

Mediators of Physical Activity on Neurocognitive Function: A Review at Multiple Levels of Analysis

Chelsea M. Stillman^{1*}, Jamie Cohen², Morgan E. Lehman², Kirk I. Erickson^{1, 2*}

¹Psychiatry, University of Pittsburgh School of Medicine, USA, ²Psychology, University of Pittsburgh, USA

Submitted to Journal:
Frontiers in Human Neuroscience

ISSN:
1662-5161

Article type:
Review Article

Received on:
11 Aug 2016

Accepted on:
24 Nov 2016

Provisional PDF published on:
24 Nov 2016

Frontiers website link:
www.frontiersin.org

Citation:
Stillman CM, Cohen J, Lehman ME and Erickson KI(2016) Mediators of Physical Activity on Neurocognitive Function: A Review at Multiple Levels of Analysis. *Front. Hum. Neurosci.* 10:626. doi:10.3389/fnhum.2016.00626

Copyright statement:
© 2016 Stillman, Cohen, Lehman and Erickson. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution and reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

This Provisional PDF corresponds to the article as it appeared upon acceptance, after peer-review. Fully formatted PDF and full text (HTML) versions will be made available soon.

MEDIATORS OF PHYSICAL ACTIVITY ON

NEUROCOGNITIVE FUNCTION: A REVIEW AT MULTIPLE

LEVELS OF ANALYSIS

Chelsea M. Stillman^{1,2}, Jamie Cohen^{2,3}, Morgan E. Lehman³, & Kirk I. Erickson^{2,3}

Author Affiliations: ¹Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; ²Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA, USA; ³Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA.

Correspondence: Chelsea Stillman, Ph.D.; email: cmstillm@gmail.com

Keywords: brain, cognition, exercise, physical activity, mechanisms, mediation

Word Count: 9,070

Tables: 2

Figures: 4

Abstract

Physical activity (PA) is known to maintain and improve neurocognitive health. However, there is still a poor understanding of the mechanisms by which PA exerts its effects on the brain and cognition in humans. Many of the most widely discussed mechanisms of PA are molecular and cellular and arise from animal models. While information about basic cellular and molecular mechanisms is an important foundation from which to build our understanding of how PA promotes cognitive health in humans, there are other pathways that could play a role in this relationship. For example, PA-induced changes to cellular and molecular pathways likely initiate changes to macroscopic properties of the brain and/or to behavior that in turn influence cognition. The present review uses a more macroscopic lens to identify potential brain and behavioral/socioemotional mediators of the association between PA and cognitive function. We first summarize what is known regarding cellular and molecular mechanisms, and then devote the remainder of the review to discussing evidence for brain systems and behavioral/socioemotional pathways by which PA influences cognition. It is our hope that discussing mechanisms at multiple levels of analysis will stimulate the field to examine both brain and behavioral mediators. Doing so is important, as it could lead to a more complete characterization of the processes by which PA influences neurocognitive function, as well as a greater variety of targets for modifying neurocognitive function in clinical contexts.

Introduction

Physical activity (PA) is important for maintaining *physical* health. PA has also been shown to maintain and improve *neurocognitive* health, but we know much less about the mechanisms by which it exerts its salutary effects on brain and cognition in humans (e.g., see Gomez-Pinilla & Hillman, 2013; Hillman, Erickson, & Kramer, 2008; Tomporowski & Ellis, 1986 for reviews). However, research has found that physical *inactivity* is a risk factor for cognitive impairment, which has stimulated interest in examining whether PA can act to improve neurocognitive function, as well as the mechanisms by which it might work.

What are the cellular and molecular, brain systems, and behavioral mechanisms by which PA influences cognitive function, and how can they be identified? There are two frameworks that are typically used for causal inference—one is related to the design of the study, and the other is related to the statistical approach used for analysis (Imai, Keele, Tingley, & Yamamoto, 2011). The gold standard for assessing causality is through an **experimental manipulation**. A study is “experimental” when an independent variable (i.e., PA) is manipulated to examine its influence on a dependent variable (i.e., cognition). In the context of exercise studies, human or animal subjects are randomly assigned to an experimental condition (i.e., exercise treatment) or control group (i.e., standard care), and the outcome of interest is assessed in each group while all other factors are held constant. In the context of PA, this type of causal evidence comes almost exclusively from *exercise training* studies when studying humans, or from animal models of exercise in which one group of animals is permitted to exercise while another group is treated as a control. Causality is established if the outcome variable (e.g., cognition) changes to a greater extent in the treatment (e.g., exercise training) group relative to the control group.

Of course, it is not always feasible or practical to randomly assign participants to groups and experimentally manipulate treatment variables such as exercise, especially when studying humans. In this case, an alternative framework for causal inference can be used. **Statistical mediation** is used to test the plausibility of causal models not only in experimental studies, but also in observational, longitudinal, or quasi-experimental designs in which random assignment did not occur and/or the treatment variable of interest was not directly manipulated. Further, statistical mediation can be used in at least two different contexts. It is important to distinguish between these contexts as they influence the type of conclusions that can be drawn from the model's results.

In the first context (i.e., observational, longitudinal, and quasi-experimental studies), mediation models allow us to evaluate alternative causal mechanisms between the treatment and outcome variables by examining the roles of several intermediate variables that lie in the causal path. The benefit of using statistical mediation models in this context is that we are able to obtain evidence of a potential causal pathway using data or designs that are inherently non-experimental. Importantly, however, it is still not possible to rule out whether some third, confounding factor is driving the pattern of statistical mediation observed in a non-experimental design.

In the second context, a “gold standard” experimental design is used alongside a statistical mediation model. Using statistical models in experimental designs allows us to further examine intermediate factors that might covary with the treatment and outcome variables, and to test their plausibility as causal paths. Significant statistical mediation in this latter context provides more definitive evidence of a causal path because random assignment minimizes the influence of confounders and the direction of the relationships in the model can be established

(i.e., it is possible to demonstrate that a manipulation caused changes in the mediator and outcome, rather than the reverse).

In both contexts described above where statistical mediation models can be used, the intermediate variable is considered a *mediator* if the coefficient describing the strength of the treatment-outcome relationship through the mediating variable (i.e., the indirect effect) is statistically significant (Preacher & Hayes, 2008). In other words, the significance of the indirect effects examines whether the mediator is a viable mechanism by which the independent (i.e., treatment) variable influences the outcome. Although statistical mediation can, and perhaps should, routinely be used in experimental studies, this approach is most frequently used to infer possible causal relationships from non-experimental data.

For the purposes of the present review, both types of causal evidence—design-related and statistical mediation—are relevant and will be discussed in the context of understanding mechanisms by which PA influences cognitive function. However, a critical caveat of the statistical mediation approach in quasi-experimental and observational studies is that causal relationships between a predictor and outcome through the mediator cannot be definitively determined, even in the case of significant statistical mediation. This is because random assignment did not occur, thus there could be pre-existing differences between the groups. However, statistical mediation approaches *can* provide evidence that one mediation pattern is more plausible than another, and they provide valuable theoretical insight for the design of future experimental studies.

Based on the description of causality outlined above, mechanisms can be conceived at multiple levels. However, most studies have taken a reductionist approach to mechanisms. To date, for example, most systematic reviews focusing on the causal mechanisms by which PA

affects cognition have focused on cellular and molecular mechanisms, hereafter referred to as those at *Level 1 of analysis*. Consequently, there is a wealth of evidence (the majority from animal models) indicating that PA likely improves cognition by promoting various cellular and molecular pathways, including those responsible for neurogenesis and angiogenesis (van Praag, Shubert, Zhao, & Gage, 2005), while decreasing others, such as inflammation (e.g., Parachikova, Nichol, & Cotman, 2008). While information about basic cellular and molecular mechanisms is an important foundation from which to build our understanding of how PA promotes cognitive health in humans, there are other possible ways of thinking about mechanisms.

Just as mechanisms can be assessed in multiple ways (e.g., statistically or experimentally), they can also be assessed at multiple levels, ranging from the cellular and molecular level (i.e., Level 1) up to other, more macroscopic levels of analysis (see Figure 1 for conceptual model). We will refer to brain systems and behavioral mechanisms as those at *Level 2* and *Level 3 of analysis*, respectively, and describe them further below. Separating mediators into different levels of analysis may be informative because PA-induced changes to cellular and molecular pathways (Level 1) likely initiate changes to macroscopic properties of the brain (Level 2) and behavior (Level 3) that in turn influence cognition. For example, changes in brain structure and function (Level 2) and behaviors, such as in socioemotional functions (e.g., mood, motivation, or sleep) (Level 3) could mediate improvements in cognitive performance following PA. Crucially, our choice to organize potential mediators into different levels is not meant to imply that the mechanisms at each level are mutually exclusive. In fact, pathways identified using Level 2 and 3 analyses are necessarily invoked by changes at lower levels of analysis, and bidirectional effects likely exist between levels (e.g., feedback loops from higher levels

influencing lower levels of analysis). For conceptual purposes, however, we have chosen to discuss evidence for mediators at each level of analysis separately.

Prior reviews have focused almost entirely on Level 1 mechanisms at the expense of the other levels. The goal of this review is to use a more macroscopic lens that attempts to identify Level 2 and 3 mediators of the association between PA and cognitive function. To accomplish this, we will briefly summarize what is known regarding cellular and molecular mechanisms and will devote the remainder of the review to discussing the brain systems and behavioral/socioemotional mechanisms at Levels 2 and 3 of analysis. It is our hope that discussing mechanisms at multiple levels of analysis will stimulate the field to examine systems and socioemotional mediators, leading to a more complete characterization of the processes by which PA influences neurocognitive function, and a greater variety of targets for modifying neurocognitive function.

In summary, the main aim of the present review is to summarize the evidence that macroscopic brain and behavioral/psychological changes can be mediators of the effects of exercise. We define high quality evidence of mediation as either coming from randomized controlled trials (RCT) or from correlational/cross-sectional work in which a statistical mediation model is tested after finding a pattern of correlations consistent with mediation. We are not aware of any other reviews to date considering such macroscopic (i.e., non-molecular) brain and behavior changes as mediators of exercise.

Key Definitions

Before we discuss the evidence for mechanisms at each level of analysis, we will first define several terms related to cognition and PA, as they will be used throughout the following sections. *Neurocognition* is a broad term referring broadly to the brain and its cognitive

functions. We will use this term when referring to general observations about the effects of PA on both brain and cognitive outcomes. *Cognition* is a slightly more specific term. We will use this when referring to particular behavioral performance measures, such as those frequently used to assess the effects of PA in experimental studies.

Physical activity (PA) is a broad term referring to an activity that raises heart rate above resting levels (Caspersen, Powell, & Christenson, 1985). This could include anything from housework or gardening, to walking or lifting weights. Importantly, the term PA has also been used to refer to coordinative activities, such as those requiring balance and higher-order cognitive processes (Voelcker-Rehage & Niemann, 2013). However, it is the former definition of PA—that referring to aerobic, heart-rate-raising activity—that will be the focus of the present review as the PA field in the context of neurocognitive function is dominated by research using this definition. Further, different types of PA may have overlapping and distinct mechanisms (Niemann, Godde, & Voelcker-Rehage, 2014; Voelcker-Rehage, Godde, & Staudinger, 2010; Voelcker-Rehage & Niemann, 2013). Aerobic PA, hereafter referred to as “PA”, is often assessed subjectively in research studies, but it can also be measured objectively using devices such as accelerometers. Regular participation in PA influences aerobic fitness. Aerobic fitness (hereafter just “fitness”) is a measure of cardiovascular efficiency and is often measured with a graded maximal exercise test. The main outcome measure from graded exercise tests is VO_{2max} , a metric describing a person’s maximal oxygen uptake. VO_{2max} is widely accepted as the gold standard of the functional limit of the cardiovascular system. As such, it is often used as the primary objective outcome of fitness in non-experimental studies, or to assess whether a PA intervention was effective. Both PA and fitness are often used to describe the results of non-experimental designs. *Exercise* refers to any structured activity that is intended to improve

physical fitness. This term is often used to describe the type of PA occurring in training studies. For the purposes of this review, we will use *PA* or *fitness* when referring to study outcomes and will use PA when discussing overall concepts or discussing mechanisms more generally. We will use *exercise* exclusively when referring to studies employing a randomized, controlled experimental design.

