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Aerobic Exercise, Cardiorespiratory Fitness, and the Human Hippocampus

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Abstract

The hippocampus is particularly susceptible to neurodegeneration. Physical activity, specifically increasing cardiorespiratory fitness via aerobic exercise, shows promise as a potential method for mitigating hippocampal decline in humans. Numerous studies have now investigated associations between the structure and function of the hippocampus and engagement in physical activity. Still, there remains continued debate and confusion about the relationship between physical activity and the human hippocampus. In this review, we describe the current state of the physical activity and exercise literature as it pertains to the structure and function of the human hippocampus, focusing on four magnetic resonance imaging measures: volume, diffusion tensor imaging, resting state functional connectivity, and perfusion. We conclude that, despite significant heterogeneity in study methods, populations of interest, and scope, there are consistent positive findings, suggesting a promising role for physical activity in promoting hippocampal structure and function throughout the lifespan.

Keywords

exercise; cardiorespiratory fitness; perfusion; white matter; magnetic resonance imaging

INTRODUCTION

The hippocampus is essential in episodic and relational memory, and is highly susceptible to damage from a variety of conditions including hypoxia, encephalitis, epilepsy, and ischemia (Knierim, 2015). Adolescence and early adulthood are critical periods during which the

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hippocampus exhibits considerable reorganization and growth, which has important consequences for cognitive performance and academic achievement (Hueston et al., 2017). Furthermore, the hippocampus deteriorates earlier and more rapidly than other brain regions in populations experiencing neurodegeneration, including Alzheimer's disease (AD; Frisoni et al., 2010), schizophrenia (Heckers & Konradi, 2002), depression (W. Liu et al., 2017), and multiple sclerosis (Sicotte et al., 2008), as well as in healthy older adults (Raz et al., 2005). These losses precede, and lead to, subsequent memory deficits and increased risk for neurologic diseases. Due to the importance of the hippocampus in memory formation and its sensitivity to disease processes, there is considerable scientific and public health interest in finding approaches for promoting the structural and functional integrity of the hippocampus throughout the human lifespan.

One widely accessible and cost-effective intervention for possibly enhancing the structure and function of the hippocampus is aerobic exercise. Aerobic exercise is a form of physical activity that requires oxygen, often challenges the oxygen capacity of the system, and engages large groups of muscles over extended periods of time. When aerobic exercise is habitual, it can lead to improvements in cardiorespiratory fitness, or the body's ability to take in and deliver oxygen to working muscles (Manley, 1996). In this review, we use the term "physical activity", broadly, to refer to all activities involving a period of movement, and the term "aerobic exercise" to refer to those studies that specifically focus on eliciting a cardiovascular response from the activity. Notably, aerobic exercise varies substantially in intensity level. Moderate-intensity activities (e.g., brisk walking) are often operationalized as requiring 3.0 to less than 6.0 metabolic equivalents (METs), whereas vigorous-intensity activities (e.g., running) require 6.0 or greater METs (2018 Physical Activity Guidelines Advisory Committee, 2018). Clinical trials that use aerobic exercise interventions frequently target moderate-to-vigorous intensity levels, particularly when recruiting from healthy young and midlife adult samples. However, even light-to-moderate intensity activity that demands 1.6 to less than 3.0 METs can elicit a substantial cardiovascular response in low fit or sedentary individuals (2018 Physical Activity Guidelines Advisory Committee, 2018). In general, clinical trials that utilize aerobic exercise interventions use the term "aerobic exercise" to refer to the behavioral intervention, regardless of the intensity, and we use the same terminology here when describing those results. In contrast, observational studies often use the more general term "physical activity" to appropriately capture a broad swath of activities assessed that are not necessarily aerobic in nature. Figure 1 depicts the various study designs and metrics of physical activity described in this review.

Rodent studies have demonstrated that aerobic exercise increases cell proliferation and survival, as well as angiogenesis, and alters gene expression for metabolic, growth factor, and signaling molecules and cascades in the hippocampus (Kerr et al., 2011; Mustroph et al., 2012; Rhodes et al., 2003; Tong et al., 2001; Van Praag et al., 1999). In humans, a major strength of neuroimaging is that it enables us to integrate multiple magnetic resonance imaging (MRI) measures to comprehensively characterize features of the structure and function of specific brain regions such as the hippocampus (Figure 2). Over the past 10 years, there has been a considerable number of human neuroimaging studies that target the hippocampus in the context of measurements of cardiorespiratory fitness or exposure to exercise. To facilitate interpretation, the frequency of the neuroimaging metrics and the measurements of physical activity and exercise in the cited literature are presented as a series of heat maps in Figure 3. Yet surprisingly, few reviews have integrated this literature. Instead, publications have either limited their reviews to specific measures of the hippocampus (i.e., volume) at the expense of functional or connectivity metrics, or have focused on whole-brain morphology, which could overlook hippocampus-specific effects (Erickson et al., 2014). For instance, Firth et al., (2018) reported that randomized clinical trials (RCTs) of aerobic exercise prevented age-related decline in left hippocampal volume and of bilateral hippocampal volume in older adults. However, this review did not include research in children, measures of hippocampal connectivity, white matter (WM), or function. Valkenborghs et al., (2019) systematically reviewed nine studies investigating the impact of exercise on brain structure and function in children and adolescents. They reported positive associations between exercise via RCTs and functional activation and connectivity in a number of regions, including the hippocampus and related functional networks. However, the authors also cited limitations due to a sparse number of studies and considerable heterogeneity across methods. Many other manuscripts have reviewed the effects of exercise on neuroimaging outcomes without specificity or focus on the hippocampus or tracts communicating with the hippocampus (Erickson et al., 2019; Sexton et al., 2016). Although such broad reviews are important, there is reason to focus the spotlight on the hippocampus given its dominant role in many disease states, its well-established cellular plasticity, and the clear links with exercise in rodents.

This review aims to address the following questions: (1) Do physical activity behaviors and related constructs, such as cardiorespiratory fitness, influence the volume, function, and integrity of the hippocampus across the lifespan?; (2) Do the effects of aerobic exercise interventions on hippocampal structure include both gray matter volume and WM connections?; (3) Does aerobic exercise influence hippocampal resting state connectivity or perfusion?; and (4) Based on this summary of the neuroimaging literature (see Table 1), are there broad conclusions and recommendations that could be generated about the effects of aerobic exercise on the hippocampus in humans? We will also address gaps in the literature and suggest future directions for the field.

HIPPOCAMPAL MORPHOLOGY

Using MRI, the morphology of the hippocampus—including volume and shape—can be characterized. The findings from cross-sectional studies utilizing physical activity questionnaires are mixed (see Table 2), with some studies reporting that greater engagement in physical activity is associated with greater hippocampal volume (Gorham et al., 2019; Hashimoto et al., 2017; Killgore et al., 2013; McEwen et al., 2015; Nunley et al., 2017; Okonkwo et al., 2014; Tarkka et al., 2019), and other studies reporting null results (Bugg & Head, 2011; Head et al., 2012; Jeon et al., 2020; M. Ortega et al., 2015; Vemuri et al., 2012). For example, in a study of 61 healthy adults aged 18-45 years, more minutes per week exercising was associated with greater left and right hippocampal volume (Killgore et al., 2013). Many other studies have reported similar findings across healthy and patient populations, including schizophrenia and type 1 diabetes (Gorham et al., 2019; McEwen et al., 2015; Nunley et al., 2017; Okonkwo et al., 2014; Tarkka et al., 2019). Several studies of older adults (Bugg & Head, 2011; Head et al., 2012; Jeon et al., 2020; Vemuri et al., 2012) and adults with human immunodeficiency virus (HIV; M. Ortega et al., 2015) have failed to find similar associations, although Head and colleagues found decreased hippocampal volume among older adults with increased stress and lower physical activity levels (2012). These mixed findings might suggest that other unmeasured factors are either conflating or moderating the association.

Are physical activity levels predictive of future changes in hippocampal volume? One longitudinal study of older adults found that greater amounts of walking at baseline, assessed via a validated physical activity questionnaire, predicted greater total hippocampal volume nine years later (Erickson et al., 2010). Many other longitudinal studies of healthy older adults utilizing validated questionnaires have demonstrated similar results (Barha et al., 2020; Best et al., 2017; Erickson et al., 2010; Maltais et al., 2019; Smith et al., 2014; Tan et al., 2017). In contrast, in a sample of older adults with subjective cognitive complaints and mild cognitive impairment (MCI), reduced total hippocampal volume was associated with conversion to AD over a 2.4-year follow-up and self-reported physical activity did not modulate this association (Reijs et al., 2017). These mixed findings suggest that more research is needed to examine the importance of physical activity with the trajectory of hippocampal volume changes among other populations. While questionnaires offer an easily accessible measure of physical activity, particularly with long-term follow-up, the reliability of self-report measures of physical activity may vary based on the type of instrument used, whether it has been validated, and the populations being tested. Thus, these self-report instruments may not provide accurate descriptions of physical activity behavior in all studies. Other measures, such as device-measured physical activity or cardiorespiratory fitness, may be better able to characterize associations with the hippocampus.

Studies using accelerometry to measure daily physical activity allow for a precise quantification of daily sedentary behaviors and walking activity, including light and moderate-to-vigorous physical activity. While several studies have failed to find an association between device-measured physical activity and hippocampal volume (Alosco et al., 2015; Spartano et al., 2019), the majority of studies have reported that greater physical activity was associated with larger hippocampal volume, with some evidence for regional specificity to the subiculum (see Table 2). The effects might also vary as a function of the intensity of the activity. That is, while some cross-sectional studies have reported that greater time spent engaging in moderate-to-vigorous intensity but not low-intensity physical activity was associated with greater hippocampal volume (Klaren et al., 2015; Makizako et al., 2015; Raichlen et al., 2019), others have found the amount of low-intensity but not moderate-to-vigorous intensity physical activity to be predictive of hippocampal volume (Varma et al., 2015, 2016). Despite this discrepancy related to the intensity of the activity, these cross-sectional results suggest that greater amounts of physical activity tend to be associated with greater hippocampal volume. Future investigations are necessary for determining whether the intensity of the physical activity is important for hippocampal volume as compared to other parameters of activity, such as the length, frequency, or type of activity.

