on-going clinical trials. The previously mentioned IGNITE and PAAD-2 studies both include neuroimaging measures of brain health with plans to assess for mediation.

Relative to the central hypotheses driving this line of research, evidence provides indirect support for the cognitive reserves hypothesis in that there is level 2b and 3b evidence supporting the idea that changes in cognitive reserve (operationalized as cerebral structure and cerebral function) may underlie observed changes in cognitive performance in response to physical activity. There is also support for the frontal hypothesis in that changes in cerebral structure and function have tended to be observed in frontal areas of the brain more so than other areas or global effects. Future research in which causal designs and mediational models are tested will be necessary to confirm the role of cognitive resources and/or frontal lobe structure and function in the observed benefits to cognition.

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