Level 1: Molecular & Cellular Mechanisms

PA and Cognitive Functioning.

Much of what is known about the cellular and molecular mechanisms linking PA to cognitive functioning comes from animal models. This is because animals (most often mice or rats) can be randomly assigned to an exercise or control group while the external environments are controlled for the duration of the study. This experimental manipulation examines whether outcomes between groups can be attributed to the exercise and not to other unmeasured factors. In a typical study, animals in the exercise group are given free access to a running wheel (i.e., voluntary exercise), while those in the control group are not given access to a running wheel to ensure they are comparatively inactive; all other environmental conditions (e.g., diet) are held constant. Cognitive function is assessed at the conclusion of the study (typically lasting 2-8 weeks), and physiological and brain changes are evaluated shortly after during autopsy.

Experimental studies employing animal models have established that PA (in particular, aerobic exercise) improves cognitive function, especially in cognitive domains dependent on the hippocampus, such as spatial or relational learning and memory , object recognition (e.g., Bechara & Kelly, 2013; Hopkins & Bucci, 2010), and avoidance learning (e.g., Baruch, Swain, & Helmstetter, 2004; Chen et al., 2008) (see van Praag, 2008 for review). In addition, exercise increases long-term potentiation, a cellular analog of learning and memory, in a hippocampal

sub-region known as the dentate gyrus (e.g., van Praag, Christie, Sejnowski, & Gage, 1999). Animal models have been critical in establishing that the changes initiated by exercise extend beyond behavior into cognition, prompting further research into the mechanisms underlying exercise-induced synaptic, and downstream cognitive, changes.

Molecular Mechanisms

Exercise exerts its salutary effects on learning and memory by modulating key growth factor cascades responsible for energy maintenance and synaptic plasticity (Figure 2). Currently, the two pathways most studied in relation to the PA-neurocognition link are brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) (for reviews of mechanisms see Cotman, Berchtold, & Christie, 2007; Gomez-Pinilla & Hillman, 2013). Exercise increases BDNF and IGF-1 gene expression and protein levels, both in the periphery, as well as in several brain regions, with the most robust and long-lasting changes in the hippocampus (Duzel, Praag, & Sendtner, 2016; Voss, Vivar, Kramer, & van Praag, 2013). BDNF and IGF-1 signaling are considered to be causal pathways underlying exercise-related neurocognitive improvements because they are *necessary* to observe exercise-induced cellular effects. That is, experimentally blocking signaling in these pathways (e.g., with receptor-blocking ligands) eliminates or attenuates the beneficial effects of exercise on cellular and molecular pathways related to cognition (e.g., long-term potentiation) (Cotman et al., 2007). Most of the initial studies manipulating the action of BDNF or IGF-1 pathways have focused on the cellular consequences of this manipulation, and not on cognition itself. However, there is evidence suggesting that blocking BDNF attenuates behavioral learning and memory improvements following exercise (Vaynman, Ying, & Gomez-Pinilla, 2004). Therefore, exercise-related increases in at least one of these growth factors has been directly linked to both cellular and cognitive changes.

Blocking IGF-1 signaling also prevents exercise-induced increases in BDNF, suggesting that the two pathways converge at certain points in their cascades (Carro, Nuñez, Busiguina, & Torres-Aleman, 2000; Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006). Thus, the results of experimental animal studies have established that both BDNF and IGF-1 are mediators of exercise-induced cognitive improvements and that their relationship may be interdependent, and also involve other molecules and cascades. Therefore, while BDNF and IGF-1 are two molecular pathways affected by exercise, there are likely many others involved. Nonetheless, the heavy theoretical focus on these two molecular pathways has spurred research into other possible cellular mechanisms underlying effects of exercise on neurocognition, such as vascular endothelial growth factor (VEGF) and various neurotransmitters (e.g., serotonin) (Cotman et al., 2007; Fabel et al., 2003; Hamilton & Rhodes, 2015).

Cellular Mechanisms

Angiogenesis, the development of new blood vessels, and neurogenesis, the development of new neurons, are complex cellular changes that result from increased growth factor production and up-regulated molecular cascades. Both processes have emerged as viable candidates mediating the relationship between exercise and cognition (Cotman et al., 2007) (Figure 2). Changes in neurovasculature precede neurogenesis in rodents, particularly in the hippocampus (van Praag, 2008). Therefore, improvements in cognition following exercise may be due, in part, to increased growth of blood vessels, which in turn stimulates cell proliferation and survival.

Neurogenesis, particularly that which occurs in the dentate gyrus, is one of the most replicated cellular changes linked to exercise (van Praag, 2008). The mediating role of neurogenesis to exercise-related cognitive changes was once controversial (Leuner, Gould, & Shors, 2006; Meshi et al., 2006), but it is now more accepted as a viable mechanism underlying

learning and memory improvements (Clark et al., 2008; van Praag, 2008). Following 2-3 weeks of voluntary exercise in rodents, there is an increase in dendritic length and complexity of existing neurons, as well as neural progenitor proliferation, in the dentate gyrus compared to control animals (Cotman & Berchtold, 2007; Eadie, Redila, & Christie, 2005). Importantly, exercise-induced increases in the number of newborn, dividing neurons occurs in regions that overlap with those showing enhanced synaptic plasticity and growth factor expression following exercise (e.g., dentate gyrus). Exercise-induced changes in vasculature are less regionally specific (Cotman et al., 2007; Vivar, Potter, & van Praag, 2013; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). Moreover, abolishing the division of new neurons during environmental enrichment manipulations that include exercise, or inhibiting the integration of these neurons into the existing hippocampal cell structure, eliminates the learning and memory improvements typically observed following such manipulations (Bruehl-Jungerman, Laroche, & Rampon, 2005; Vivar et al., 2012). Thus, animal studies have suggested that neurogenesis and the survival and integration of new neurons into existing cellular networks are *necessary* to observe some cognitive improvements, particularly in the domain of learning and memory, following exercise. Yet, several studies have suggested that neurogenesis alone is not enough to induce cognitive changes, and that cognitive changes only arise when the new neurons successfully integrate themselves within an existing body of cells. This pattern of results establishes neurogenesis – potentially by way of angiogenesis – as another, slightly more macroscopic mechanism at Level 1 of analysis and further highlights the importance of examining mechanisms from multiple perspectives, even within our conceptualized three levels of analysis.

The bulk of evidence for the molecular and cellular mechanisms of exercise comes from animal models. One limitation of animal models is that the results cannot always be directly

extrapolated to humans. Indeed, the cellular and molecular mechanisms of exercise-induced improvements to cognitive functioning in humans (not only in regards to learning and memory, but also other cognitive domains) remain largely unknown. This is, in part, because there are limited techniques available to measure *cellular and molecular pathways* in the human brain.

Despite these limitations, animal models have been critical in establishing that molecular and cellular changes occur in response to PA, particularly in the hippocampus. They have provided evidence that changes in molecular and/or cellular pathways mediate cognitive changes, supporting that these pathways are underlying mechanisms of the PA-cognition link. We have spoken about Level 1 mechanisms in brevity above because of the multitude of reviews already published summarizing this literature (e.g., Cotman et al., 2007; Gomez-Pinilla & Hillman, 2013; Hillman et al., 2008; Lista & Sorrentino, 2009; van Praag, 2008). However, these molecular and cellular mechanisms likely invoke more macroscopic changes in the brain, which leads us to Level 2 of analysis.

Level 2: Macroscopic Brain Systems

Statistical Mediation – Cross-Sectional Studies

The molecular and cellular mechanisms of exercise in humans have been difficult to establish because it is not possible to experimentally manipulate or measure cellular and molecular processes in humans in the same way we do in animals – through the use of brain tissue samples. Fortunately, advances in neuroimaging have allowed us to examine, in vivo and non-invasively, more macroscopic effects of PA on the structure and function of brain regions and circuits. But this leads to a critical question: Do the effects of exercise and fitness on neuroimaging markers (e.g., volume) have a mediating effect on cognitive outcomes, or are they just a meaningless by-product of increased exercise?

Most studies assessing mechanisms at Level 2 of analysis have examined how gray and white matter morphology are associated with PA and, in turn, whether these associations mediate differences in cognitive performance. We use the term *morphology* as a broad way to refer to changes in brain structure, most often assessed by measuring the volume of grey and/or white matter, or white matter integrity. Separate bodies of literature have demonstrated that brain morphology relates to cognitive function (e.g., David J. Madden et al., 2012; Zhang et al., 2015) or to PA (e.g., Burzynska et al., 2014; J. C. Smith et al., 2014). However, it is a comparatively new concept to test brain morphology as a mechanism through which PA or fitness influences cognition. For example, in a cross-sectional study Erickson and colleagues (2009) examined the possibility that links between fitness and memory function could be accounted for by hippocampal volume. Using statistical mediation modeling, they demonstrated that hippocampal volume significantly mediated the relationship between fitness and spatial memory. The authors used a statistical framework to test their mechanistic hypothesis because the study was not an experimental manipulation of PA (i.e., a randomized controlled trial). However, the results provide insight into a possible casual role of the hippocampus that would be further tested in later experimental manipulations, as described below.

Similar statistical mediation has been reported across the lifespan, suggesting that these associations may be independent of age. For example, in a group of 49 preadolescent children, Chaddock and colleagues (2010) found that higher-fit children had larger hippocampal volumes compared to lower-fit children, and that larger hippocampal volumes were associated with superior relational memory performance. Importantly, they found that bilateral hippocampal volume mediated the relationship between fitness and memory task performance. A study of older adults with mild cognitive impairment reported similar pattern of results using

hippocampal volume (Makizako et al., 2015). The results of these studies are consistent with animal studies demonstrating that the cognitive-enhancing effects of exercise can be traced to changes in the molecular and cellular architecture of the hippocampus. However, one limitation from human studies is that we cannot determine which molecular and cellular pathways are mediating the associations with hippocampal volume (Braun & Jessberger, 2014).

Importantly, PA research in humans has also revealed that the hippocampus is not the only region mediating the link between exercise and cognition. Recent work suggests that changes to regions other than the hippocampus (e.g., prefrontal cortex) mediate some cognitive improvements in humans. For example, in a cross-sectional study, Weinstein and colleagues (2012) demonstrated that higher cardiorespiratory fitness levels were associated with better performance on both executive control and working memory tasks. Fitness levels were also associated with greater gray matter volume in several prefrontal brain regions. Further, the volume of these prefrontal regions statistically mediated the relationship between fitness and executive function and working memory performance. Similarly, Verstynen and colleagues (2012) found that caudate nucleus volume statistically mediated the relationship between fitness and cognitive flexibility, a function known to be supported by this region. Thus, in addition to the hippocampus, volumetric differences in the prefrontal cortex and caudate nucleus may mediate fitness- or exercise-related improvements in executive control and cognitive flexibility. These results demonstrate, as would be expected, that brain regions that support certain cognitive processes are the same regions that also statistically mediate associations between fitness or PA and cognitive performance in particular domains.

In addition to the cross-sectional studies showing that gray matter volume may statistically mediate the fitness-cognition relationship, the integrity of white matter tracts may

also mediate the link between PA and cognitive functioning. The first line of evidence for this idea comes from studies showing that white matter integrity has a clear association with cognitive performance across a number of domains (Bennett & Madden, 2014; Fjell, Westlye, Amlie, & Walhovd, 2011). The second line of evidence comes from studies showing that higher levels of PA are associated with greater white matter integrity (J. C. Smith et al., 2016). Given these patterns of findings, white matter integrity is another potential mediator of the link between PA and cognitive performance. This mechanism has only recently been tested. In two independent samples with a total of 267 healthy older adults, Oberlin and colleagues (2016) reported that white matter integrity in diffuse tracts statistically mediated the relationship between cardiorespiratory fitness (as measured by a VO_{2max} test) and spatial working memory performance. These tracts included those connecting the medial temporal to prefrontal cortices – the same brain regions discussed above that have been found to be associated with fitness and PA in studies examining gray matter volume. Overall, these results extend the research on brain volume by demonstrating that aerobic fitness may also be associated with cognition through its associations with white matter microstructure.