Most studies that have examined the association between cardiorespiratory fitness and hippocampal volume have reported a significant positive association (see Table 2), but several have failed to find an association among older adults (Cole et al., 2020; Engeroff et al., 2018; Honea et al., 2009; Raichlen et al., 2019; Wood et al., 2016). Particularly, cross-sectional studies have reported that higher cardiorespiratory fitness levels are associated with greater hippocampal volume among healthy children and adults, with some evidence for regional specificity to the left anterior hippocampus (Boots et al., 2015; Chaddock et al., 2010; Dougherty et al., 2017; Erickson et al., 2009; Fletcher et al., 2016; Herting & Nagel, 2012; McAuley et al., 2011; F. B. Ortega et al., 2017; Stillman et al., 2018; Szabo et al., 2011). Similar cross-sectional results have been found among patients with conditions that often affect the volume of the hippocampus, including multiple sclerosis (Motl et al., 2015), MCI (Makizako et al., 2013), overweight or obesity (Aghjayan et al., 2020; Bugg et al., 2012; Esteban-Cornejo et al., 2017), and breast cancer survivors (Chaddock-Heyman et al., 2015). Interestingly, one study of 7-9-year-old children found that higher cardiorespiratory fitness levels were associated with expansion in some parts, and contraction in other parts, of the right hippocampus (F. B. Ortega et al., 2017). These findings suggest that cardiorespiratory fitness may be associated with total volume of the hippocampus because of more regionally-specific associations with particular subfields. This general pattern is consistent with the animal literature demonstrating that aerobic exercise increases cell proliferation and synaptic plasticity in a regionally specific manner (Van Praag et al., 1999). The reasons for why some studies fail to find this association remain a mystery but could be related to the population, the way in which cardiorespiratory fitness was measured, the range of fitness levels, or third variables that have been unaccounted for.

While cross-sectional studies provide insight into the association between cardiorespiratory fitness and hippocampal volume, studies that utilize RCT designs are better positioned to make causal inferences about engagement in exercise and changes to hippocampal morphology. Although changes to hippocampal volume have been studied within the context of aerobic exercise interventions, the results remain rather equivocal. A recent meta-analysis of 14 RCTs in adults found that aerobic exercise prevents a reduction in left hippocampal volume, but does not influence total or right hippocampal volume (Firth et al., 2018). An examination of the individual studies included in the meta-analysis indicates that aerobic exercise had a significant positive effect on total, regional, or lateral hippocampal volume depending on the population included in the study. This suggests that hippocampal volume is particularly sensitive to various factors including age, neurological health, and psychiatric health. However, a number of studies have failed to find significant effects in healthy adolescents and adults with a range of psychiatric and neurological conditions known to affect the hippocampus (Bunketorp Käll et al., 2015; Frederiksen et al., 2018; Krogh et al., 2014; Malchow et al., 2016; Scheewe et al., 2013; Tarumi et al., 2019). However, one of these studies reported an exercise adherence rate of only 36% (Krogh et al., 2014), raising methodological and theoretical questions about the inclusion of studies with both poor or good (>80%) adherence rates. A recent meta-analysis of exercise interventions found a significant reduction in control groups' total hippocampal volume from pre- to post-intervention, but not left or right hippocampal volume, while an overall increase in the intervention group was not significant (Wilckens et al., 2021). When examining the characteristics of the samples and interventions, the overall effect was significant for adults 65 years and older, interventions 24 weeks or longer, and interventions providing up to 150 minutes of exercise per week (Wilckens et al., 2021). These findings suggest that the parameters of the intervention and sample characteristics may account for some of the heterogeneity in findings across the field.

Improvements in cardiorespiratory fitness may be a precondition for intervention effects on hippocampal volume. Several studies reported in Firth et al. (2018) found that exercise-induced increases in hippocampal volume were correlated with increases in cardiorespiratory fitness across healthy and patient populations (Erickson et al., 2011; Jonasson et al., 2016; Maass et al., 2015; Morris et al., 2017; Niemann et al., 2014; Pajonk et al., 2010). However, these findings were not unanimous. For example, one study found significant changes in hippocampal volume in women with early psychosis despite failing to find significant improvements in cardiorespiratory fitness among the intervention group (Lin et al., 2015). In children, no significant effect of a curriculum-based physical activity intervention was found on hippocampal volume despite significant increases in cardiorespiratory fitness among boys following the intervention (Bunketorp Käll et al., 2015). Thus, the extant literature suggests that (a) exercise interventions, at the very least, might be an effective method for preventing hippocampal atrophy and shrinkage – a finding that could have significant public health implications, (b) increases in cardiorespiratory fitness might be a critical precondition for finding effects of the intervention on the hippocampus, suggesting that studies of greater intensity and longer length might be more likely to alter hippocampal volume, and (c) effects might be moderated by age or the presence of disease states in which the hippocampus is affected. Notably, significant heterogeneity across intervention parameters, adherence, level of supervision, monitoring of intensity, and other factors make the conclusions about the impact of exercise interventions on hippocampal volume even muddier. Consistency and harmonization of methodology, a focus on greater adherence, and larger sample sizes are needed to clarify these results.

It remains poorly understood how long the effects of exercise on hippocampal morphology persist after the conclusion of the intervention. One study found in sedentary young to middle-aged adults that exercise-induced increases in hippocampal volume returned to baseline levels approximately six weeks following the completion of the six-week intervention (Thomas et al., 2016). This is likely not a surprising finding since maintaining positive consequences (i.e., hippocampal volume) of a behavioral change (i.e., exercise) often requires that the behavioral change itself also be maintained. As an analogy, dietary changes would likely influence glucose regulation but would not be maintained if someone returns to an unhealthy diet. This is an important consideration since most interventions fail to report the time between the conclusion of the intervention and when hippocampal morphology was assessed. Thus, it is likely that interventions that measure hippocampal volume several weeks or months after the completion of an intervention might be missing any positive benefits of the exercise intervention if their participants discontinue exercising. Unfortunately, because studies fail to report the average length of time between the end of the exercise intervention and when the assessment of hippocampal volume occurred, it is unknown whether this factor could explain some of the murkiness of the literature.

Taken together, these mixed results suggest that while aerobic exercise might have an effect on hippocampal volume, the effect could be small, transient, or there may be other factors moderating or better explaining it. For example, more robust and consistent results were found for older adults and patients with early AD, whereas results were heterogeneous for patients with schizophrenia, suggesting that one potential moderator may be the population studied. The parameters of the intervention, such as the mode, duration of exercise bout, frequency, intensity, and/or length of intervention are also likely moderating the impact of exercise on hippocampal morphology. Although there is strong support for a relationship between cardiorespiratory fitness and hippocampal volume, it remains equivocal whether increases in cardiorespiratory fitness via an aerobic exercise intervention are a necessary precondition for detecting changes in hippocampal volume. Furthermore, very few aerobic exercise interventions have targeted children, highlighting a need for future studies to elucidate the effect of exercise on hippocampal volume in youth.

HIPPOCAMPAL WHITE MATTER

The WM tracts most associated with the hippocampal formation include the fornix, which provides direct connection to the mammillary bodies of the hypothalamus, septal nuclei, and nucleus accumbens, as well as the cingulum, which interconnects the entorhinal cortex of the hippocampal formation to structures in the frontal, parietal, and temporal lobes. The health of WM pathways can be characterized using a number of techniques, including whole brain or regional volumetrics, identifying lesions, and assessing the microstructural integrity of WM fibers. Investigations using these measures have shown that WM structural health declines broadly with age and in the presence of pathology, such as AD (Bartzokis et al., 2001, 2004; Mielke et al., 2012; Villain et al., 2008; Westlye et al., 2009). As discussed in the systematic review conducted by Sexton and colleagues (2016), at present, few studies have investigated the potentially protective or enhancing effect of physical activity on WM structure, and the findings related to WM tracts connected to the hippocampus are mixed.

White Matter Microstructure

Diffusion tensor imaging (DTI) estimates the orientation, direction, and rate of water diffusion within brain tissue and provides detailed insight into the characteristics of WM fiber structure (Pfefferbaum & Sullivan, 2002). The most commonly used DTI parameter is fractional anisotropy (FA), a measure of the directional preference of water diffusion, which reflects various aspects of WM organization. Typically, higher FA values are positively related to axonal and myelin integrity, as well as fiber density. WM integrity, and specifically the integrity of the fornix and cingulum, has been consistently linked to aging and cognitive performance, including processing speed and memory function (Burzynska et al., 2017; Madden et al., 2008; Turken et al., 2008; Vernooij et al., 2009).

WM microstructure has received more attention than other indices of WM health in the exercise and cardiorespiratory fitness literature, although the findings are mixed and span widespread tracts that interconnect the bilateral frontal, temporal, parietal, and occipital gray matter, as well as global WM integrity (Chaddock-Heyman et al., 2014; Clark et al., 2019; K. Ding et al., 2018; Gow et al., 2012; Johnson et al., 2012; Maltais et al., 2020; Rodriguez-Ayllon, Esteban-Cornejo, et al., 2020; Teixeira et al., 2016; Tseng et al., 2013; Voss et al., 2013). In large part, studies focused on WM tract integrity have used an exploratory approach, rather than targeting specific pathways. Still, a considerable amount of evidence has shown associations between physical activity, and related measures such as cardiorespiratory fitness, and WM microstructure specific to hippocampal projections. In a study including two large, independent samples of 113 and 154 older adults (Oberlin et al., 2016), higher cardiorespiratory fitness was correlated with greater FA in the cingulum bundle and fornix. Furthermore, FA in the left cingulum partially mediated the relationship between cardiorespiratory fitness and spatial working memory, suggesting that WM integrity is a critical component in the relationship between cardiorespiratory fitness and elevated spatial memory performance. In healthy midlife to older adults, higher cardiorespiratory fitness was associated with higher FA in the right hippocampal segment of the cingulum and the left cerebral peduncle (F.-T. Chen et al., 2020). Similarly, in a sample of 15 older adults, Marks and colleagues (2011) found that cardiorespiratory fitness explained 28.5% of the variance in FA in the left cingulum. Another study that focused on both cardiorespiratory fitness and device-measured physical activity levels in low-fit older adults reported that greater engagement in light physical activity and higher cardiorespiratory fitness were associated with greater FA in the temporal lobe (Burzynska et al., 2014). However, the relationship with cardiorespiratory fitness was reduced to trend level upon correction for covariates.

Most studies of physical activity, cardiorespiratory fitness, and WM integrity have focused on FA. However, several other attributes of hippocampal WM microstructural health may be associated with physical activity. For instance, in children, WM fiber density (mean diffusivity) was associated with parent-reported physical activity across multiple WM tracts, including the hippocampal cingulum (Rodriguez-Ayllon, Derks, et al., 2020). A study of older adults with early AD did not find significant associations between cardiorespiratory fitness and FA in the cingulum bundles (Perea et al., 2016). However, the authors reported a trending association between higher cardiorespiratory fitness and lower myelin damage (radial diffusivity) in the right cingulum. Similarly, in post-menopausal women, Harasym and colleagues (2020) found a significant relationship between higher fitness and higher axonal integrity (axial diffusivity) in the hippocampal segments of the cingulum. Bracht and colleagues (2016) found that greater amounts of device-measured engagement in physical activity was associated with greater myelination (myelin water fraction), but not FA, in the right parahippocampal cingulum in healthy young adults. Their findings suggest that myelin health may underlie associations between physical activity and WM integrity. However, continued work combining multiple parameters of WM integrity will be necessary to shed light on which aspects of WM microstructure, particularly in the fornix and hippocampal cingulum, are sensitive to physical activity.