The studies described above provide evidence that changes in the structure of both gray and white matter statistically mediate the relationship between PA (or fitness, in the case of cross-sectional work) and cognition. However, PA could also induce changes to the functioning, most often operationalized as functional activation or connectivity, of certain brain regions as a result, *or independent of*, changes in brain structure. Functional MRI (fMRI) markers have been found to differ between groups or change in response to an intervention; the question is if these changes mediate improvements in cognition. Several recent, cross-sectional studies examined functional activation as a statistical mediator of the effects of PA on cognition. Building on

evidence of a relationship between fitness, executive control, and prefrontal functioning (Colcombe et al., 2004), Wong and colleagues (2015) examined the relationship between cardiorespiratory fitness (via $\text{VO}_{2\text{max}}$), executive functioning (via dual-task processing), and prefrontal cortex activation. A statistical mediation model revealed that activation of a region in the anterior cingulate/prefrontal cortex significantly mediated the relationship between cardiorespiratory fitness and dual task performance, such that those who were more fit had more activation in this region. Similarly, Hyodo et al. (2016) found that the level of activation in the left dorsolateral prefrontal cortex statistically mediated the association between higher fitness and less cognitive interference (via a Stroop task). A recent study reported a pattern of relationships consistent with a mediating role of prefrontal cortex activation to the fitness-executive control relationship using functional Near Infrared Spectroscopy; fNIRS (Albinet, Mandrick, Bernard, Perrey, & Blain, 2014). The pattern of results reported in these cross-sectional studies supports the argument that PA influences cognition through its effects on the functional allocation of neural resources (i.e., functional activation) during cognitive tasks. The results of several other cross-sectional studies assessing links between fitness, neural functioning, and cognition provide support for this general idea (Dupuy et al., 2015; Gauthier et al., 2015). However, these studies did not fully test for mediation because they either did not observe or did not test for the prerequisite correlations amongst the variables.

Cross-sectional studies utilizing statistical mediation provide a theoretical and mechanistic foundation about the relationships between cardiorespiratory fitness, brain, and cognition. However, their correlational nature leaves open the possibility that the observed behavioral and structural fitness-related differences between high and low-fit groups are caused by some unmeasured factor. Randomized controlled trials (RCTs) are necessary to account for

potential selection bias, as well as to establish a direct, causal relationship in humans between aerobic fitness, brain structure, and cognitive functioning.

Experimental Mediation – Randomized Controlled Trials

There have been numerous randomized controlled trials (RCT) examining the effects of exercise on cognition *or* on brain outcomes (Hillman et al., 2008; Kramer, Erickson, & Colcombe, 2006; P. J. Smith et al., 2010). However, only a small subset has examined both brain *and* cognitive outcomes in the same study, allowing for causal inference. Even fewer of the existing RCTs on this topic have included both cognitive and brain changes within a statistical model in order to definitively demonstrate a mechanism of exercise at Level 2 of analysis. In fact, while many of the RCTs that will be discussed below have shown promising patterns, only one tested for statistical mediation.

Changes in brain structure.

As in the human cross-sectional work, most RCTs examining mechanisms of PA at Level 2 of analysis have focused on its effects on brain structure, particularly on gray matter volume. In general, this literature has shown that exercise training increases brain volume particularly in the hippocampus, and these volumetric changes partially account for cognitive improvements following the intervention. In a seminal study on this topic, 120 inactive older adults were randomly assigned to a 12-month aerobic walking (experimental) group, or to a stretching and toning (control) group (Erickson et al., 2011). Following the intervention, the aerobic exercise group showed greater gray matter volume in the anterior hippocampus compared to the control group. These findings represent the first experimental evidence linking changes in exercise to changes in both gray matter volume and cognitive performance in aging humans in the context of a RCT. Further, the findings are consistent with animal models of regional specificity for the

effects of exercise on the brain, such that volume changes are particularly robust in the anterior portion of the hippocampus.

One limitation of the Erickson et al. (2011) study was that they did not test whether the relation between changes in fitness levels and spatial memory could be statistically accounted for by changes in hippocampal volume. It is therefore possible that another factor associated with both changes in fitness and gray matter volume accounted for the cognitive changes. In fact, the control group in this study also showed improvements in memory performance, despite showing *decreases* in hippocampal volume, making the causal links between changes in fitness and changes in hippocampal volume and spatial memory in the experimental group tenuous. Further, only the volumes of subcortical regions were assessed; potential changes in cortical regions, such as the prefrontal cortex, were not examined (but see Colcombe et al., 2006; Ruscheweyh et al., 2011 for evidence of cortical volume changes). Nonetheless, these results are important, as they were the first experimental evidence to suggest that exercise training can increase the volume of the hippocampus and improve memory in older adults.

In addition to examining mechanisms of exercise in healthy older adults, RCTs have also examined whether exercise can increase gray matter volume and cognition in clinical samples. The patient groups studied are those in which there are well-known hippocampal deficits, including schizophrenia (Pajonk et al., 2010), major depressive disorder (Krogh et al., 2014), and mild cognitive impairment (MCI) (ten Brinke et al., 2015). Each of these studies reported increases in grey matter volume in the hippocampus, but results were mixed regarding whether the exercise intervention improved cognition. For example, Pajonk et al. (2010) conducted a study with 24 participants, 16 of whom had schizophrenia. Eight of the patients and all of the healthy participants (n=8) were enrolled in an aerobic (cycling) exercise intervention (n=16),

while the other eight patients played table tennis as a low-aerobic control activity. The authors found that hippocampal volume increased and short-term memory improved in the exercise group following the intervention, but not in the non-exercising control group. Short-term memory and schizophrenic symptom severity improved with changes in hippocampal volume in schizophrenics, suggesting a possible mediating role of hippocampal changes on behavioral outcomes. Unfortunately, these associations were not tested using a statistical mediation framework (see Firth, Cotter, Elliott, French, & Yung, 2015 for mixed findings).

Increased cerebral perfusion has also been suggested as a possible mechanism for the cognitive-enhancing effects of exercise. For example, Maass et al. (2015) combined brain volume, perfusion, and memory change outcomes from their 3-month intervention and found that changes in gray matter volume could be accounted for by changes in cerebral perfusion. These results suggest that perfusion changes may mediate the effects of exercise on both gray matter volume *and* memory performance. **Thus, while gray matter volume is the most widely studied Level 2 mechanism of exercise on cognitive outcomes, there are other neuroimaging modalities tapping into different components of brain health that could shed light on the mechanisms of volumetric and cognitive changes (e.g., see Zimmerman et al., 2014).**

Changes in white matter microstructure may be another mechanism for the effects of PA on cognition because white matter supports communication between brain regions. Greater PA is linked to white matter preservation (Sexton et al., 2016) and decreased white matter integrity is linked to cognitive deficits (Roberts, Anderson, & Husain, 2013). This pattern raises the possibility that white matter health is a mechanism underlying the effects of PA on cognition. In the first RCT to examine this possibility, Voss and colleagues (2013) evaluated the effects of a 12-month exercise intervention on white matter integrity and cognitive performance in healthy

older adults. Seventy older adults were randomly assigned to either an aerobic walking or toning/stretching group; the groups participated in their respective activities for 40 minutes per day, 3 days per week. Increases in temporal and prefrontal white matter integrity, assessed via fractional anisotropy (FA), and memory were positively associated with improvements in fitness. However, the exercise-induced changes in FA were not associated with changes in memory performance. One possible explanation for this null finding is that the sample size was too small, limiting the statistical power to detect a relationship between FA and memory. This is a limitation that applies to many of the RCTs conducted to date.

Exercise-induced changes in brain function.

Changes in brain function in response to exercise, as measured by fMRI, could potentially precede changes in brain structure. It is also possible that exercise induces changes in brain function that are independent of changes in structure (i.e., not simply a byproduct of structural changes). Functional imaging studies of exercise therefore offer information about another potential brain mechanism underlying cognitive changes in response to exercise. Although less studied compared to structural change, exercise-related changes in brain function have been examined in the context of several RCTs (e.g., Chaddock-Heyman et al., 2013; Hillman et al., 2014; Kamijo et al., 2011; Krafft et al., 2014; Voss et al., 2010). Unlike RCTs examining structural outcomes, however, most of the RCTs focusing on functional outcomes have focused on changes in prefrontal cortex functioning, rather than the hippocampus. For example, using functional MRI (fMRI), Chaddock-Heyman et al. (2013) observed that children participating in a 9-month exercise intervention, 5 days per week, showed improved executive control performance and increased prefrontal activation patterns following the intervention, similar to the pattern seen in a healthy adult comparison group. Krafft et al., (2014) reported a

similar pattern of findings in obese children: Following an 8-month intervention, obese children showed improved cognitive control and increased activation in a comparable set of prefrontal brain regions to those reported by Chaddock-Heyman. Further, using similarly-aged (i.e., childhood) samples, two additional studies by Kamijo et al. (2011) and Hillman et al. (2014) observed that exercise improved cognitive performance (i.e., working memory and cognitive flexibility, respectively) and increased frontal electrophysiological indices of cognitive preparation and flexibility (i.e., contingent negative variation and P3 amplitude, respectively) following 9-month exercise interventions. Thus, in the pre-pubescent, developing brain, exercise has been shown to improve executive functioning, and these improvements have been associated with increased activation or neural responsiveness in prefrontal brain regions.

At least two RCTs suggest that the functional changes induced by exercise extend to older adults, although perhaps in a less regionally-specific manner. Using fMRI, Voss et al. (2010) showed that a 12-month walking intervention increased functional connectivity among regions within two large-scale brain networks: The default mode and the frontal executive networks (FEN). The increased functional connectivity in the FEN, a network that includes several prefrontal brain regions, was associated with improvements in executive control performance. A seminal study by Colcombe and colleagues (2004) reported similar findings in the functioning and recruitment of the FEN following a shorter, 6-month exercise intervention in older adults, supporting the claim that changes to large scale brain networks may occur relatively soon after the commencement of exercise training. Since large-scale brain networks are known to become less efficient and less flexible with age, these results suggest that exercise may exert more global effects on the efficiency and flexibility in which networks of brain regions interact in older adults, leading to preserved cognitive performance.

There have been a number of RCTs examining the effects of exercise on both brain outcomes and cognition. While many have demonstrated brain *or* cognitive changes following an exercise intervention, few have gone on to test for statistical mediation after finding a pattern of results consistent with a causal mechanism. Doing so, however, is important to establish the behavioral relevance of changes in neuroimaging metrics in PA-induced improvements in cognitive functioning (Figure 3). Further, the various differences in study design, measurement techniques, analytic approach, and study samples employed across the existing RCTs limit the mechanistic conclusions that can be drawn and highlight the need for more RCTs in this area. In particular, there is a need for RCTs to include larger samples and multiple imaging modalities in order to tease apart mechanistic questions related to temporal precedence. **There is also a need to look at the activation of networks of brain regions, as well as the connectivity between them, as potential mediators. Given the recent shift in the field to focus on functional brain networks, it seems unlikely that any single brain region works in isolation to mediate cognitive improvements. More complex mediation models may prove useful for more fully capturing the mechanisms underlying the effects of PA on cognition.** Nonetheless, the results of the existing body of literature are promising in that they indicate that exercise has multi-modal effects on the brain that likely underlie improvements in cognition. Further, the convergence of results, despite various differences across the studies, speaks to the robustness of the effects of exercise on both brain and cognition, and pinpoints PA as an effective tool to preserve and promote neurocognitive functioning across the lifespan.

Level 3: Behavioral & Socioemotional Mechanisms

The evidence described above implicates a number of molecular, cellular, and brain processes involved in PA, but it is likely that PA also exerts changes in other behaviors that

contribute to cognitive improvements (Figure 4). Unfortunately, few studies have examined how mechanisms at Level 3 of analysis might underlie the effects of exercise on cognitive performance. From a clinical standpoint, however, changes in human behavior are much easier to observe and may reflect a cost-effective approach to understanding behavioral mechanisms by which exercise improves cognitive function. Thus, there is added practical value in understanding potential mechanisms at the behavioral and socioemotional level.

Sleep as a Mediator

Sleep quantity and quality are important for healthy cognitive function (Yaffe, Falvey, & Hoang, 2014). For example, both the amount and quality of sleep are considered to be important in memory consolidation and learning processes (Walker, 2009). There is also a wealth of cross-sectional and experimental evidence that supports the idea that high quality sleep leads to better performance on a variety of cognitive tasks (see Ellenbogen, 2005 for review). Sleep is therefore a critical contributor to cognitive performance.

There is also evidence that increased PA improves sleep quality. The first RCTs to examine this demonstrated that relatively brief (e.g., 10-week) exercise interventions boosted self-reported sleep quality in older adults compared to non-exercise control groups (King, Oman, Brassington, Bliwise, & Haskell, 1997; Singh, Clements, & Fiatarone, 1997). These studies did not include measures of cognitive performance, so the effects of exercise-induced sleep improvements on cognition could not be determined. However, given the connections between sleep and cognition, and between sleep and PA, it is possible that PA improves cognitive outcomes by influencing sleep quality and efficiency.

The only study to date that included PA, sleep, and cognition in one model tested the hypothesis that sleep mediates the relationship between PA and executive functioning in 109

young (n=59) and older adults (Wilckens, Erickson, & Wheeler, In Press). Both PA and sleep were objectively measured with accelerometry. Wilckens et al., found that PA energy expenditure was positively associated with sleep efficiency, as well as executive functioning and processing speed. Further, sleep efficiency statistically mediated the relationship between PA and several measures of cognitive performance. Although limited by the cross-sectional nature of the design, these findings provide evidence that sleep may be a behavioral mechanism by which PA influences cognitive performance. Future RCTs in which participants are randomly assigned to multiple sleep and exercise conditions are needed to test this hypothesis directly.

Mood as a Mediator

Low mood, often assessed using measures of depressive symptomology, is associated with poorer performance on a variety of cognitive tests (see Austin, Mitchell, & Goodwin, 2001; Lichtenberg, Ross, Millis, & Manning, 1995 for reviews). These cognitive deficits typically manifest in the domains of executive functioning, attention, and memory—the same domains that are most affected by PA (McClintock, Husain, Greer, & Cullum, 2010).

Increased PA is associated with improved mood, and is an efficacious approach to reduce symptoms of depression and anxiety (Byrne & Byrne, 1993; Fox, 1999; Penedo & Dahn, 2005; Ströhle, 2009; see for review Bridle, Spanjers, Patel, Atherton, & Lamb, 2012). In fact, PA is increasingly being used as an adjunct treatment for clinically significant depression (Mead et al., 2008). Interestingly, there is also evidence that the relationship between PA and mood is bidirectional, such that poorer mood may lead to decreased PA (Roshanaei-Moghaddam, Katon, & Russo, 2009).

Despite the fact that mood has been linked both to PA and cognitive function, only a handful of studies have considered mood as a mediating pathway through which PA influences

cognition. For example, Vance et al. (2005) and Robitaille et al. (2014) both used statistical mediation in cross-sectional studies to examine the effects of several socioemotional factors (i.e., social support, depressive symptoms, cognitive activity) on the relationship between PA and cognitive performance. Consistent with their predictions and results from previous work, there were positive relationships between PA and tests of cognition, specifically in the domains of memory, processing speed, and visuospatial functioning. However, the two studies found disparate results when examining the behavioral predictors. In particular, Vance et al. (2005) found that physical inactivity had significant indirect associations with cognitive functioning through depressive symptomology and social support, while Robitaille et al. (2014) did not find that depression scores mediated the associations between PA and cognitive performance. Instead, they found that social support and cognitive engagement mediated the effects of PA on cognition (Robitaille et al., 2014). However, the indirect effects of these factors varied by cognitive outcome, suggesting that the mechanisms may vary across cognitive domains.

Unfortunately, the results of RCTs have not provided any more clarity regarding the role of factors, such as mood, on the PA-cognition relationship. One RCT examined mood as a mediating pathway with 64 younger adults randomly assigned to an exercise or control group (Lichtman & Poser, 1983). Following the intervention, the exercise group performed significantly better on an executive control test (i.e., a Stroop task) compared to the control group. The exercise group also showed a significant decrease in their depression and anxiety symptoms compared to baseline. However, the control group also exhibited decreases in depression and anxiety. Albinet and colleagues (2016) found similar results in a sample of 36 older adults who either participated in aerobic exercise or stretching control intervention for 21 weeks (Albinet, Abou-Dest, André, & Audiffren, 2016). While both groups showed

improvement in self-reported depressive symptomology, only the exercise group showed neurocognitive improvements. This pattern of results indicates that exercise was not the primary mechanism for the mood or cognitive improvements.

There are also studies in which mood changes following an exercise RCT, but no cognitive effects are observed. Another early RCT examined changes in psychological (including mood) and neuropsychological functioning following a 4-month aerobic exercise intervention in older adults (Blumenthal et al., 1989). Participants across three randomized groups (i.e., aerobic exercise, yoga and flexibility control, or waitlist control) did not show any clear pattern of differences on neuropsychological tests following the intervention. However, males in the aerobic exercise group showed a significant decline in depression and anxiety scores compared the control groups. There was still no clear pattern of cognitive improvements following exercise, even after training was extended for up to 10 months (Blumenthal et al., 1991; D. J. Madden, Blumenthal, Allen, & Emery, 1989).

Conversely, there are RCTs in which neurocognition changes, but mood does not. For example, Williams and Lord (1997) conducted an RCT examining the effects of a 42-week exercise intervention on mood and cognitive functioning in a group of older, community-dwelling women. Following the intervention, the exercise group performed better than the control group on measures of memory and processing speed. In addition, within the exercise group, individuals who reported higher baseline levels of anxiety and depression showed greater improvements in cognitive performance compared to individuals in the exercise group who reported lower baseline levels. However, as with Lichtman and Poser (1983), there were no group differences in mood symptoms following the intervention, and so exercise may not be driving the cognitive changes they observed. While none of these correlational studies were

conclusive regarding whether mood mediates exercise-induced cognitive improvements, the results provide evidence that the relationship between exercise, cognition, and mood merits further exploration.

Testing the influence of exercise on cognition in clinical populations has not been as common in the literature. In a RCT of 73 older adults with Chronic Obstructive Pulmonary Disease (COPD), Emery and colleagues (1998) examined the effects of exercise, education about COPD, and stress management on psychological and cognitive functioning. Participants were randomized to three groups, only one of which had an exercise component (in addition to stress management and education). Post-intervention analyses revealed that the group receiving exercise (hereafter referred to as the “exercise group”) showed lower depressive symptomatology compared to their baseline scores and to the post-intervention scores of the education-only group. Participants in the exercise group also showed improved verbal fluency scores, while the other two groups’ scores did not change from their pre-intervention levels. While Emery and colleagues did not directly test a mediation model in this RCT, the fact that only the exercise group showed improvements in both mood and cognitive performance suggests a possible mediating link between exercise, changes in mood, and changes in cognition. However, it is difficult to interpret the exact nature of these effects because there was no group that *only* engaged in exercise. Thus, it is unclear whether the mood and cognitive improvements were due to exercise alone or to some synergistic effect of exercise, education, and stress management. Further, given that these results—the only experimental evidence to date to show both mood and cognitive changes in an exercising group—were reported in a clinical sample with known disturbances in mood (Maurer et al., 2008) and cognitive functioning (Liesker et al., 2004), it remains an open question whether the same mechanisms would underlie exercise-

related changes to cognition in healthy populations. These results of the studies of PA and mood reviewed indicate that we do not yet understand whether, to what extent, and how changes to mood mediate the effects of PA on cognition.

Discussion

The main motivation for writing the present review was to highlight the basic idea that mechanisms of PA on cognitive outcomes can be conceptualized on multiple levels, and it is possible to examine them using a variety of study designs. Historically, the discussion of mechanisms of PA or exercise on cognitive outcomes has been limited to Level 1 of analysis. There have been numerous reviews in the past decade that have described in detail the molecular and cellular mechanisms of PA. Since excellent evidence for these mechanisms already exists, we did not explain them in detail. Instead, we focused on evidence for mechanisms of PA on cognition at Level 2 and took stock of the (limited) evidence for mechanisms of PA on cognition at Level 3 of analysis.

Mechanisms at Level 2 (i.e., structural and functional brain changes) are only just beginning to be discussed in the scientific literature. Our review suggests that regional gray matter volume statistically mediates the relationship between cardiorespiratory fitness or PA and cognitive functioning, but most of these studies have been limited to cross-sectional designs. In addition, white matter microstructure and functional brain activity may also be mediating associations between fitness or PA and cognition (e.g., Oberlin et al., 2016; Wong et al., 2015). Across the studies, brain changes do not occur equally or uniformly throughout the brain; rather, they seem specific to several brain regions in particular, namely, the hippocampus and prefrontal cortex. The regional specificity of PA-related structural and functional brain changes is

important because it mirrors some of the regional specificity observed in animal models (i.e., hippocampus).

Consistent with the cross-sectional work, RCTs also support the argument that changes in brain structure and function may be mechanisms underlying the relationship between PA and cognitive performance. Specifically, the majority of RCTs have reported changes in brain structure or function, as well as in cognition following the exercise intervention. However, of the 13 RCTs including both cognitive and neuroimaging measures conducted to date, only 1 has used a statistical mediation model. Thus, it has not been possible in the majority of RCTs to rule out the possibility that another, unmeasured factor that covaries with both the treatment and outcome is underlying the intervention effects observed in the brain and/or cognitive performance.

The search for mechanisms at Level 2 is further complicated for several reasons. First, while the volume or function of specific brain regions (again, mostly the hippocampus and prefrontal cortex) consistently change following exercise interventions, the evidence has been less consistent with regard to cognitive performance. For example, although the majority of RCTs discussed above report cognitive changes that are exclusive to the exercise group following training, several reported cognitive improvements in both the exercise *and* control groups—i.e., a lack of group-by-time interaction (Erickson et al., 2011; Krafft et al., 2014; Ruscheweyh et al., 2011; Voss, Heo, et al., 2013). This makes it difficult to link exercise and brain changes exclusively to the cognitive changes observed. It also highlights a key limitation of RCTs in humans: It is extremely difficult to control the behavior of participants outside of the context of the RCT. Thus, even using this gold standard design, extra-training behaviors (e.g., those in the “control” condition might inadvertently increase their PA) could lead to unexpected

effects. Second, there is variability in the design of the existing RCTs in terms of, for example, activity level/engagement of the control group, intervention length, type and frequency of PA, adherence, exclusionary criteria, neurocognitive outcomes assessed, and analytic techniques. It is therefore difficult to know whether null findings are the result of this inter-study variability or a true lack of effect. Finally, there are many factors that may moderate the effects of PA on neurocognition. Despite the favorable effects of physical activity and cardiorespiratory fitness on brain health and cognitive function reviewed above, there is significant inter-individual variability within studies regarding the extent to which any one individual will reap the physical and cognitive benefits of PA. Thus, it is likely that mediators are being moderated by other factors, such as the presence of pathology, age, genotype, gender, and diet (see Leckie, Weinstein, Hodzic, & Erickson, 2012 for review). However, the convergence of the effects of PA on brain health, despite this wide range of variability, speaks to the robustness of PA on both brain health outcomes and cognitive function.