In contrast to the cross-sectional studies described above, there have been fewer published RCTs examining the impact of aerobic exercise training on WM integrity, and these results are mixed (Clark et al., 2019; Sexton et al., 2020). For instance, Burzynska and colleagues (2017) randomized 174 older adult participants into either a walking, dancing, walking/nutrition, or active control group. Only the dancing group showed an effect of training on FA, specifically in the fornix. In another study focusing on adults with schizophrenia and healthy controls, Svatkova and colleagues (2015) found that a six-month cycling intervention resulted in increased FA in multiple fiber tracts, although not pathways connected to the hippocampus. Further, Voss and colleagues (2013) conducted a year-long, aerobic exercise intervention in 70 older adults, consisting of an aerobic walking group and a stretching control group. Here, the authors did not find significant group-level effects of exercise training. However, greater post-intervention fitness levels were associated with increased frontal and temporal FA, as well as enhanced short-term memory. Even fewer exercise RCTs have focused on WM integrity in children. In a recent intervention, Chaddock-Heyman and colleagues (2014) randomized 143 children between the ages of 7 to 9 into a nine-month moderate-to-vigorous exercise training program or a waitlist control condition. The intervention group showed significantly greater increase in FA in the genu of the corpus callosum. In another intervention with 8 to 11-year-old children with overweight, the intervention group showed a greater increase in FA in the uncinate fasciculus after 8 months of exercise (Schaeffer et al., 2014). However, in both of these studies, the authors did not examine the effects of the intervention on hippocampal WM tracts, and thus, the influence of aerobic exercise on hippocampal WM in children requires further investigation.

This mixed pattern of findings raises a number of possible explanations. First, aerobic exercise interventions typically use a timeframe ranging between several months to a year. Although participating in continuous aerobic exercise increases cardiorespiratory fitness, it may be possible that more long-term maintenance of physical activity is necessary to influence WM projections to and from the hippocampus. Overall, the small number of exercise interventions, coupled with heterogeneity in study scope, demographics, length, and method of exercise, limit the generalizability of results and make interpretation difficult. Of further note, in comparison to other major WM pathways, fiber bundles communicating with the hippocampal formation are structurally narrow and winding (i.e., ‘crossing fibers’), posing a challenge for neuroimaging research focused on characterizing the structural health of these pathways (Maller et al., 2019; Nieuwenhuys et al., 1988). Thus, studies with high fidelity neuroimaging data that incorporate multiple measures of microstructural integrity may be particularly important in elucidating the associations between fitness and WM connections to and from the hippocampus.

White Matter Volume

While several investigations in older adults and children have found positive associations between cardiorespiratory fitness, self-reported physical activity, and exercise training using RCTs with WM volumes in various pathways (Colcombe et al., 2006; Erickson et al., 2007; Esteban-Cornejo et al., 2019; Ho et al., 2011), others have yielded null results (Gordon et al., 2008; Honea et al., 2009). Sexton and colleagues (2016) reported meta-analytic results, which revealed that higher levels of physical activity and cardiorespiratory fitness were significantly associated with higher global WM volume, albeit with small effect sizes. Their analyses did not establish support for associations between physical activity or fitness and localized WM volume in the temporal lobe (i.e., near the hippocampus). However, similar to studies of WM integrity, studies focused on WM volume and physical activity are highly variable in scope and methodology. Furthermore, there is a paucity of studies focusing on associations between exercise, fitness, and WM volume in tracts that communicate with the hippocampus. Accordingly, associations between exercise exposure, cardiorespiratory fitness and volume of the fornix and cingulum remain poorly understood.

One question raised by the mixed findings of studies targeting WM integrity and physical activity metrics is whether current techniques, such as DTI, are sensitive enough to detect differences in the WM changes that appear to be predicted by animal models (Lin Chen et al., 2020; Graham et al., 2019; Xiao et al., 2018). Techniques for WM imaging in humans have greatly improved over the past decade, which raises a potential challenge with interpreting results across the literature since earlier studies may obscure the sensitivity of findings from studies using more recent, higher resolution techniques. Nonetheless, there have been significant improvements in sensitivity across most imaging domains, which may be to the benefit of continued work examining the influence of physical activity on hippocampal health across neuroimaging metrics. Notably, as previously mentioned, Bracht and colleagues (2016) reported that myelination as a measure of WM integrity may be more sensitive than traditional DTI parameters, yet this approach has not been frequently used in the physical activity literature. Further, multishell methods of imaging have facilitated our ability to quantify microstructural integrity even in regions of crossing fibers and may enable increased sensitivity in human studies.

White Matter Hyperintensities

WM hyperintensities (WMH) are lesions that are considered to be clinically significant and are predictive of increased risk of cardiovascular events, stroke, dementia, and mortality (Debette & Markus, 2010). WM lesions specific to the fornix and cingulum bundles, in both animals and humans, have been linked to memory impairment and decline (Aggleton et al., 1995, 2010; Gaffan, 1994; Gaffan & Gaffan, 1991; Lockhart et al., 2012; Shamy et al., 2010). While several investigations have assessed the relationship between self-reported physical activity and WMH throughout the brain, many of these reports have been cross-sectional and yielded null findings (Ho et al., 2011; Rosano et al., 2010). In contrast, several studies reported that higher fitness and self-reported and device-measured physical activity was correlated with reduced overall lesion volume (Burzynska et al., 2014; Saczynski et al., 2008; Sen et al., 2012; Wirth et al., 2014). Similarly, one longitudinal investigation reported that greater amounts of self-reported physical activity at baseline was linked to lower lesion volume three years later (Gow et al., 2012). However, WMH are typically identified using global, rather than localized approaches, and at present, human studies of exercise or fitness have not specifically discussed WMH in hippocampal projections.

HIPPOCAMPAL FUNCTIONAL CONNECTIVITY

Whereas structural MRI studies reveal valuable information about the associations between aerobic exercise and hippocampal morphology, including white matter projections, other techniques such as resting state functional connectivity (rsFC) can provide further insight into the health of hippocampal circuitry (Gusnard & Raichle, 2001). rsFC measures temporal correlations in blood oxygen level dependent (BOLD) signal of spatially distributed brain regions at rest to identify “functional networks”, or networks of brain regions that tend to co-activate in various states. A number of such networks have received considerable attention in recent years, most prominently the default mode network (DMN). The DMN includes parts of the hippocampal formation and the medial frontal, posterior parietal, posterior cingulate, and retrosplenial cortices (Buckner et al., 2008). Disruptions in the connectivity of the DMN regions are found in aging (Andrews-Hanna et al., 2007), MCI (Lustig et al., 2003), and AD (Greicius et al., 2004), and correlate with impaired cognitive performance. Further, the regions of the DMN that are most sensitive to aging may also be sensitive to physical activity and cardiorespiratory fitness (Voss et al., 2016). Accordingly, there has recently been an increased interest in exercise as a method for enhancing the connectivity of the DMN and related functional brain networks and regions.

Cross-sectional reports demonstrate relationships between exercise engagement and/or cardiorespiratory fitness and rsFC between regions of the hippocampal formation and diffuse brain areas. Voss and colleagues (2016) found that higher cardiorespiratory fitness, but not accelerometry-measured physical activity, was associated with greater rsFC in a number of large-scale cortical networks in healthy older adults. These effects were strongest within the DMN, particularly in prefrontal and medial temporal regions, including the parahippocampal gyrus. In a study focused on connectivity among various seed locations, higher cardiorespiratory fitness associated with greater parahippocampal, but not hippocampal, interhemispheric rsFC in 284 healthy midlife adults (Ikuta & Loprinzi, 2019). Another recent investigation of 50 healthy young adults reported that higher cardiorespiratory fitness was associated with higher rsFC of the left anterior hippocampus to the frontal pole, middle frontal gyrus (MFG), and parahippocampus (Stillman et al., 2018). However, the authors also reported a surprising inverse relationship between cardiorespiratory fitness and rsFC in the right anterior hippocampus to the right superior frontal gyrus, reflecting possible hemispheric differences in the associations of cardiorespiratory fitness with hippocampal connectivity. Further, in an observational study, composite variables reflecting current physical activity and physical activity accumulated over a decade were associated with rsFC in the posterior cingulate cortex of the DMN, but not the hippocampus (Boraxbekk et al., 2016). Notably, the composite variables used to index physical activity reflect health characteristics commonly associated with physical activity, but do not clearly estimate fitness or engagement in exercise. Overall, these cross-sectional studies suggest that cardiorespiratory fitness and physical activity may be important for functional connectivity between medial temporal regions, including the hippocampus, and other brain structures that support memory function and executive functioning in adults.

Several RCTs have also investigated changes in rsFC between the hippocampus and multiple brain regions following exercise training, with mixed findings. One trial found that older adults participating in a four-month walking intervention showed increased overall connectivity between the hippocampus and the rest of the brain, particularly the anterior cingulate cortex (ACC), as compared to controls (Burdette et al., 2010). In contrast, Flodin and colleagues (2017) reported no significant differences in rsFC between older adults in an aerobic exercise and active control group after six months of intervention. However, post-hoc analyses revealed that improvements in cardiorespiratory fitness predicted higher rsFC of the right hippocampus to frontal and parietal areas, and lower rsFC of the left hippocampus to the precentral gyrus. Similar to findings reported by Stillman and colleagues (2018), these results indicate laterality differences in rsFC of the hippocampus in association with cardiorespiratory fitness, though in opposite directions. Although these hemispheric differences may be related to differential recruitment of resources, the discrepancies with regard to which hemisphere of the hippocampus showed increased rsFC makes interpretation difficult. It is possible that these differences relate to the age groups included in the studies, but research across the lifespan will be needed to clarify these questions.

Overall, evidence from observational and intervention research indicates that greater engagement in aerobic exercise and/or higher cardiorespiratory fitness may be beneficial to functional connectivity between the hippocampus and a diffuse array of brain regions critical for various cognitive functions. Yet studies focused on hippocampal rsFC are few in number, particularly aerobic exercise interventions. A handful of studies have investigated associations between acute bouts of aerobic exercise and rsFC, and they have reported that single sessions of light or moderate-intensity aerobic exercise predict rsFC in multiple networks. These networks include prefrontal, temporal, and parietal connections that overlap with the DMN (Voss et al., 2020) and the hippocampal-cortical network (Weng et al., 2017). Still, clarity regarding the similarities and differences in the effects of acute exercise on rsFC is warranted prior to drawing any conclusions. Moreover, cross-sectional studies of cardiorespiratory fitness and hippocampal connectivity have largely focused on young and midlife adults, whereas interventions have targeted older adults. Additional work in children and adolescents could provide valuable information about relationships between exercise, fitness, and hippocampal connectivity early in life.