Along these lines, if PA is thought to enhance cognition by improving brain structure and function, then eliminating PA should have the opposite effect. Examination of the effects of PA cessation has been comparatively unexplored to date. However, there have been two recent studies on this topic that support this idea (Alfini et al., 2016; Thomas et al., 2016). Alfini et al., (2016), showed that cortical and hippocampal resting brain perfusion decreases following PA cessation after just 10 days in older adult athletes. In addition, Thomas et al (2016) found that hippocampal volume gains following an exercise intervention in young-middle aged adults, were abolished following 2-weeks of exercise cessation. These results are interesting and important for the field because they support PA as the causal variable in mechanistic models (i.e., removing PA reverses the brain effects attributed to this behavior). However, Alfini and colleagues did not

administer a full cognitive battery, thereby limiting an interpretation of their results with regard to cognition. Thomas and colleagues administered a brief cognitive battery, but found no change in cognition following their 6-week intervention. It was therefore not possible to thoroughly evaluate whether cognition (our outcome variable of interest) also decreased following PA cessation. Such evidence is needed, as it would further strengthen the causal role Level 2 mediators play in PA-related cognitive effects.

Mechanisms of PA on cognition at Level 3 of analysis have not been frequently considered or assessed. However, there are a handful of studies suggesting that this level may be important to consider for future studies (Table 2). Changes in sleep quality, for example, are linked to both cognition and to PA. However, only one study to date (Wilckens et al., In Press) has combined all three variables in a statistical model to test whether sleep can account for the relationship between PA and cognitive performance—the results of this initial study suggest that it can. Similarly, mood is linked both to cognitive performance and PA. While several studies have considered mood along with other behavioral or socioemotional factors in statistical models assessing mechanisms of PA, virtually none have considered the unique or independent contribution of mood to the PA-cognition relationship.

We highlighted sleep and mood as two examples of potential mechanisms at Level 3 because there are literatures linking these factors to both cognition and PA, thus making them candidate mediators. However, it is important to note that there are likely many other possible behavioral mechanisms (e.g., self-efficacy, motivation, fatigue, pain) that should be examined in future work (e.g., see relevant reviews McAuley & Blissmer, 2000; Mullen, McAuley, Satariano, Kealey, & Prohaska, 2012; Teixeira, Carraça, Markland, Silva, & Ryan, 2012). Identifying such mechanisms is important, as they would provide additional outcome targets to assess the

effectiveness of PA interventions. These additional possible behavioral mechanisms were not addressed in the current review because, to our knowledge, there are no studies to date examining them as potential mediators of the PA-cognition relationship. Additional studies including both psychological and neurocognitive functioning as outcome variables are needed to enhance our understanding of this level of analysis.

The studies reviewed above suggest that the individual pieces of a model from PA to cognitive functioning through behavioral changes, such as sleep or mood, exist, but they have not been succinctly combined in one cohesive model. Future work should address the gaps in our understanding of how behavioral mechanisms modulate the effects of PA on cognition by conducting RCTs with participants aged across the lifespan and measuring both behavioral and cognitive outcomes at multiple time points. Designs with these components would allow us to test not only for experimental mediation, but also for statistical mediation following exercise interventions.

Conclusions & Limitations

One important point of consideration/limitation for studies examining the mechanisms of PA relates to the sample size needed to test for mediation. There are a number of publications addressing this topic (Cerin, Taylor, Leslie, & Owen, 2006; Fritz & Mackinnon, 2007; MacKinnon, Fairchild, & Fritz, 2007). These articles suggest that the sample size needed to detect mediation effects depends on the size of the effect expected and the statistical method used to test for mediation. Effect sizes generally decrease with increasing variability of the outcome and so, although not always practical, larger samples are likely needed to detect mediation effects when outcome measures are highly variable (i.e., as is often the case in neuroimaging data) (Preacher & Kelley, 2011). Randomized clinical trials (RCT) in which

groups are made to more extremely differ on a manipulated independent variable is one possible way to decrease variability (by the making groups differ extremely) and therefore increase power to detect mediation. Thus, RCTs might be the best context in which to test for Level 2 mediators. In terms of analytical method, bootstrapping methods of testing mediation generally require smaller samples, while causal-steps approaches require the most (Cerin et al., 2006). The recommended sample size to test for a small-moderate mediation effect range from as few as $N = 50$ -100 people using bootstrapping methods (e.g., Cerin et al., 2006) to anywhere from 400 to > 20,000 people using more conservative causal-steps approaches (e.g., Fritz & Mackinnon, 2007). Many of the studies of PA cited above do not meet these recommended power requirements, increasing the likelihood of Type I and II error. Future studies should keep these guidelines in mind when budgeting and planning for recruitment.

Despite these considerations, there are many studies that implicate mechanisms of PA on cognition at Levels 2 and 3 of analysis that have given us the groundwork to construct our proposed mechanistic models (Figures 2, 3), but very few have actually tested for statistical mediation. Doing so is critically important in order to rule out the possibility that the more macroscopic brain and socioemotional changes linked to PA are meaningless byproducts of PA. While we currently have the foundation to think about more macroscopic mechanisms that may mediate the relationship between PA and cognition, and potentially provide new, clinically-relevant targets, these components need to be combined in testable models in future studies.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Author Contributions

CS, JC, ML, and KE have seen and approved this manuscript for submission and are accountable for all aspects of the work. CS, JC, ML, and KE made substantial contributions to conceptualizing, drafting, and revising the manuscript.

Funding

CS is supported by NIH/NIMH T32 MH109986. JC was supported by the Dietrich Arts and Sciences Fellowship, Department of Psychology, University of Pittsburgh. KE was supported by National Institutes of Health grants R01 DK095172, R01 CA196762, R01 AG053952, P30 MH90333, and P30 AG024827.

Acknowledgements

The authors would like to thank BACH Lab undergraduate, Melanie Ciecuch, for assistance with the literature search for this review.

Tables

Table 1. Evidence for mechanisms of PA at Level 2 of analysis.

Lead author	Year	Sample	Mechanistic Finding	Type Mediation
Albinet	2014	34 older adults (all female)	Increases in cerebral oxygen responses in the right DLPFC partially mediate relationship between aerobic fitness and executive control performance	Statistical
Chaddock	2010	49 preadolescent children	Hippocampal volume mediates relationship between aerobic fitness and relational memory	Statistical
Chaddock-Heyman	2013	23 preadolescent children	Increases in prefrontal activation and executive functioning following a 9-month aerobic exercise intervention	Experimental
Colcombe	2004	41 older adults (study 1); 29 older adults (study 2)	Greater activation in prefrontal, parietal, and anterior cingulate cortex, and well as increased cognitive control performance in higher aerobically fit (study 1) or aerobically trained (study 2) individuals	Statistical (Study 1); Experimental (Study 2)
Erickson	2009	165 older adults	Hippocampal volume mediates relationship between cardiorespiratory fitness and spatial memory	Statistical
Erickson	2011	120 older adults	Volume of the hippocampus and memory performance increase following a 12-month aerobic exercise intervention	Experimental
Hillman	2014	221 preadolescent children	Frontal activation, cognitive inhibition, and flexibility increases following 9-month aerobic exercise intervention	Experimental
Hyodo	2015	60 male older adults	Activation of left dorsolateral prefrontal cortex mediates relationship between fitness and cognitive control	Statistical
Kamijo	2011	43 preadolescent children	Increases in cognitively-relevant frontal ERP component (CNV) and in working memory following a 9-month aerobic exercise intervention	Experimental
Kraft	2014	43 overweight children	Activity increases in the anterior cingulate cortex and decreases in precentral gyrus and parietal cortex following 8-month aerobic exercise intervention; Improved cognitive control performance	Experimental *no group x time interactions for any neurocognitive outcome
Krogh	2014	79 clinically depressed older adults	Positive association between change in hippocampal volume and changes in memory	Experimental *issues with

			following a 3-month aerobic exercise intervention	adherence; no group x time interactions
Maass	2015	40 older adults	Hippocampal volume, perfusion, and memory increases following a 3-month aerobic exercise intervention; Changes in perfusion statistically mediate relationship between volume and memory	Experimental and Statistical
Makizako	2015	310 older adults with MCI	Hippocampal volume mediates the association between PA and memory in older adults with MCI	Statistical
Oberlin	2016	241 older adults across 2 studies	White matter integrity mediates relationship between fitness and spatial working memory	Statistical
Pajonk	2010	24 schizophrenic patients	Hippocampal volume and short-term memory improve following 3-month aerobic exercise intervention; Changes in volume correlate with changes in memory	Experimental
Ruscheweyh	2012	62 older adults	Positive association between changes in PA and episodic memory following a 6 month mixed-intensity intervention no longer significant after accounting for the variance associated with change in anterior cingulate gray matter volume	Experimental * no group x time interactions
Ten Brinke	2015	86 female older adults	Hippocampal volume increases following 6-month aerobic exercise intervention. Changes in volume negatively associated with changes in short-term memory	Experimental
Verstynen	2012	179 older adults	Volume of the caudate nucleus mediates relationship between fitness and cognitive flexibility	Statistical
Voss	2010	62 older adults	Connectivity of large-scale brain networks and executive functioning improve following 6-month aerobic exercise intervention; changes in connectivity correlate with changes in executive functioning.	Experimental
Voss	2013	70 older adults	Improved fitness is associated with changes in prefrontal and temporal white matter integrity following a 12-month aerobic exercise intervention; no changes in short-term memory	Experimental *no group x time interaction for neurocognitive outcome

			performance reported between groups; no mediation model could be tested	
Weinstein	2012	142 older adults	Volume of prefrontal cortex mediates the relationship between cardiorespiratory fitness and working memory, as well as that between fitness and inhibitory control	Statistical
Wong	2015	128 older adults	Greater anterior cingulate cortex activation mediates relationship between fitness and dual task performance	Statistical

Table 2. Evidence for mechanisms of PA at Level 3 of analysis.

Lead Author	Year	Sample	Mechanistic Finding	Type of Mediation
Albinet	2016	36 older adults	Improvements in cognition following a 21-week exercise intervention are independent of improvements in mood	Experimental
Blumenthal	1989	101 older adults	A 4-month exercise intervention improves mood symptoms in males, but does not show any clear pattern of improvements in cognition	Experimental
Blumenthal	1991	101 older adults	4, 8, or 14 months of exercise training does not improve cognitive task performance	Experimental
Emery	1998	73 Chronic Obstructive Pulmonary Disorder patients	Exercise improves verbal fluency and reduces depressive symptoms compared to baseline scores and non-exercising groups	Experimental
King	1997	43 older adults	Improvements in self-rated sleep quality in exercising group following 16-week exercise intervention	Statistical
Lichtman	1983	64 young and mid-life adults	A 4-month exercise intervention improves performance on the Stroop Task	Statistical
Madden	1989	85 older adults and 24 younger adults	4 or 8 months of exercise does not improve cognitive task performance	Experimental
Robitaille	2014	470 older adults	Social support and cognitive engagement mediate the effects of PA on cognition	Statistical
Singh	1997	32 older adults	Exercise improves self-rated sleep quality following a 10-week intervention	Statistical
Vance	2005	158 older adults	Sedentary behavior has significant indirect associations with neurocognitive functioning through depression and social	Statistical

			support	
Wilckens	In press	109 adults (59 younger, 50 older)	Sleep mediates the relationship between PA and executive functioning	Statistical
Williams	1997	187 older women	Exercise improves performance on tests of memory and processing speed following a 12-month intervention. Depression and anxiety symptoms decrease following the intervention for participants reporting the highest symptoms at baseline, though not differently from the non-exercising group.	Experimental *no group x time interaction for mood outcomes

Figure Captions

Figure 1. Conceptual model of mechanisms of PA at multiple levels of analysis. There are various possible mediating pathways and bidirectional effects. Several possibilities are denoted with dotted arrows.

Figure 2. Level 1 of analysis: Possible molecular and cellular mechanisms of PA. **HPA = Hypothalamic-pituitary-adrenal axis activity.**

Figure 3. Level 2 of Analysis: Possible brain systems-level mechanisms of PA.

Figure 4. Level 3 of analysis: Possible behavioral mechanisms of PA.

References

- Albinet, C. T., Abou-Dest, A., André, N., & Audiffren, M. (2016). Executive functions improvement following a 5-month aquaerobics program in older adults: Role of cardiac vagal control in inhibition performance. *Biological Psychology*, 115, 69–77.
<https://doi.org/10.1016/j.biopsycho.2016.01.010>
- Albinet, C. T., Mandrick, K., Bernard, P. L., Perrey, S., & Blain, H. (2014). Improved cerebral oxygenation response and executive performance as a function of cardiorespiratory fitness in older women: a fNIRS study. *Frontiers in Aging Neuroscience*, 6, 272.
<https://doi.org/10.3389/fnagi.2014.00272>
- Alfini, A. J., Weiss, L. R., Leitner, B. P., Smith, T. J., Hagberg, J. M., & Smith, J. C. (2016). Hippocampal and Cerebral Blood Flow after Exercise Cessation in Master Athletes. *Frontiers in Aging Neuroscience*, 184. <https://doi.org/10.3389/fnagi.2016.00184>
- Austin, M.-P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression. *The British Journal of Psychiatry*, 178(3), 200–206.
<https://doi.org/10.1192/bjp.178.3.200>
- Baruch, D. E., Swain, R. A., & Helmstetter, F. J. (2004). Effects of exercise on Pavlovian fear conditioning. *Behavioral Neuroscience*, 118(5), 1123–1127.
<https://doi.org/10.1037/0735-7044.118.5.1123>
- Bechara, R. G., & Kelly, Á. M. (2013). Exercise improves object recognition memory and induces BDNF expression and cell proliferation in cognitively enriched rats. *Behavioural Brain Research*, 245, 96–100.
<https://doi.org/10.1016/j.bbr.2013.02.018>

- 852 Bennett, I. J., & Madden, D. J. (2014). Disconnected aging: cerebral white matter integrity
 853 and age-related differences in cognition. *Neuroscience*, 276, 187–205.
 854 <https://doi.org/10.1016/j.neuroscience.2013.11.026>
- 855 Blumenthal, J. A., Emery, C. F., Madden, D. J., George, L. K., Coleman, R. E., Riddle, M. W., ...
 856 Williams, R. S. (1989). Cardiovascular and Behavioral Effects of Aerobic Exercise
 857 Training in Healthy Older Men and Women. *Journal of Gerontology*, 44(5), M147–
 858 M157. <https://doi.org/10.1093/geronj/44.5.M147>
- 859 Blumenthal, J. A., Emery, C. F., Madden, D. J., Schniebolck, S., Walsh-Riddle, M., George, L. K., ...
 860 Coleman, R. E. (1991). Long-term effects of exercise on psychological functioning in
 861 older men and women. *Journal of Gerontology*, 46(6), P352–361.
- 862 Braun, S. M. G., & Jessberger, S. (2014). Adult neurogenesis: mechanisms and functional
 863 significance. *Development*, 141(10), 1983–1986.
 864 <https://doi.org/10.1242/dev.104596>
- 865 Bridle, C., Spanjers, K., Patel, S., Atherton, N. M., & Lamb, S. E. (2012). Effect of exercise on
 866 depression severity in older people: systematic review and meta-analysis of
 867 randomised controlled trials. *The British Journal of Psychiatry: The Journal of Mental*
 868 *Science*, 201(3), 180–185. <https://doi.org/10.1192/bjp.bp.111.095174>
- 869 Bruel-Jungerman, E., Laroche, S., & Rampon, C. (2005). New neurons in the dentate gyrus
 870 are involved in the expression of enhanced long-term memory following
 871 environmental enrichment. *The European Journal of Neuroscience*, 21(2), 513–521.
 872 <https://doi.org/10.1111/j.1460-9568.2005.03875.x>
- 873 Burzynska, A. Z., Chaddock-Heyman, L., Voss, M. W., Wong, C. N., Gothe, N. P., Olson, E. A., ...
 874 Kramer, A. F. (2014). Physical Activity and Cardiorespiratory Fitness Are Beneficial

- 875 for White Matter in Low-Fit Older Adults. *PLOS ONE*, 9(9), e107413.
 876 <https://doi.org/10.1371/journal.pone.0107413>
- 877 Byrne, A., & Byrne, D. G. (1993). The effect of exercise on depression, anxiety and other
 878 mood states: a review. *Journal of Psychosomatic Research*, 37(6), 565–574.
- 879 Carro, E., Nuñez, A., Busiguina, S., & Torres-Aleman, I. (2000). Circulating Insulin-Like
 880 Growth Factor I Mediates Effects of Exercise on the Brain. *The Journal of*
 881 *Neuroscience*, 20(8), 2926–2933.
- 882 Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and
 883 physical fitness: definitions and distinctions for health-related research. *Public*
 884 *Health Reports*, 100(2), 126–131.
- 885 Cerin, E., Taylor, L. M., Leslie, E., & Owen, N. (2006). Small-scale randomized controlled
 886 trials need more powerful methods of mediational analysis than the Baron–Kenny
 887 method. *Journal of Clinical Epidemiology*, 59(5), 457–464.
 888 <https://doi.org/10.1016/j.jclinepi.2005.11.008>
- 889 Chaddock-Heyman, L., Erickson, K. I., Voss, M. W., Knecht, A. M., Pontifex, M. B., Castelli, D.
 890 M., ... Kramer, A. F. (2013). The effects of physical activity on functional MRI
 891 activation associated with cognitive control in children: a randomized controlled
 892 intervention. *Frontiers in Human Neuroscience*, 7.
 893 <https://doi.org/10.3389/fnhum.2013.00072>
- 894 Chaddock, L., Erickson, K. I., Prakash, R. S., Kim, J. S., Voss, M. W., VanPatter, M., ... Kramer, A.
 895 F. (2010). A neuroimaging investigation of the association between aerobic fitness,
 896 hippocampal volume, and memory performance in preadolescent children. *Brain*
 897 *Research*, 1358, 172–183. <https://doi.org/10.1016/j.brainres.2010.08.049>

- 898 Chen, H.-I., Lin, L.-C., Yu, L., Liu, Y.-F., Kuo, Y.-M., Huang, A.-M., ... Jen, C. J. (2008). Treadmill
 899 exercise enhances passive avoidance learning in rats: The role of down-regulated
 900 serotonin system in the limbic system. *Neurobiology of Learning and Memory*, 89(4),
 901 489–496. <https://doi.org/10.1016/j.nlm.2007.08.004>
- 902 Clark, P. J., Brzezinska, W. J., Thomas, M. W., Ryzhenko, N. A., Toshkov, S. A., & Rhodes, J. S.
 903 (2008). Intact neurogenesis is required for benefits of exercise on spatial memory
 904 but not motor performance or contextual fear conditioning in C57BL/6J mice.
 905 *Neuroscience*, 155(4), 1048–1058.
 906 <https://doi.org/10.1016/j.neuroscience.2008.06.051>
- 907 Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., ... Kramer, A. F.
 908 (2006). Aerobic Exercise Training Increases Brain Volume in Aging Humans. *The*
 909 *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 61(11),
 910 1166–1170.
- 911 Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., ... Elavsky, S.
 912 (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the*
 913 *National Academy of Sciences of the United States of America*, 101(9), 3316–3321.
 914 <https://doi.org/10.1073/pnas.0400266101>
- 915 Cotman, C. W., & Berchtold, N. C. (2007). Physical activity and the maintenance of cognition:
 916 Learning from animal models. *Alzheimer's & Dementia*, 3(2, Supplement), S30–S37.
 917 <https://doi.org/10.1016/j.jalz.2007.01.013>
- 918 Cotman, C. W., Berchtold, N. C., & Christie, L.-A. (2007). Exercise builds brain health: key
 919 roles of growth factor cascades and inflammation. *Trends in Neurosciences*, 30(9),
 920 464–472. <https://doi.org/10.1016/j.tins.2007.06.011>

- 921 Ding, Q., Vaynman, S., Akhavan, M., Ying, Z., & Gomez-Pinilla, F. (2006). Insulin-like growth
 922 factor I interfaces with brain-derived neurotrophic factor-mediated synaptic
 923 plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience*,
 924 *140*(3), 823–833. <https://doi.org/10.1016/j.neuroscience.2006.02.084>
- 925 Dupuy, O., Gauthier, C. J., Fraser, S. A., Desjardins-Crèpeau, L., Desjardins, M., Mekary, S., ...
 926 Bherer, L. (2015). Higher levels of cardiovascular fitness are associated with better
 927 executive function and prefrontal oxygenation in younger and older women.
 928 *Frontiers in Human Neuroscience*, *9*, 66. <https://doi.org/10.3389/fnhum.2015.00066>
- 929 Duzel, E., Praag, H. van, & Sendtner, M. (2016). Can physical exercise in old age improve
 930 memory and hippocampal function? *Brain*, *139*(3), 662–673.
 931 <https://doi.org/10.1093/brain/awv407>
- 932 Eadie, B. D., Redila, V. A., & Christie, B. R. (2005). Voluntary exercise alters the
 933 cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation,
 934 dendritic complexity, and spine density. *The Journal of Comparative Neurology*,
 935 *486*(1), 39–47. <https://doi.org/10.1002/cne.20493>
- 936 Ellenbogen, J. M. (2005). Cognitive benefits of sleep and their loss due to sleep deprivation.
 937 *Neurology*, *64*(7), E25–27. <https://doi.org/10.1212/01.WNL.0000159942.64562.AD>
- 938 Emery, C. F., Schein, R. L., Hauck, E. R., & MacIntyre, N. R. (1998). Psychological and
 939 cognitive outcomes of a randomized trial of exercise among patients with chronic
 940 obstructive pulmonary disease. *Health Psychology: Official Journal of the Division of*
 941 *Health Psychology, American Psychological Association*, *17*(3), 232–240.

- 942 Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., ... Kramer, A. F.
 943 (2009). Aerobic fitness is associated with hippocampal volume in elderly humans.
 944 *Hippocampus*, 19(10), 1030–1039. <https://doi.org/10.1002/hipo.20547>
- 945 Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., ... Kramer, A. F.
 946 (2011). Exercise training increases size of hippocampus and improves memory.
 947 *Proceedings of the National Academy of Sciences*, 108(7), 3017–3022.
 948 <https://doi.org/10.1073/pnas.1015950108>
- 949 Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., ... Palmer, T. D. (2003). VEGF
 950 is necessary for exercise-induced adult hippocampal neurogenesis. *The European*
 951 *Journal of Neuroscience*, 18(10), 2803–2812.
- 952 Firth, J., Cotter, J., Elliott, R., French, P., & Yung, A. R. (2015). A systematic review and meta-
 953 analysis of exercise interventions in schizophrenia patients. *Psychological Medicine*,
 954 45(07), 1343–1361. <https://doi.org/10.1017/S0033291714003110>
- 955 Fjell, A. M., Westlye, L. T., Amlien, I. K., & Walhovd, K. B. (2011). Reduced White Matter
 956 Integrity Is Related to Cognitive Instability. *The Journal of Neuroscience*, 31(49),
 957 18060–18072. <https://doi.org/10.1523/JNEUROSCI.4735-11.2011>
- 958 Fox, K. R. (1999). The influence of physical activity on mental well-being. *Public Health*
 959 *Nutrition*, 2(3A), 411–418.
- 960 Fritz, M. S., & Mackinnon, D. P. (2007). Required sample size to detect the mediated effect.
 961 *Psychological Science*, 18(3), 233–239. [https://doi.org/10.1111/j.1467-](https://doi.org/10.1111/j.1467-9280.2007.01882.x)
 962 [9280.2007.01882.x](https://doi.org/10.1111/j.1467-9280.2007.01882.x)
- 963 Gauthier, C. J., Lefort, M., Mekary, S., Desjardins-Crépeau, L., Skimminge, A., Iversen, P., ...
 964 Hoge, R. D. (2015). Hearts and minds: linking vascular rigidity and aerobic fitness