Lastly, few studies have focused on hippocampal rsFC in patient populations in the context of physical activity and related metrics. One study of midlife adults with multiple sclerosis reported associations between rsFC and device-monitored physical activity levels from an accelerometer worn for 7 days during waking hours (Prakash et al., 2011). Higher levels of physical activity were associated with increased rsFC from the hippocampus to the posteromedial cortex, parahippocampal gyrus, superior frontal gyrus, and the medial frontal cortex. Similarly, Leavitt and colleagues (2014) reported preliminary results of an RCT, in which patients with multiple sclerosis in a three-month aerobic exercise group, but not controls, showed increased rsFC within the hippocampus. Together, these results suggest that patients with conditions involving altered hippocampal function might especially benefit from engaging in aerobic exercise.

HIPPOCAMPAL PERFUSION

Arterial spin labeling (ASL) perfusion MRI provides a quantitative measure of blood flow and offers information about how the brain meets and regulates its metabolic demand (Hales et al., 2014). Few cross-sectional studies have examined the relationship between hippocampal perfusion and physical activity or cardiorespiratory fitness. One study reported that greater device-measured sedentary time was associated with greater left hippocampal perfusion in sedentary older adults at genetic risk for AD (Zlatar et al., 2014). The authors speculated that the elevated perfusion might represent a compensatory mechanism for metabolic changes in preclinical AD. Among children, one study reported an association between higher cardiorespiratory fitness levels and greater hippocampal cerebral blood flow (CBF), with specific associations for the posterior hippocampus (Chaddock-Heyman et al., 2016). To date, no studies have examined the relationship between self-reported physical activity and hippocampal perfusion. Although there is promising evidence for differences in hippocampal perfusion as a function of cardiorespiratory fitness across the lifespan, future research is needed to explore these relationships further.

While few studies have examined the association between cardiorespiratory fitness and hippocampal CBF, a growing body of literature shows that aerobic exercise interventions increase hippocampal CBF (Burdette et al., 2010; Maass et al., 2015; Pereira et al., 2007). In particular, three to four months of an aerobic exercise intervention increased hippocampal CBF relative to non-exercising control groups in older adults (Burdette et al., 2010; Maass et al., 2015). Among midlife adults, three months of aerobic exercise increased CBF in the dentate gyrus subregion of the hippocampus (Pereira et al., 2007). When older adults with a history of long-term endurance training stopped all physical activity for 10 days, CBF within the left and right hippocampus decreased significantly, suggesting that exercise training was a critical component to hippocampal perfusion and that the benefits of exercise are transient or must be maintained (Alfini et al., 2016). While these effects have been examined in studies with small sample sizes (i.e., $N_{Pereira}$=11, N_{Alfini}=12) and have not yet been studied in other patient populations, preliminary rodent studies have examined these effects in the context of Parkinson's disease (Wang et al., 2015) and depression (Linmu Chen et al., 2017) and found similar results. Although the literature is scarce, these results suggest that hippocampal perfusion increases in response to exercise. Importantly, there have been no aerobic exercise interventions targeting children and hippocampal CBF, highlighting a need for future studies to elucidate the effect of exercise on hippocampal perfusion in youth.

There has been speculation for many years that the cognitive-enhancing effects of exercise might be occurring through increased CBF (Davenport et al., 2012). Animal literature demonstrates that exercise increases the production of new capillary beds, which provides increased nutrients and energy to the brain and might result in increased cerebral blood volume or flow (Swain et al., 2003). Evidence from RCTs of aerobic exercise interventions suggests that similar increases in hippocampal CBF can be detected in humans and might have an impact on disease or cognition. Increases in hippocampal perfusion have been associated with improvements in spatial object recall and recognition in older adults (Maass et al., 2015) and verbal recall among midlife adults (Pereira et al., 2007). Further work is needed to replicate these findings and extend them to other populations.

Of particular importance is whether increasing cardiorespiratory fitness through aerobic exercise interventions is a critical precondition for finding effects on hippocampal CBF. Several of the aforementioned interventions found that exercise-induced improvements in cardiorespiratory fitness were associated with increases in CBF in the hippocampus among older adults (Maass et al., 2015) and the dentate gyrus of midlife adults (Pereira et al., 2007). Although there is limited research, these results suggest that exercise interventions targeting improvements in cardiorespiratory fitness may increase hippocampal CBF. However, it remains to be tested whether changes in cardiorespiratory fitness are *necessary* to detect changes in hippocampal CBF following an intervention.

MECHANISMS

At present, the precise mechanisms by which engaging in physical activity influences the hippocampus remain poorly understood in humans. Nevertheless, exercise has been implicated in reducing multiple peripheral risk factors for neural decline, and thus has been described as uniquely positioned to promote brain health (Cotman et al., 2007). Rodent research has identified multiple cellular and molecular mechanisms that provide a foundation for explaining the associations among exercise, cardiorespiratory fitness, and the hippocampus in humans, specifically: (i) neurotrophins, (ii) stress hormones, (iii) inflammation, and (iv) insulin sensitivity. Although speculative, it is possible that one or more of these mechanisms explain the associations between exercise, fitness, and the hippocampal findings in humans.

Animal studies suggest that exercise training increases levels of growth factors and neurotrophins that influence cell proliferation and survival (Q. Ding et al., 2006; Van Praag et al., 2005), including brain-derived neurotrophic factor (BDNF; Rossi et al., 2006), vascular endothelial growth factor (VEGF; Fabel et al., 2003), and insulin-like growth factor 1 (IGF-1; Trejo, Carro, & Torres-Aleman, 2001). For example, BDNF is important in the growth and survival of neurons, axonal transport, long-term potentiation and memory formation (O'Bryant et al., 2009), and axonal growth (Ghiani et al., 2007). Importantly, exercise increases BDNF expression levels in the hippocampus (P. Liu & Nusslock, 2018; Neeper et al., 1995; Vaynman et al., 2004). Animal models have demonstrated greater BDNF synthesis during high-intensity exercise compared to low-intensity exercise and sedentary behaviors (de Almeida et al., 2013). Further, increases in hippocampal BDNF expression have been found after short (e.g., one week; Griffin et al., 2009) and long (e.g., four weeks; Y.-F. Liu et al., 2009) lengths of exercise. Human studies have reported that exercise-induced changes in hippocampal volume were correlated with changes to serum-derived BDNF among healthy older adults (Erickson et al., 2011). Aerobic exercise interventions have proven effective in increasing serum BDNF levels across several patient populations, including AD and schizophrenia (Choi et al., 2018; Green et al., 2011; Hock et al., 2000; H. Kim et al., 2014; Kuo et al., 2013). BDNF might also be an important mediator of cardiorespiratory fitness and exercise associations with white matter. Lower levels of plasma BDNF have been correlated with a steeper decline of WM volume in females (Driscoll et al., 2012). Single-nucleotide polymorphisms that influence the regulated secretion of BDNF have also been associated with lower WM volume and higher WMH burden (Huang et al., 2014). However, more research is needed to investigate whether exercise-related increases in BDNF, and other neurotrophic factors, influence the integrity of hippocampal WM projections. Nonetheless, alterations in neurotrophic factors may be one mechanism through which exercise contributes to overall increases in hippocampal health.

Changes to the hypothalamic-pituitary-adrenal (HPA) axis might be another mechanism by which engaging in exercise influences the hippocampus. Chronic stress has been associated with altered synaptic terminal structure in the rat hippocampus (Magariños et al., 1996) and suppressed hippocampal neurogenesis (Egeland et al., 2015; Gould & Tanapat, 1999). Likewise, decreases in dendritic spine density and severity of hippocampal atrophy have been associated with elevated release of corticosterone (Foy et al., 1987; Woolley et al., 1990). In contrast, voluntary exercise has been linked to reduced plasma cortisol and improved memory in young and old rodents (Estrada et al., 2019). Other work (D.-M. Kim & Leem, 2016) suggests that exercise reduces the impact of chronic stress on the rat hippocampus by enhancing the activity of Adenosine monophosphate-activated protein kinase (AMPK), which is important in the induction of BDNF expression and hippocampal neurogenesis (Yoon et al., 2008). Cross-sectional work focusing on older adult humans has indicated a convergent pattern of findings, such that self-reported physical activity moderated the association between lifetime stress and hippocampal volume and memory. Lower engagement in physical activity was associated with greater stress-related hippocampal decline when compared to higher physical activity engagement (Head et al., 2012). Further, research in young adult males has shown that varying intensities of exercise activate the HPA axis differently: moderate-to-vigorous intensity aerobic exercise increased cortisol and decreased adrenocorticotropic hormone concentrations but low-intensity activity had the opposite effect (Hill et al., 2008). However, further research is needed to determine the threshold necessary to induce a cortisol response. Summarily, engagement in exercise may mitigate the deleterious effects of chronic stress and its by-products on the hippocampus by modulating cortisol levels and the activity of AMPK and BDNF.

Chronic inflammation is a risk factor for a number of neurodegenerative diseases (Amor et al., 2010; Perry, 2004), and the hippocampus is quite susceptible to reduced decline as a result of chronic systemic and neuroinflammation (Barrientos et al., 2015). Engagement in habitual exercise may create an anti-inflammatory response by inducing long-term changes in circulating cytokines (Petersen & Pedersen, 2005). Studies in rats have shown compelling evidence of a long-term anti-inflammatory effect of aerobic exercise (Ryan & Nolan, 2016), and an associated reduction in hippocampal decline (Gomes da Silva et al., 2013; Lovatel et al., 2013). Although findings in humans are less consistent, there is also evidence of an immune-regulating influence of aerobic exercise in human adults (Sallam & Laher, 2015; Woods et al., 2011). Similarly, higher levels of cardiorespiratory fitness have been associated with lower circulating levels of pro-inflammatory cytokines, such as interleukin (IL) −6, and greater circulating levels of anti-inflammatory cytokines, such as IL-10 (Kullo et al., 2007; Wedell-Neergaard et al., 2018). However, research suggests that intense exercise may induce an excessive inflammatory response by down-regulating anti-inflammatory cytokine IL-10 and up-regulating the pro-inflammatory cytokines IL-1 and IL-1R1, whereas mild exercise may induce a mild inflammatory response by up-regulating the pro-inflammatory cytokine IL-1β and suppressing the pro-inflammatory cytokine TNF (Inoue et al., 2015). Accordingly, the potential anti-inflammatory effect of engaging in exercise may serve a protective role for the structural and functional health of the hippocampus depending on the intensity of the exercise.