- 965 with cognitive aging. *Neurobiology of Aging*, 36(1), 304–314.
 966 <https://doi.org/10.1016/j.neurobiolaging.2014.08.018>
- 967 Gomez-Pinilla, F., & Hillman, C. (2013). The Influence of Exercise on Cognitive Abilities.
 968 *Comprehensive Physiology*, 3(1), 403–428. <https://doi.org/10.1002/cphy.c110063>
- 969 Hamilton, G. F., & Rhodes, J. S. (2015). Exercise Regulation of Cognitive Function and
 970 Neuroplasticity in the Healthy and Diseased Brain. *Progress in Molecular Biology and*
 971 *Translational Science*, 135, 381–406.
 972 <https://doi.org/10.1016/bs.pmbts.2015.07.004>
- 973 Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: exercise
 974 effects on brain and cognition. *Nature Reviews Neuroscience*, 9(1), 58–65.
 975 <https://doi.org/10.1038/nrn2298>
- 976 Hillman, C. H., Pontifex, M. B., Castelli, D. M., Khan, N. A., Raine, L. B., Scudder, M. R., ...
 977 Kamijo, K. (2014). Effects of the FITKids Randomized Controlled Trial on Executive
 978 Control and Brain Function. *Pediatrics*, 134(4), e1063–e1071.
 979 <https://doi.org/10.1542/peds.2013-3219>
- 980 Hopkins, M. E., & Bucci, D. J. (2010). BDNF Expression in Perirhinal Cortex is Associated
 981 with Exercise-Induced Improvement in Object Recognition Memory. *Neurobiology of*
 982 *Learning and Memory*, 94(2), 278–284. <https://doi.org/10.1016/j.nlm.2010.06.006>
- 983 Hyodo, K., Dan, I., Kyutoku, Y., Suwabe, K., Byun, K., Ochi, G., ... Soya, H. (2016). The
 984 association between aerobic fitness and cognitive function in older men mediated
 985 by frontal lateralization. *NeuroImage*, 125, 291–300.
 986 <https://doi.org/10.1016/j.neuroimage.2015.09.062>

- 987 Imai, K., Keele, L., Tingley, D., & Yamamoto, T. (2011). Unpacking the Black Box of Causality:
 988 Learning about Causal Mechanisms from Experimental and Observational Studies.
 989 *American Political Science Review*, 105(04), 765–789.
 990 <https://doi.org/10.1017/S0003055411000414>
- 991 Kamijo, K., Pontifex, M. B., O’Leary, K. C., Scudder, M. R., Wu, C.-T., Castelli, D. M., & Hillman,
 992 C. H. (2011). The effects of an afterschool physical activity program on working
 993 memory in preadolescent children. *Developmental Science*, 14(5), 1046–1058.
 994 <https://doi.org/10.1111/j.1467-7687.2011.01054.x>
- 995 King, A. C., Oman, R. F., Brassington, G. S., Bliwise, D. L., & Haskell, W. L. (1997). Moderate-
 996 intensity exercise and self-rated quality of sleep in older adults. A randomized
 997 controlled trial. *JAMA*, 277(1), 32–37.
- 998 Krafft, C. E., Schwarz, N. F., Chi, L., Weinberger, A. L., Schaeffer, D. J., Pierce, J. E., ...
 999 McDowell, J. E. (2014). An 8-month randomized controlled exercise trial alters brain
 1000 activation during cognitive tasks in overweight children. *Obesity*, 22(1), 232–242.
 1001 <https://doi.org/10.1002/oby.20518>
- 1002 Kramer, A. F., Erickson, K. I., & Colcombe, S. J. (2006). Exercise, cognition, and the aging
 1003 brain. *Journal of Applied Physiology*, 101(4), 1237–1242.
 1004 <https://doi.org/10.1152/jappphysiol.00500.2006>
- 1005 Krogh, J., Rostrup, E., Thomsen, C., Elfving, B., Videbech, P., & Nordentoft, M. (2014). The
 1006 effect of exercise on hippocampal volume and neurotrophines in patients with
 1007 major depression--a randomized clinical trial. *Journal of Affective Disorders*, 165, 24–
 1008 30. <https://doi.org/10.1016/j.jad.2014.04.041>

- 1009 Leckie, R. L., Weinstein, A. M., Hodzic, J. C., & Erickson, K. I. (2012). Potential Moderators of
 1010 Physical Activity on Brain Health. *Journal of Aging Research, Journal of Aging*
 1011 *Research*, 2012, e948981. <https://doi.org/10.1155/2012/948981>,
 1012 10.1155/2012/948981
- 1013 Leuner, B., Gould, E., & Shors, T. J. (2006). Is there a link between adult neurogenesis and
 1014 learning? *Hippocampus*, 16(3), 216–224. <https://doi.org/10.1002/hipo.20153>
- 1015 Lichtenberg, P. A., Ross, T., Millis, S. R., & Manning, C. A. (1995). The relationship between
 1016 depression and cognition in older adults: a cross-validation study. *The Journals of*
 1017 *Gerontology. Series B, Psychological Sciences and Social Sciences*, 50(1), P25–P32.
- 1018 Lichtman, S., & Poser, E. G. (1983). The effects of exercise on mood and cognitive
 1019 functioning. *Journal of Psychosomatic Research*, 27(1), 43–52.
 1020 [https://doi.org/10.1016/0022-3999\(83\)90108-3](https://doi.org/10.1016/0022-3999(83)90108-3)
- 1021 Liesker, J. J. W., Postma, D. S., Beukema, R. J., ten Hacken, N. H. T., van der Molen, T.,
 1022 Riemersma, R. A., ... Kerstjens, H. A. M. (2004). Cognitive performance in patients
 1023 with COPD. *Respiratory Medicine*, 98(4), 351–356.
 1024 <https://doi.org/10.1016/j.rmed.2003.11.004>
- 1025 Lista, I., & Sorrentino, G. (2009). Biological Mechanisms of Physical Activity in Preventing
 1026 Cognitive Decline. *Cellular and Molecular Neurobiology*, 30(4), 493–503.
 1027 <https://doi.org/10.1007/s10571-009-9488-x>
- 1028 Maass, A., Düzel, S., Goerke, M., Becke, A., Sobieray, U., Neumann, K., ... Düzel, E. (2015).
 1029 Vascular hippocampal plasticity after aerobic exercise in older adults. *Molecular*
 1030 *Psychiatry*, 20(5), 585–593. <https://doi.org/10.1038/mp.2014.114>

- 1031 MacKinnon, D. P., Fairchild, A. J., & Fritz, M. S. (2007). Mediation Analysis. *Annual Review of*
 1032 *Psychology*, 58, 593. <https://doi.org/10.1146/annurev.psych.58.110405.085542>
- 1033 Madden, D. J., Bennett, I. J., Burzynska, A., Potter, G. G., Chen, N., & Song, A. W. (2012).
 1034 Diffusion tensor imaging of cerebral white matter integrity in cognitive aging.
 1035 *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1822(3), 386–400.
 1036 <https://doi.org/10.1016/j.bbadis.2011.08.003>
- 1037 Madden, D. J., Blumenthal, J. A., Allen, P. A., & Emery, C. F. (1989). Improving aerobic
 1038 capacity in healthy older adults does not necessarily lead to improved cognitive
 1039 performance. *Psychology and Aging*, 4(3), 307–320.
- 1040 Makizako, H., Liu-Ambrose, T., Shimada, H., Doi, T., Park, H., Tsutsumimoto, K., ... Suzuki, T.
 1041 (2015). Moderate-intensity physical activity, hippocampal volume, and memory in
 1042 older adults with mild cognitive impairment. *The Journals of Gerontology. Series A,*
 1043 *Biological Sciences and Medical Sciences*, 70(4), 480–486.
 1044 <https://doi.org/10.1093/gerona/glu136>
- 1045 Maurer, J., Rebbapragada, V., Borson, S., Goldstein, R., Kunik, M. E., Yohannes, A. M., &
 1046 Hanania, N. A. (2008). Anxiety and Depression in COPD. *Chest*, 134(4 Suppl), 43S–
 1047 56S. <https://doi.org/10.1378/chest.08-0342>
- 1048 McAuley, E., & Blissmer, B. (2000). Self-efficacy determinants and consequences of physical
 1049 activity. *Exercise and Sport Sciences Reviews*, 28(2), 85–88.
- 1050 McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between
 1051 depression severity and neurocognitive function in major depressive disorder: a
 1052 review and synthesis. *Neuropsychology*, 24(1), 9–34.
 1053 <https://doi.org/10.1037/a0017336>

- 1054 Mead, G. E., Morley, W., Campbell, P., Greig, C. A., McMurdo, M., & Lawlor, D. A. (2008).
 1055 Exercise for depression. *The Cochrane Database of Systematic Reviews*, (4),
 1056 CD004366. <https://doi.org/10.1002/14651858.CD004366.pub3>
- 1057 Meshi, D., Drew, M. R., Saxe, M., Ansorge, M. S., David, D., Santarelli, L., ... Hen, R. (2006).
 1058 Hippocampal neurogenesis is not required for behavioral effects of environmental
 1059 enrichment. *Nature Neuroscience*, 9(6), 729–731. <https://doi.org/10.1038/nn1696>
- 1060 Mullen, S. P., McAuley, E., Satariano, W. A., Kealey, M., & Prohaska, T. R. (2012). Physical
 1061 Activity and Functional Limitations in Older Adults: The Influence of Self-Efficacy
 1062 and Functional Performance. *The Journals of Gerontology Series B: Psychological*
 1063 *Sciences and Social Sciences*, 67B(3), 354–361.
 1064 <https://doi.org/10.1093/geronb/gbs036>
- 1065 Niemann, C., Godde, B., & Voelcker-Rehage, C. (2014). Not only cardiovascular, but also
 1066 coordinative exercise increases hippocampal volume in older adults. *Frontiers in*
 1067 *Aging Neuroscience*, 6, 170. <https://doi.org/10.3389/fnagi.2014.00170>
- 1068 Oberlin, L. E., Verstynen, T. D., Burzynska, A. Z., Voss, M. W., Prakash, R. S., Chaddock-
 1069 Heyman, L., ... Erickson, K. I. (2016). White matter microstructure mediates the
 1070 relationship between cardiorespiratory fitness and spatial working memory in older
 1071 adults. *NeuroImage*, 131, 91–101.
 1072 <https://doi.org/10.1016/j.neuroimage.2015.09.053>
- 1073 Pajonk, F.-G., Wobrock, T., Gruber, O., Scherk, H., Berner, D., Kaizl, I., ... Falkai, P. (2010).
 1074 Hippocampal plasticity in response to exercise in schizophrenia. *Archives of General*
 1075 *Psychiatry*, 67(2), 133–143. <https://doi.org/10.1001/archgenpsychiatry.2009.193>

- 1076 Parachikova, A., Nichol, K. E., & Cotman, C. W. (2008). Short-term exercise in aged Tg2576
 1077 mice alters neuroinflammation and improves cognition. *Neurobiology of Disease*,
 1078 30(1), 121–129. <https://doi.org/10.1016/j.nbd.2007.12.008>
- 1079 Penedo, F. J., & Dahn, J. R. (2005). Exercise and well-being: a review of mental and physical
 1080 health benefits associated with physical activity. *Current Opinion in Psychiatry*,
 1081 18(2), 189–193.
- 1082 Preacher, K. J., & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing
 1083 and comparing indirect effects in multiple mediator models. *Behavior Research*
 1084 *Methods*, 40(3), 879–891. <https://doi.org/10.3758/BRM.40.3.879>
- 1085 Preacher, K. J., & Kelley, K. (2011). Effect size measures for mediation models: quantitative
 1086 strategies for communicating indirect effects. *Psychological Methods*, 16(2), 93–115.
 1087 <https://doi.org/10.1037/a0022658>
- 1088 Roberts, R. E., Anderson, E. J., & Husain, M. (2013). White Matter Microstructure and
 1089 Cognitive Function. *The Neuroscientist*, 19(1), 8–15.
 1090 <https://doi.org/10.1177/1073858411421218>
- 1091 Robitaille, A., Muniz, G., Lindwall, M., Piccinin, A. M., Hoffman, L., Johansson, B., & Hofer, S.
 1092 M. (2014). Physical activity and cognitive functioning in the oldest old: within- and
 1093 between-person cognitive activity and psychosocial mediators. *European Journal of*
 1094 *Ageing*, 11(4), 333–347. <https://doi.org/10.1007/s10433-014-0314-z>
- 1095 Roshanaei-Moghaddam, B., Katon, W. J., & Russo, J. (2009). The longitudinal effects of
 1096 depression on physical activity. *General Hospital Psychiatry*, 31(4), 306–315.
 1097 <https://doi.org/10.1016/j.genhosppsych.2009.04.002>