Increased production of inflammatory cytokines, along with mitochondrial dysfunction, can also contribute to systemic insulin resistance, further accelerating neural decline (Pratchayasakul et al., 2015; Sripetchwandee et al., 2018). Healthy insulin signaling is essential for proper brain function. In the hippocampus, studies in rodents and healthy humans have suggested that the activation of insulin receptors results in insulin-induced enhancement of cognitive function (Biessels & Reagan, 2015). Here, too, preliminary studies in humans have found physical activity to improve metabolic function in both the brain and in the periphery by increasing insulin sensitivity and mitochondrial efficiency (Neufer et al., 2015). Such cellular and molecular changes then increase neural plasticity and promote the structural and functional integrity of the brain (Colcombe et al., 2004).

In all, research in animals and humans suggests multiple promising mechanistic explanations for associations between exercise, cardiorespiratory fitness, and the brain. It has also been suggested that exercise induces a cascade of systemic events that contribute to its impact on brain health and cognition, suggesting that the mechanisms outlined in this section may operate together, in sequence, or additively to promote hippocampal structure and function. Further work will be needed to elucidate nuances of how these mechanisms may operate and whether these explanations can account for broad influences on hippocampal structure and function, or if the effects are specific to certain metrics. For example, while hippocampal morphology and white matter connections may be mediated by BDNF expression, resting state connectivity and perfusion may be mediated by other mechanisms. An alternative perspective of mechanisms is to ask whether one measure of the hippocampus (e.g., volume) mediates its effects on other measures of the hippocampus (e.g., rsFC). Unfortunately, the majority of studies described in prior sections have utilized only a single neuroimaging technique in their analytical approach.

A major strength of neuroimaging is that it lends the ability to combine multiple MRI measures into a single analytical model to help better our understanding of the underlying mechanisms. In addition to larger datasets, studies that use multiple MRI measures allow us to assess how physical activity and exercise influence the structure and function of the hippocampus, as well as their interaction. A handful of studies have utilized a multi-modal analytical approach to better characterize the hierarchical nature of these metrics and attempt to resolve questions about whether one neuroimaging metric explains associations in another. Specifically, changes in hippocampal volume following an exercise intervention have been closely linked to changes in hippocampal perfusion, such that increased hippocampal blood flow largely accounted for increased volume (Maass et al., 2015). In contrast, Thomas and colleagues (2016) found that increases in hippocampal volume following an exercise intervention were better accounted for by an increase in myelinated fibers within hippocampal gray matter rather than increased vasculature. However, it cannot be ruled out whether other microstructural changes may also have contributed to increases in hippocampal volume. Furthermore, Stillman and colleagues (2018) found that associations between cardiorespiratory fitness and rsFC of the left anterior hippocampus were not explained by including left anterior hippocampal volume in the model, thereby indicating some independence of associations between rsFC and volumetric measures. Still, in light of the numerous metrics of hippocampal health that have been associated with cardiorespiratory fitness and exercise, the results of these multi-modal neuroimaging studies suggest that there may be mechanisms at multiple levels of hippocampal health.

CONCLUSION

This review highlights the considerable evidence that participation in aerobic exercise and increasing cardiorespiratory fitness are promising methods for promoting hippocampal health in humans. This conclusion comes from a summary of literature that includes much variability in experimental design, populations studied, measurements of physical activity and exercise, and neuroimaging measures of the hippocampus (see Figure 3). It is remarkable that, despite this level of heterogeneity in the science, there are consistent positive findings between physical activity, cardiorespiratory fitness, and hippocampal measurement. However, it is important to note that given the difficulty in publishing null-results, the synthesis of the studies included in this review might be a biased sample of all relevant studies. There are clearly significant gaps in knowledge (described in more detail below), but the bird's eye view of the field indicates a positive association between physical activity and the hippocampus in humans. It is also clear from this review that there is a need for future RCTs of exercise to use high-quality study designs and high-fidelity neuroimaging techniques to make more definitive conclusions about the role of exercise on hippocampal outcomes. Lastly, there is a need for a meta-analysis to synthesize the data reported in this review using a statistically rigorous approach to address questions such as the clinical importance of the effect and the consistency of the effect.

Cognitive Implications

An important question that arises from this literature is: are these effects of exercise on the hippocampus just meaningless by-products of engaging in exercise or do they have relevance for memory formation or academic performance? Although some volumetric studies have found a relationship between increased hippocampal volume and improvements in memory following an exercise intervention (Erickson et al., 2011; Maass et al., 2015), other interventions examining volumetric changes have not reported such cognitive benefits (Jonasson et al., 2016; Thomas et al., 2016). Furthermore, increases in hippocampal perfusion have been associated with improvements in spatial object recall and recognition, and verbal recall (Maass et al., 2015; Pereira et al., 2007), and associations between cardiorespiratory fitness and the cingulum were associated with spatial working memory in older adults (Oberlin et al., 2016). Thus, it seems that often studies that find significant associations between metrics of physical activity or cardiorespiratory fitness and the hippocampus also report associations in relevant domains of cognition. Still, it is not known whether there is a dose-response relationship modulating this effect, and what time course may be necessary for the detection of potential cognitive benefits associated with fitness and exercise. Ultimately, as more studies elucidate the effects of exercise training on the hippocampus, they should also target the related cognitive impact of these changes. In addition, many studies utilized small sample sizes, which limits the ability to reliably interrogate correlations with cognitive performance. Even fewer studies employ hippocampal-dependent memory tasks that would presume to be more strongly associated with the hippocampal measures described in this review.

Gaps in the literature

Among the studies included in this review, there are a number of apparent gaps in the literature. Specifically: (i) we have very little information about the impact of exercise on the hippocampal formation in children and adolescents, (ii) we have little knowledge of the effects of exercise on the hippocampal formation in certain disease states in which the hippocampus is affected, (iii) we have a poor understanding of the persistence of effects because few studies conduct follow-up assessments after completion of an intervention, (iv) we know little about the effects of acute exercise on hippocampal function, and (v) we have little information about specific exercise intervention parameters that are necessary to achieve changes to hippocampal health.

The majority of studies described in this review were conducted in older adults. While this has significant implications for aging-related cognitive outcomes, healthy hippocampal development is also crucial earlier in the lifespan, as adolescence and early adulthood are critical periods during which the hippocampus exhibits considerable reorganization and growth. While several studies have found a relationship between cardiorespiratory fitness and hippocampal volume, perfusion, and WM microstructure in adolescents, the literature in this area is still sparse. Furthermore, few exercise interventions examining hippocampal volume, perfusion, white matter, and rsFC have targeted children, highlighting a critical area for future research. Although older adults are a population at more immediate risk for hippocampal degeneration, intervention early in life may set the stage for healthy behavioral habits that have consequences for brain development and maturation later in life. In addition, the literature focusing on particular disease states that affect the hippocampus is also small, indicating a need for future research to assess various patient populations and the impact on disease course. This is particularly relevant for conditions that involve hippocampal deterioration, such as dementia and MCI (Pennanen et al., 2004), schizophrenia (Harrison, 2004), and multiple sclerosis (Roosendaal et al., 2010).

Much remains to be established with regard to the characteristics that make an exercise training protocol sufficient to impart benefits to the hippocampus. For instance, although there is consistent support for a relationship between cardiorespiratory fitness and the hippocampus, there is less consensus about whether increasing cardiorespiratory fitness is a necessary precondition for detecting changes in hippocampal health in the context of aerobic exercise interventions. This is an important distinction and may help differentiate among forms of exercise that are most effective in targeting the hippocampus. Furthermore, few intervention studies examined how long the effects of exercise on hippocampal volume, perfusion, white matter, and rsFC persist after the conclusion of the intervention, hindering our ability to assess whether the effects are transient or more long-lasting. Studies with extended follow-up periods can help provide valuable information about the longevity of benefits. Further, RCTs are essential in allowing us to examine causality, but they also offer little insight into the process of change, which can be better captured by observational studies. In addition, experiments examining the impact of acute exercise may also help bridge our understanding of whether brief bouts of activity have any discernible impact on the hippocampus. Ultimately, the field will benefit from the inclusion of an array of well-designed study approaches that aim to address such nuances in the degree to which various forms of physical activity may be effective in promoting hippocampal health.

There was considerable variability in intervention parameters across studies, including the mode, duration of exercise bout, frequency, intensity, and length. Heterogeneity across adherence, level of supervision, and monitoring of intensity are among other factors that reduce our certainty in any conclusions about the impact of exercise interventions on hippocampal structure and function. Given the variability in intervention parameters, there might be significant pieces of information lost when grouping across studies of varying sensitivity and precision – particularly about the importance of specific parameters in detecting effects. Future studies examining which intervention factors are critical for influencing hippocampal health are needed. There is also a need for consistency and harmonization of methodology in the field of exercise research, a focus on greater adherence, and larger sample sizes in order to clarify these results.

In summary, there are many consistent findings between physical activity and multiple metrics of hippocampal health, specifically: gray matter volume, white matter structure, resting state functional connectivity, and perfusion. This review primarily focused on exercise training that was aerobic in nature; however, there are a number of other forms of mixed-aerobic and non-aerobic activities associated with brain aging and the hippocampus, such as Tai Chi Chuan and Baduanjin practice (Tao et al., 2016, 2017), yoga (Hariprasad et al., 2013), and resistance training (Cassilhas et al., 2012; Liu-Ambrose & Donaldson, 2009). Moreover, studies included in this review that utilized self-report estimates of physical activity may have captured leisure time activity that encompasses both aerobic and non-aerobic physical activity. Thus, future research should investigate how different forms of physical activity may influence the hippocampus and other brain regions. Although the current research is promising, much more work using longitudinal approaches, and rigorous and standardized intervention methods, across the lifespan will elucidate how exercise and fitness influence hippocampal health and which aspects of its structure and function are particularly good targets of intervention.

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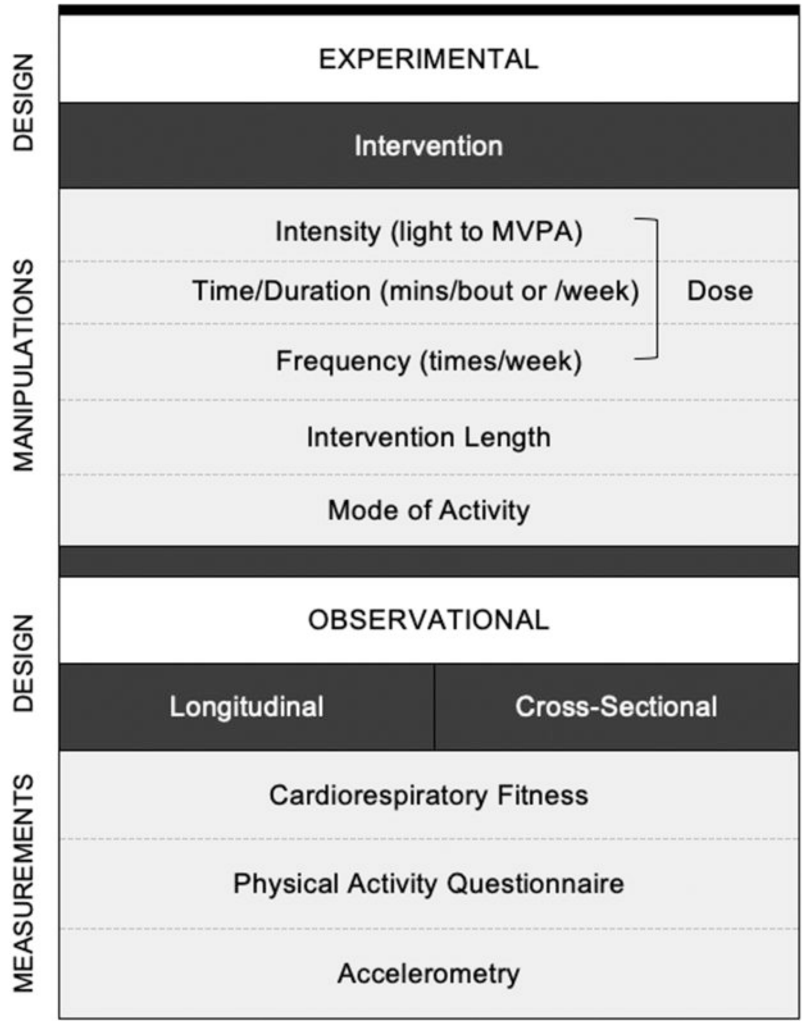

Figure 1.

Conceptual illustration representing the diversity of study designs and physical activity related measurements employed in the studies included in this review.

Note. Exercise dose is defined as intensity (ranging from light to moderate-to-vigorous physical activity [MVPA]), duration (e.g. minutes per bout or week of exercise), and frequency (e.g. number of exercise bouts per week).

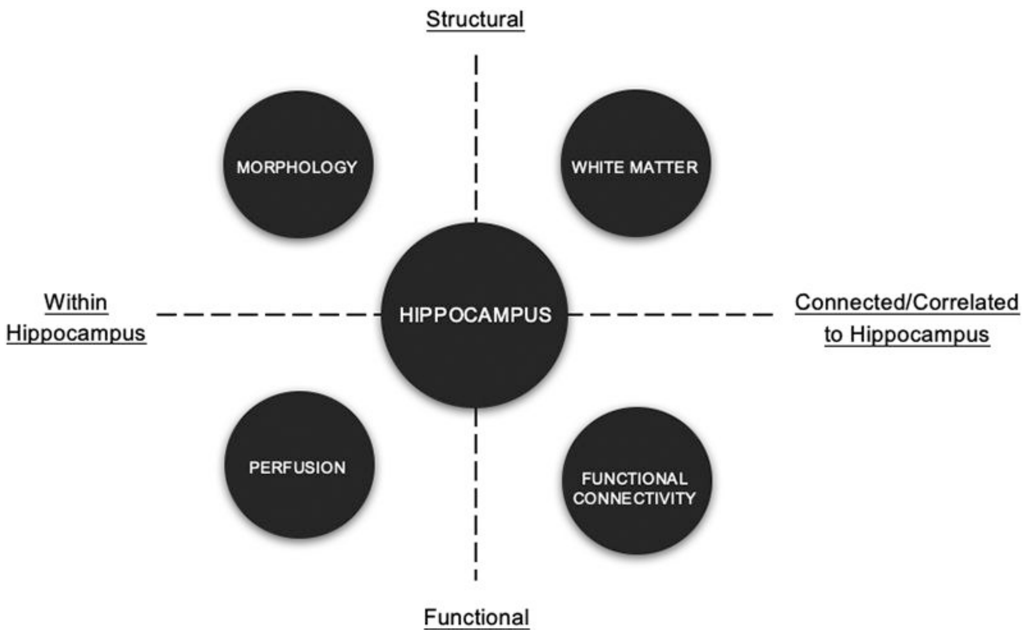

Figure 2.

Conceptual illustration representing the neuroimaging measurements focused on in this review and how they can be viewed with respect to the hippocampus.

Note. This is a simplified conceptual scheme rather than a theoretical or mechanistic model.

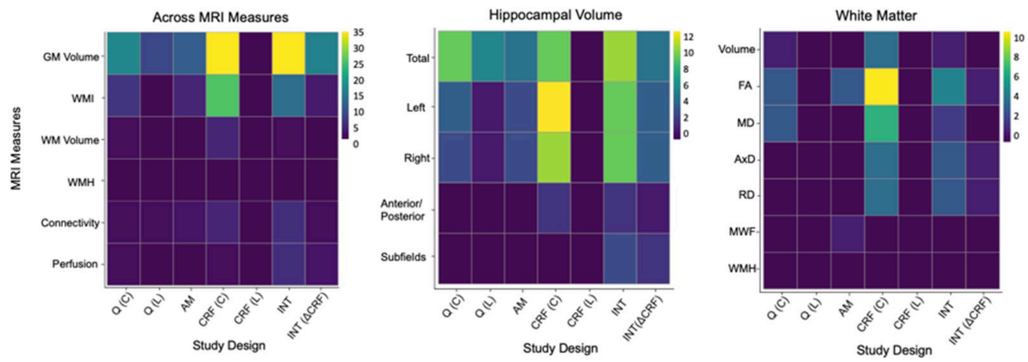

Figure 3.

Heat map illustration of the number of analyses outlined in this review, assessing hippocampal integrity (y-axis) using magnetic resonance imaging (MRI) measures of morphology (GM Volume), white matter integrity (WMI), white matter volume (WM Volume), white matter hyperintensities (WMH), functional connectivity, and perfusion to examine associations with physical activity measurements.

Note. Physical activity study designs (x-axis) include: (1) cross-sectional physical activity questionnaires (Q[C]); (2) longitudinal physical activity questionnaires (Q[L]); (3) accelerometry (AM); (4) cross-sectional cardiorespiratory fitness (CRF[C]); (5) longitudinal cardiorespiratory fitness (CRF[L]), including only observational studies and not randomized clinical trials; (6) interventions, including randomized clinical trials, training studies, and detraining studies, specifically measuring outcomes pre- and post-intervention (INT); and (7) interventions using the relative change in cardiorespiratory fitness as the main outcome (INT[ΔCRF]). The observations included in the heat maps are based on individual analyses within studies, as numerous studies conducted multiple analyses using various metrics of hippocampal integrity and physical activity. a) The number of analyses (n = 205) assessing any of the four magnetic resonance imaging measures reviewed in this study with relation to physical activity. b) The number of analyses (n = 124) assessing hippocampal morphology using total volume, left and right hippocampal seeds, anterior and posterior seeds, and subfields, examined in association with measures of physical activity. c) Number of analyses assessing (n = 58) white matter connections to the hippocampus using total volume, measures of white matter integrity, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), radial diffusivity (RD), and myelin water fraction (MWF), and white matter hyperintensities (WMH), examined in association with measures of physical activity.

Table 1.

Magnetic resonance imaging measures included in this review and their metrics.

Magnetic Resonance Imaging Measures	Metrics
Volumetric	Using methods such as T1-weighted or T2-weighted imaging, we are able to characterize the morphology of the cortex and subcortical areas, including volume, shape, and thickness.
Diffusion Weighted Imaging and White Matter	White matter microstructural integrity may be characterized using a number of metrics including radial diffusivity (RD), mean diffusivity (MD), axial diffusivity (AxD), or the summary measure (FA). Other metrics of integrity include myelin water fraction. White matter volume and volume of white matter lesions can also be quantified using methods such as T1-weighted or T2-weighted imaging.
Functional Connectivity	Correlated functional activation in various brain regions, at rest and during task performance, allow for the detection of functionally connected brain regions.
Perfusion	Arterial spin labeling perfusion MRI provides a quantitative measure of blood flow and offers information about how the brain meets and regulates its metabolic demand.

Table 2.

A description of studies examining the association of physical activity or exercise with metrics of hippocampal health.

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
MORPHOLOGY			
Cross-sectional Physical Activity Questionnaire			
Significant Findings			
Gorham et al. (2019)	Children (9-11 years)	Total, left, and right	Greater number of sports was associated with larger total and left HV, but not right HV.
Hashimoto et al. (2017)	Older adults (58-94 years)	Total	Hippocampal atrophy was associated with leisure-time physical inactivity.
Killgore et al. (2013)	Healthy adults (18-45 years)	Left and right	More minutes per week exercising was associated with greater left and right HV.
McEwen et al. (2015)	Patients with first-episode schizophrenia (18-45 years)	Total, left, and right	Lower PA was associated with decreased total and left HV, but not right HV.
Nunley et al. (2017)	Middle-aged adults with and without type 1 diabetes (35-60 years)	Total	Higher PA was associated with larger HV among type 1 diabetes subjects but not control subjects.
Okonkwo et al. (2014)	Late-middle-aged adults (40-65 years)	Total	Increasing age was associated with decreased HV, but effect was attenuated by 43% for active participants compared to inactive subjects.
Tarkka et al. (2019)	Male monozygotic twins (mean age 34.5 years)	Cluster in left	More-active co-twins had greater HV than less-active co-twins.
Null Findings			
Bugg et al. (2011)	Older adults (55-79 years)	Total	PA alone did not account for unique variance in HV.
Head et al. (2012)	Older adults (mean age 72.5 years)	Total	PA alone did not account for unique variance in HV. Compared to the high-exercise group, the low-exercise group had decreased HV with increasing stress.
Jeon et al. (2020)	Older adults with healthy cognition or MCI (55-90 years)	Total	Retrospective report of midlife PA was not associated with HV.
Ortega et al. (2015)	Adults with HIV (mean age 41.6 years)	Total	No HV differences between physically active and sedentary groups.
Vemuri et al. (2012)	Older adults with healthy cognition or MCI (70-90 years)	Total	PA was not associated with HV.
Longitudinal Physical Activity Questionnaire			
Significant Findings			
Barha et al., (2020)	Older adults (70-79 years)	Left and right	Maintaining time spent walking over 10 years predicted smaller left HV for women and larger left HV for men. Null results were found for right HV.
Best et al., (2017)	Older adults (70-79 years)	Total	Maintaining time spent walking over 10 years predicted less reduction in HV.
Erickson et al., (2010)	Older adults (≥65 years)	Total	Greater PA predicted greater HV 9 years later.
Maltais et al., (2019)	Older adults at risk of cognitive decline (mean age 75.3 years)	Total	Any level of PA was associated with a reduced decline in HV compared to inactivity over 3 years.
Smith et al., (2014)	Older adults (65-89 years)	Total	Those with low PA and one or both APOE ε4 alleles (High Risk/Low PA) had decreased HV compared to

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
			those all other groups over 18 months (i.e., Low Risk/Low PA, High Risk/High PA, Low Risk/High PA).
Tan et al., (2017)	Older adults (≥60 years)	Total	Greater PA was associated with greater HV over 10 years.
Null Findings			
Reijs et al., (2017)	Older adults with cognitive complaints and MCI (≥55 years)	Total	Lower HV was associated with conversion to AD-type dementia over 2.4 years, but it was not modulated by PA.
Cross-sectional Accelerometer			
Significant Findings			
(Hamer et al., 2018)	Middle-aged adults (40-69 years)	Left and right	More overall PA was associated with greater left and right HV.
Klaren et al. (2015)	Adults with multiple sclerosis (18-64 years)	Total	More time spent in moderate-to-vigorous PA was associated with greater HV, but light PA behavior and sedentary behavior were not.
Makizako et al. (2015)	Older adults with MCI (≥65 years)	Total	More time spent in moderate PA was associated with greater HV, but light PA and total PA were not.
Raichlen et al. (2019)	Middle-aged to older adults (45-80 years)	Left and right	More time spent in moderate-to-vigorous PA was associated with greater left and right HV.
Varma et al. (2015)	Older adults (≥60 years)	Total	Greater amount, duration, and frequency of total daily walking activity and low-intensity daily walking activity were associated with larger HV among women but not men.
Verma et al. (2016)	Older adults (≥60 years)	Left and right shape	Greater number of steps/day was associated with outward shape differences along the subiculum of the left and right hippocampus in women but not men. Greater low-intensity walking activity was associated with outward shape differences along the subiculum of the left hippocampus in women but not men. Moderate-to-vigorous PA was not significantly correlated with hippocampal shape in men or women.
Null Findings			
Alosco et al. (2015)	Older adults with heart failure (50-85 years)	Total	Daily step count was not associated with HV.
Spartano et al. (2019)	Mean age 53 years	Total	HV was not associated with time spent in moderate-to-vigorous PA, light PA, or total PA.
Cross-sectional Cardiorespiratory Fitness			
Significant Findings			
Aghjayan et al. (2020)	Middle-aged adults with overweight or obesity (18-55 years)	Left, right, and shape	Higher CRF was associated with greater left HV, with outward shape differences along the surface of the subiculum and CA1 regions. Null results were found for right HV.
Boots et al. (2015)	Middle-aged adults at risk for AD (40-65 years)	Total	Higher CRF was associated with greater HV.
Bugg et al. (2012)	Older adults with obesity (65-75 years)	Total	CRF accounted for unique variance in HV after controlling for age, gender, and waist circumference.
Chaddock et al. (2010)	Preadolescent children (9-10 years)	Left and right	Higher-fit children had greater left and right HV compared to lower-fit children.
Chaddock-Heyman et al. (2015)	Breast cancer survivors (41-73 years)	Total, left and right anterior, and left and right posterior	Higher CRF was associated with greater total HV. Lower-fit cancer survivors had smaller total, left and right anterior, and left and right posterior HV than higher-fit control subjects. Lower-fit cancer survivors had smaller left posterior HV compared to lower-fit control subjects.

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
Dougherty et al. (2017)	Older adults at risk for AD (50-75 years)	Total	Higher CRF was associated with greater HV for women but not men.
Erickson et al. (2009)	Older adults (59-81 years)	Left and right	Higher CRF was associated with greater left and right HV.
Esteban-Cornejo et al. (2017)	Children with overweight or obesity (8-11 years)	Cluster in left	Higher CRF was associated with greater left HV.
Fletcher et al. (2016)	Older adults (55-87 years)	Total	Higher CRF was associated with greater HV.
Herting et al. (2012)	Male adolescents (15-18 years)	Left and right	Higher CRF was associated with greater left and right HV.
Makizako et al. (2013)	Older adults with MCI (≥65 years)	Cluster in left	Higher exercise capacity was associated with greater left HV.
McAuley et al. (2011)	Older adults (60-80 years)	Total	Higher CRF was associated with greater HV.
Motl et al. (2015)	Adults with multiple sclerosis (18-64 years)	Total	Higher CRF was associated with greater HV.
Ortega et al. (2017)	Children (mean age 9.7 years)	Left and right shape	CRF was associated with the shape (expansions/ contractions) of the right hippocampus, but not the left hippocampal.
Stillman et al. (2018)	Young adults (20-38 years)	Left and right anterior, and left and right posterior	Higher CRF was associated with greater left anterior HV.
Szabo et al. (2011)	Older adults (60-80 years)	Total	Higher CRF was associated with greater HV.
Null Findings			
Cole et al. (2020)	Older adults (60-76 years)	Total, left, and right	CRF was not significantly associated with total, left, or right HV.
Engeroff et al. (2018)	Older adults (≥65 years)	Left and right	CRF was not significantly associated with left or right HV.
Honea et al. (2009)	Older adults with healthy cognition and early-stage AD (≥65 years)	Total	No significant relationship of CRF with HV in either group.
Raichlen et al. (2019)	Middle-aged to older adults (45-80 years)	Left and right	CRF was not associated with left or right HV.
Wood et al. (2016)	Master athletes and active adults (45-73 years)	Left and right	CRF was not associated with left or right HV regardless of group.
Randomized Clinical Trials			
Significant Findings			
Erickson et al., (2011)	Sedentary older adults (55-80 years)	Left and right anterior, and left and right posterior	The aerobic group had an increase in left and right HV compared to the control group, which had a decrease in left and right HV over the 12-month intervention. Aerobic exercise increased left and right anterior HV but not left or right posterior HV compared to the control group, which had a decrease in left and right anterior HV but not left and right posterior HV. Greater improvements in CRF were associated with greater increases in left and right anterior HV, and left and right posterior HV.
Jonasson et al., (2016)	Sedentary old adults (64-78 years)	Total	Increased CRF following the 6-month intervention was associated with increased HV.
Leavitt et al. (2014)	Female patients with memory impairment and multiple sclerosis (33-44 years)	Total	The aerobic group showed an increase in HV following the 3-month intervention but the non-aerobic group did not.

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
Lin et al., (2015)	Women with early psychosis (16-60 years)	Total, left, and right	Aerobic exercise over 12 weeks was associated with increased HV, mainly related to increases in the left hippocampus. Changes in CRF did not differ significantly across the groups.
Maass et al., (2015)	Sedentary older adults (60-77 years)	Head, body, and tail	Increased CRF was associated with increased hippocampal head volume over 12 weeks, although hippocampal head volume did not increase overall in the exercise group. Null results were found for the body and tail.
Morris et al., (2017)	Older adults with early-stage AD (≥55 years)	Total	Increased CRF was associated with increased HV over 26 weeks.
Niemann et al., (2014)	Older adults (62-79 years)	Total, left, and right	Total and left HV increased in the aerobic exercise group over the 12-month intervention. Null results were found for the right hippocampus. Changes in CRF significantly explained variance in total and left HV, but not right HV.
Pajonk et al., (2010)	Men with chronic schizophrenia and matched healthy subjects (20-51 years)	Total	Among both aerobic exercise groups, HV increased by 14% over the 12-week intervention. Greater changes in CRF were associated with larger increases in HV.
Rosano et al., (2017)	Sedentary older adults at risk for mobility disability (70-89 years)	Total, left, and right	The PA group had greater left, right, and total HV following a 24-month intervention, although the right hippocampus was attenuated after controlling for regional baseline volume.
ten Brinke et al., (2015)	Women with probable MCI (70-80 years)	Total, left, and right	Compared with the control group, the aerobic group significantly improved left, right, and total HV following a 6-month intervention.
Thomas et al., (2016)	Sedentary, young to middle-aged adults (mean age 33.7 years)	Anterior	The 6-week exercise intervention significantly increased anterior HV, but it returned to baseline after an additional 6 weeks following the completion of the study.
Null Findings			
Bunketorp Käll et al., (2015)	Students in grades 5 and 6	Left and right	Neither left nor right HV differed significantly between groups, despite greater increases in CRF among the boys in the intervention group compared to the boys in the control group.
Frederiksen et al., (2018)	Patients with mild to moderate AD (50-90 years)	Left, right, and subfields	There was no effect of a 16-week intervention on HV or subfield volume. There was no significant correlation between CRF and HV.
Krogh et al., (2014)	Adults with major depression (18-60 years)	Left, right, and total	There was no difference in left, right, or total HV between groups following a 3-month intervention. Changes in CRF were not associated with changes in HV.
Malchow et al., (2016)	Patients with schizophrenia and healthy controls (18-60 years)	Total, left, right, and subfields	No significant changes in HV or subfield volume were found in patients or controls following a 3-month intervention.
Scheewe et al., (2013)	Patients with schizophrenia and healthy controls (18-48 years)	Left and right	The 6-month intervention did not have a significant effect on HV in patients or controls.
Tarumi et al., (2019)	Patients with amnestic MCI (55-80 years)	Total	The 12-month intervention did not have a significant effect on HV, despite significant improvements in CRF in the exercise group compared to the control group.
WHITE MATTER			
White Matter Integrity			
Cross-sectional Physical Activity Questionnaire			
Significant Findings			

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
Rodriguez-Ayllon, Derks, et al., (2020)	Children (10 years)	Cingulum ROI: hippocampal cingulum and cingulate gyrus	PA was negatively correlated with MD among all WM tracts of interest. There was no association between total PA and FA when controlling for sociodemographic factors.
Gow et al., (2012)	Older Adults (mean age 69.5 years at baseline)	ROI: FA and MD composite factors, consisting of 12 ROIS, including the rostral cingulum bundles	Higher PA was significantly associated with higher composite FA, but not MD.
Null Findings			
Maltais et al., (2020)	Older adults without dementia ≥ 70 years.	ROI included the hippocampal cingulum	Null relationship between PA and FA. Associations between lower PA and faster MD worsening did not include the hippocampal cingulum.
Cross-sectional Accelerometer			
Significant Findings			
Burzynska et al., (2014)	Low-fit older adults (60-78 years)	ROI included the anterior cingulum, temporal lobe WM, and medial temporal/para-hippocampal WM	Light PA was associated with temporal ROI FA. In addition, sedentary behavior was related to lower parahippocampal FA.
Bracht et al., (2016)	Adults (mean age 25.5 years)	ROI: fornix and bilateral parahippocampal cingulum	Positive correlation between activity level and MWF, but not FA, in the right parahippocampal cingulum.
Null Findings			
Burzynska et al., (2017)	Low-active older adults (60–80 years)	ROIs included the fornix and anterior and posterior cingulum (as well as parahippocampal WM)	Neither light nor moderate-to-vigorous PA were correlated with change in FA in hippocampal ROIs.
Cross-sectional Cardiorespiratory Fitness (CRF)			
Significant Findings			
Chen et al., (2020)	Midlife to older adults (55–65 years)	ROIs included the hippocampal cingulum & cingulate gyrus	Higher CRF was associated with higher FA in multiple WM tracts, including the hippocampal cingulum.
Ding et al., (2018)	Older adults with healthy cognition (mean age 66 years) or amnestic MCI (mean age 65 years)	Whole-brain	Higher CRF was associated with higher FA, and lower MD and RD, in a number of WM tracts, including the cingulum.
Harasym et al., (2020)	Post-menopausal women (mean age 59 years)	ROIs included the hippocampal cingulum & cingulate gyrus	Higher CRF related to higher AD in the hippocampal cingulum (but no associations with FA, MD, or RD).
Marks et al., (2011)	Sedentary older adults (60–76 years)	ROI: bilateral anterior, middle, and posterior cingulum	Higher CRF was associated with higher FA in the left middle cingulum.
Oberlin et al., (2016)	Older adults (60–81 years)	Whole-brain	Higher CRF was associated with higher FA in a number of WM tracts, including the fornix and cingulum.
Null Findings			
Burzynska et al., (2014)	Low-fit older adults (60-78 years)	ROIs included the anterior cingulum, temporal lobe WM, and medial temporal/para-hippocampal WM	Null associations between CRF and FA in hippocampal regions. After controlling for age and gender, and association between higher temporal FA and CRF was reduced to trend level.
Burzynska et al., (2017)	Low-active older adults (60–80 years)	ROIs included the fornix and anterior and posterior cingulum (and parahippocampal WM)	Null associations between CRF and FA in hippocampal regions.

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
Clark et al., (2019)	Sedentary older adults (57 to 86 years)	Whole-brain	Null associations between CRF and both FA and MD.
Perea et al., (2016)	Sedentary older adults with early stage AD (mean age 72.35 years)	Whole-brain and ROI including bilateral cingulum bundles.	No significant positive association between CRF and cingulum FA, MD, RD, or AD, although there was a trending relationship between higher CRF and lower RD in the right cingulum.
Teixeira et al., (2016)	Older adults with amnestic MCI (57–80)	Whole-brain	Significant associations between higher CRF and higher FA, lower MD, lower RD, and lower AD did not include WM connections to the hippocampus.
Tseng et al., (2013)	Sedentary older adults (66–82 years) and master athletes (61–80 years)	Whole-brain	Higher CRF was associated with higher FA in multiple WM pathways, but not in hippocampal projections. (Notably, relative to sedentary older adults, master athletes showed significantly lower MD (but not FA) in the hippocampal cingulum.)
Randomized Clinical Trials			
Significant Findings			
Voss et al., (2013)	Sedentary older adults (55-80 years)	Lobular ROIs: Frontal, Temporal, Parietal, and Occipital	Increased CRF over the course of the 12-month intervention was associated with increased temporal, frontal, and parietal FA (but not AD or RD) in the exercise group but not the control group. There were no significant main effects of group assignment.
Burzynska et al., (2017)	Low-active older adults (60–80 years)	ROIs included the fornix and anterior and posterior cingulum (as well as parahippocampal WM)	Significant group by time interaction, such that fornix FA increased in the dance group after 6-months of intervention, and decreased in the walking and control groups. RD and MD showed significantly less decrease in the dance group.
Null Findings			
Clark et al., (2019)	Sedentary older adults (57–86 years)	Whole-brain	Lower FA and higher MD following 6-months of an aerobic exercise intervention did not include hippocampal WM connections.
Sexton et al., (2020)	Older adults (60–85 years)	Whole-brain	No significant effects of a 3-month aerobic exercise intervention on FA, AD, or RD.
Svatkova et al., (2015)	Patients with schizophrenia and healthy controls (18–48 years)	Whole-brain	The exercise group demonstrated significant increases in FA over the 6-month intervention in several WM pathways, but not including connections to the hippocampus.
White Matter Volume			
Cross-sectional Physical Activity Questionnaire			
Null Findings			
Ho et al., (2011)	Older adults (mean age 77.9 years)	Whole-brain	Self-reported PA (kcal/weekly expenditure) was not significantly associated with volume in WM of hippocampal connections.
Cross-sectional Cardiorespiratory Fitness (CRF)			
Significant Findings			
Esteban-Cornejo et al., (2019)	Children (7–11 years)	Whole-brain	Higher CRF was associated with greater WM volume in regions including the cingulate gyrus, among children with overweight/obesity but not children with BMI in the healthy range.
Honea et al., (2009)	Older adults with healthy cognition or early-stage AD (≥65 years)	Whole-brain and ROIs targeting hippocampal and parahippocampal regions	In early-stage AD, higher CRF was associated with greater WM volume in the left hippocampal ROI. No significant association between CRF and WM volume in cognitively normal older adults.
Null Findings			

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
Erickson et al., (2007)	Post-menopausal women (58–80 years)	Whole-brain	Significant positive associations between CRF and WM volume did not include hippocampal tracts.
Gordon et al., (2008)	Young adults (20–28 years) and older adults (65–81)	Whole-brain	Null association between CRF and WM volume.
Randomized Clinical Trials			
Null Findings			
Colcombe et al., (2006)	Sedentary older adults (60–79 years)	Whole-brain	Greater WM volume over 6-months of intervention in the exercise group did not include hippocampal tracts.
FUNCTIONAL CONNECTIVITY			
Cross-sectional Accelerometer			
Significant Findings			
Prakash et al., (2011)	Midlife adults with multiple sclerosis (30–58 years)	Left and right hippocampal seeds	Higher PA was associated with higher rsFC of both the left and right hippocampus to the posteromedial cortex
Null Findings			
Voss et al., (2016)	Older adults (60–80 years)	Network ROIs, including the DMN	No significant associations among rsFC networks and physical activity.
Cross-sectional Cardiorespiratory Fitness			
Significant Findings			
Flodin et al., (2017)	Sedentary older adults (64–78 years)	Whole-brain analyses and left and right hippocampal and parahippocampal seeds	Right medial temporal lobe positively correlated with rsFC to frontal, parietal, and occipital areas and negatively correlated to the right thalamus and right occipital cortex.
Ikuta & Loprinzi, (2019)	Midlife adults (mean age 42.5 years)	Left and right hippocampal and parahippocampal seeds	Higher CRF was associated with more positive parahippocampal, but not hippocampal interhemispheric rsFC.
Stillman et al., (2018)	Young adults (20–38 years)	Left and right anterior and posterior hippocampal seeds	Higher CRF was associated with more positive rsFC of the left and right anterior hippocampus to regions including the frontal pole, middle frontal gyrus, and parahippocampus. Negative correlation between CRF and rsFC of right anterior hippocampus and right superior frontal gyrus.
Voss et al., (2016)	Older adults (60–80 years)	Network ROIs, including the DMN, and exploratory analysis of correlations between whole-brain seeds and the DMN core	Positive associations between CRF and rsFC in multiple networks, with most robust results within the DMN. Positive associations between fitness level and rsFC between the DMN core and several seeds, one of which extended to the left and right hippocampus.
Randomized Clinical Trials			
Significant Findings			
Burdette et al., (2010)	Older adults (70–85 years)	Whole-brain	After 4-months of intervention, the exercise group showed greater rsFC within the hippocampus, and from the hippocampus to the anterior cingulate cortex, as compared to controls.
Flodin et al., (2017)	Sedentary older adults (64–78 years)	Whole-brain analyses and left and right hippocampal and parahippocampal seeds, as well as network ROIs including the DMN	Increase in CRF following 6-months of intervention was associated with increased rsFC between the right hippocampus and frontal and parietal regions, and decreased rsFC between the left hippocampus and right precentral gyrus. Increase in CRF was correlated with increased rsFC between the DMN and left prefrontal cortex. No significant group by time interactions on rsFC.
Leavitt et al., (2014)	Female patients with memory impairment and	Left hippocampal seed	Aerobic exercise group, but not the control group, showed an increase in rsFC from the left to the right hippocampus.

Study (Year)	Sample (Age)	Hippocampus (Defined As)	Summary of Findings
	patients with multiple sclerosis (33-44 years)		
Voss et al., (2020)	Older adults (60–80) years	ROIs included posterior and anterior hippocampus and parahippocampal cortex seeds	Effects of acute bouts of moderate intensity exercise in hippocampal-cortical rsFC in the DMN did not survive correction for multiple comparisons, but did predict increases in rsFC in these regions following 12-weeks of aerobic exercise training.
Weng et al., (2017)	Young adults (mean age 23.2 years) and older adults (mean age 66.3 years)	Network ROIs, including the DMN and a hippocampal cortical network	Single session of moderate intensity exercise were associated with rsFC within the hippocampus, and from the hippocampal cortical network to the medial prefrontal cortex, temporal pole, and intracalcarine cortex.
PERFUSION			
Cross-sectional Physical Activity Questionnaire			
Significant Findings			
Zlatar et al., (2014)	Sedentary older adults at genetic risk for AD (52-81 years)	Left and right	Greater sedentary time was associated with greater left hippocampal perfusion for APOE ε4 carriers but not noncarriers. Null results were found for the right hippocampus.
Cross-sectional Cardiorespiratory Fitness (CRF)			
Significant Findings			
Chaddock-Heyman et al., (2016)	Preadolescent children (7-9 years)	Total, anterior, and posterior	Higher CRF was associated with greater total and posterior hippocampal perfusion, but not anterior.
Randomized Clinical Trials			
Significant Findings			
Alfini et al., (2016)	Master athletes (≥50 years)	Left and right	Perfusion decreased in the left and right hippocampus after 10 days of no exercise training.
Burdette et al., (2010)	Older adults (≤85 years)	Total	The exercise training group had greater hippocampal perfusion than the control group following a 4-month intervention.
Maass et al., (2015)	Sedentary older adults (60-77 years)	Total	Increased hippocampal perfusion for the exercise group following a 3-month intervention, but not the control group. Increased CRF was associated with greater hippocampal perfusion.
Pereira et al., (2007)	Adults (21-45 years)	Dentate gyrus, CA1 subfield, subiculum, and entorhinal cortex	Perfusion in the dentate gyrus increased over a 3-month intervention. Increases in dentate gyrus perfusion were associated with increases in CRF.

Notes. Within the WM section of the table, the “Hippocampus (Defined As) column” describes studies that: (1) first used an exploratory, whole-brain approach and then identified regions of significance (“exploratory”); and (2) defined regions-of-interest, including WM tracts connecting to the hippocampus, prior to running analyses (“ROI”). Findings defined as null specifically pertain to results targeting the hippocampus. WMH is not included in this table as few studies have examined measurements of physical activity and localized lesions and none in relation to hippocampal WM connections. CRF = cardiorespiratory fitness, HV = hippocampal volume, PA = physical activity, MCI = mild cognitive impairment, AD = Alzheimer’s disease, HIV = human immunodeficiency virus, WM = white matter, FA = fractional anisotropy, MD = mean diffusivity, RD = radial diffusivity, AxD = axial diffusivity, MWF = myelin water fraction, rsFC = resting state functional connectivity.