- 1098 Ruscheweyh, R., Willemer, C., Krüger, K., Duning, T., Warnecke, T., Sommer, J., ... Flöel, A.
 1099 (2011). Physical activity and memory functions: an interventional study.
 1100 *Neurobiology of Aging*, 32(7), 1304–1319.
 1101 <https://doi.org/10.1016/j.neurobiolaging.2009.08.001>
- 1102 Sexton, C. E., Betts, J. F., Demnitz, N., Dawes, H., Ebmeier, K. P., & Johansen-Berg, H. (2016). A
 1103 systematic review of MRI studies examining the relationship between physical
 1104 fitness and activity and the white matter of the ageing brain. *NeuroImage*, 131, 81–
 1105 90. <https://doi.org/10.1016/j.neuroimage.2015.09.071>
- 1106 Singh, N. A., Clements, K. M., & Fiatarone, M. A. (1997). Sleep, sleep deprivation, and
 1107 daytime activities. A randomized controlled trial of the effect of exercise on sleep.
 1108 *Sleep*, 20(2), 95–101.
- 1109 Smith, J. C., Lancaster, M. A., Nielson, K. A., Woodard, J. L., Seidenberg, M., Durgerian, S., ...
 1110 Rao, S. M. (2016). Interactive effects of physical activity and APOE-ε4 on white
 1111 matter tract diffusivity in healthy elders. *NeuroImage*, 131, 102–112.
 1112 <https://doi.org/10.1016/j.neuroimage.2015.08.007>
- 1113 Smith, J. C., Nielson, K. A., Woodard, J. L., Seidenberg, M., Durgerian, S., Hazlett, K. E., ... Rao,
 1114 S. M. (2014). Physical activity reduces hippocampal atrophy in elders at genetic risk
 1115 for Alzheimer's disease. *Frontiers in Aging Neuroscience*, 6.
 1116 <https://doi.org/10.3389/fnagi.2014.00061>
- 1117 Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K.,
 1118 ... Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: a meta-
 1119 analytic review of randomized controlled trials. *Psychosomatic Medicine*, 72(3), 239–
 1120 252. <https://doi.org/10.1097/PSY.0b013e3181d14633>

- 1121 Ströhle, A. (2009). Physical activity, exercise, depression and anxiety disorders. *Journal of*
 1122 *Neural Transmission (Vienna, Austria: 1996)*, 116(6), 777–784.
 1123 <https://doi.org/10.1007/s00702-008-0092-x>
- 1124 Teixeira, P. J., Carraça, E. V., Markland, D., Silva, M. N., & Ryan, R. M. (2012). Exercise,
 1125 physical activity, and self-determination theory: A systematic review. *International*
 1126 *Journal of Behavioral Nutrition and Physical Activity*, 9, 78.
 1127 <https://doi.org/10.1186/1479-5868-9-78>
- 1128 Ten Brinke, L. F., Bolandzadeh, N., Nagamatsu, L. S., Hsu, C. L., Davis, J. C., Miran-Khan, K., &
 1129 Liu-Ambrose, T. (2015). Aerobic exercise increases hippocampal volume in older
 1130 women with probable mild cognitive impairment: a 6-month randomised controlled
 1131 trial. *British Journal of Sports Medicine*, 49(4), 248–254.
 1132 <https://doi.org/10.1136/bjsports-2013-093184>
- 1133 Thomas, A. G., Dennis, A., Rawlings, N. B., Stagg, C. J., Matthews, L., Morris, M., ... Johansen-
 1134 Berg, H. (2016). Multi-modal characterization of rapid anterior hippocampal volume
 1135 increase associated with aerobic exercise. *NeuroImage*, 131, 162–170.
 1136 <https://doi.org/10.1016/j.neuroimage.2015.10.090>
- 1137 Tomporowski, P. D., & Ellis, N. R. (1986). Effects of exercise on cognitive processes: A
 1138 review. *Psychological Bulletin*, 99(3), 338–346. [https://doi.org/10.1037/0033-](https://doi.org/10.1037/0033-2909.99.3.338)
 1139 [2909.99.3.338](https://doi.org/10.1037/0033-2909.99.3.338)
- 1140 Vance, D. E., Wadley, V. G., Ball, K. K., Roenker, D. L., & Rizzo, M. (2005). The effects of
 1141 physical activity and sedentary behavior on cognitive health in older adults. *Journal*
 1142 *of Aging and Physical Activity*, 13(3), 294–313.

- 1143 Van Praag, H. (2008). Neurogenesis and Exercise: Past and Future Directions.
 1144 *NeuroMolecular Medicine*, 10(2), 128–140. <https://doi.org/10.1007/s12017-008->
 1145 8028-z
- 1146 Van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances
 1147 neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the*
 1148 *National Academy of Sciences of the United States of America*, 96(23), 13427–13431.
- 1149 Van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise Enhances Learning and
 1150 Hippocampal Neurogenesis in Aged Mice. *The Journal of Neuroscience*, 25(38), 8680–
 1151 8685. <https://doi.org/10.1523/JNEUROSCI.1731-05.2005>
- 1152 Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy
 1153 of exercise on synaptic plasticity and cognition. *The European Journal of*
 1154 *Neuroscience*, 20(10), 2580–2590. <https://doi.org/10.1111/j.1460->
 1155 9568.2004.03720.x
- 1156 Verstynen, T. D., Lynch, B., Miller, D. L., Voss, M. W., Prakash, R. S., Chaddock, L., ... Erickson,
 1157 K. I. (2012). Caudate Nucleus Volume Mediates the Link between Cardiorespiratory
 1158 Fitness and Cognitive Flexibility in Older Adults, Caudate Nucleus Volume Mediates
 1159 the Link between Cardiorespiratory Fitness and Cognitive Flexibility in Older Adults.
 1160 *Journal of Aging Research, Journal of Aging Research*, 2012, 2012, e939285.
 1161 <https://doi.org/10.1155/2012/939285>, 10.1155/2012/939285
- 1162 Vivar, C., Potter, M. C., Choi, J., Lee, J.-Y., Stringer, T. P., Callaway, E. M., ... van Praag, H.
 1163 (2012). Monosynaptic inputs to new neurons in the dentate gyrus. *Nature*
 1164 *Communications*, 3, 1107. <https://doi.org/10.1038/ncomms2101>

- 1165 Vivar, C., Potter, M. C., & van Praag, H. (2013). All About Running: Synaptic Plasticity,
 1166 Growth Factors and Adult Hippocampal Neurogenesis. *Current Topics in Behavioral*
 1167 *Neurosciences*, 15, 189–210. https://doi.org/10.1007/7854_2012_220
- 1168 Voelcker-Rehage, C., Godde, B., & Staudinger, U. M. (2010). Physical and motor fitness are
 1169 both related to cognition in old age. *European Journal of Neuroscience*, 31(1), 167–
 1170 176. <https://doi.org/10.1111/j.1460-9568.2009.07014.x>
- 1171 Voelcker-Rehage, C., & Niemann, C. (2013). Structural and functional brain changes related
 1172 to different types of physical activity across the life span. *Neuroscience and*
 1173 *Biobehavioral Reviews*, 37(9 Pt B), 2268–2295.
 1174 <https://doi.org/10.1016/j.neubiorev.2013.01.028>
- 1175 Voss, M. W., Heo, S., Prakash, R. S., Erickson, K. I., Alves, H., Chaddock, L., ... Kramer, A. F.
 1176 (2013). The influence of aerobic fitness on cerebral white matter integrity and
 1177 cognitive function in older adults: results of a one-year exercise intervention.
 1178 *Human Brain Mapping*, 34(11), 2972–2985. <https://doi.org/10.1002/hbm.22119>
- 1179 Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T., & Kramer, A. F. (2011). Exercise, brain, and
 1180 cognition across the life span. *Journal of Applied Physiology*, 111(5), 1505–1513.
 1181 <https://doi.org/10.1152/jappphysiol.00210.2011>
- 1182 Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., ... Kramer, A. F.
 1183 (2010). Plasticity of brain networks in a randomized intervention trial of exercise
 1184 training in older adults. *Frontiers in Aging Neuroscience*, 2.
 1185 <https://doi.org/10.3389/fnagi.2010.00032>

- 1186 Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human
 1187 models of exercise-induced brain plasticity. *Trends in Cognitive Sciences*, 17(10),
 1188 525–544. <https://doi.org/10.1016/j.tics.2013.08.001>
- 1189 Walker, M. P. (2009). The role of sleep in cognition and emotion. *Annals of the New York*
 1190 *Academy of Sciences*, 1156, 168–197. <https://doi.org/10.1111/j.1749->
 1191 6632.2009.04416.x
- 1192 Weinstein, A. M., Voss, M. W., Prakash, R. S., Chaddock, L., Szabo, A., White, S. M., ... Erickson,
 1193 K. I. (2012). The association between aerobic fitness and executive function is
 1194 mediated by prefrontal cortex volume. *Brain, Behavior, and Immunity*, 26(5), 811–
 1195 819. <https://doi.org/10.1016/j.bbi.2011.11.008>
- 1196 Wilckens, K., Erickson, K. I., & Wheeler, M. E. (In Press). Wilckens, KA., Erickson, KI.,
 1197 Wheeler, ME. Physical activity and cognition: A mediating role of efficient sleep.
 1198 *Behavioral Sleep Medicine*.
- 1199 Williams, P., & Lord, S. R. (1997). Effects of group exercise on cognitive functioning and
 1200 mood in older women. *Australian and New Zealand Journal of Public Health*, 21(1),
 1201 45–52.
- 1202 Wong, C. N., Chaddock-Heyman, L., Voss, M. W., Burzynska, A. Z., Basak, C., Erickson, K. I., ...
 1203 Kramer, A. F. (2015). Brain activation during dual-task processing is associated with
 1204 cardiorespiratory fitness and performance in older adults. *Frontiers in Aging*
 1205 *Neuroscience*, 154. <https://doi.org/10.3389/fnagi.2015.00154>
- 1206 Yaffe, K., Falvey, C. M., & Hoang, T. (2014). Connections between sleep and cognition in
 1207 older adults. *The Lancet Neurology*, 13(10), 1017–1028.
 1208 [https://doi.org/10.1016/S1474-4422\(14\)70172-3](https://doi.org/10.1016/S1474-4422(14)70172-3)

- 1209 Zhang, S., Chen, Y., Liu, Z., Zhang, J., Li, X., Cui, R., & Zhang, Z. (2015). Association of White
1210 Matter Integrity and Cognitive Functions in Chinese Non-Demented Elderly with the
1211 APOE ϵ 4 Allele. *Journal of Alzheimer's Disease*, 48(3), 781–791.
1212 <https://doi.org/10.3233/JAD-150357>
- 1213 Zimmerman, B., Sutton, B. P., Low, K. A., Fletcher, M. A., Tan, C. H., Schneider-Garces, N., ...
1214 Fabiani, M. (2014). Cardiorespiratory fitness mediates the effects of aging on
1215 cerebral blood flow. *Frontiers in Aging Neuroscience*, 6.
1216 <https://doi.org/10.3389/fnagi.2014.00059>
1217

Provisional

Figure 01.TIFF

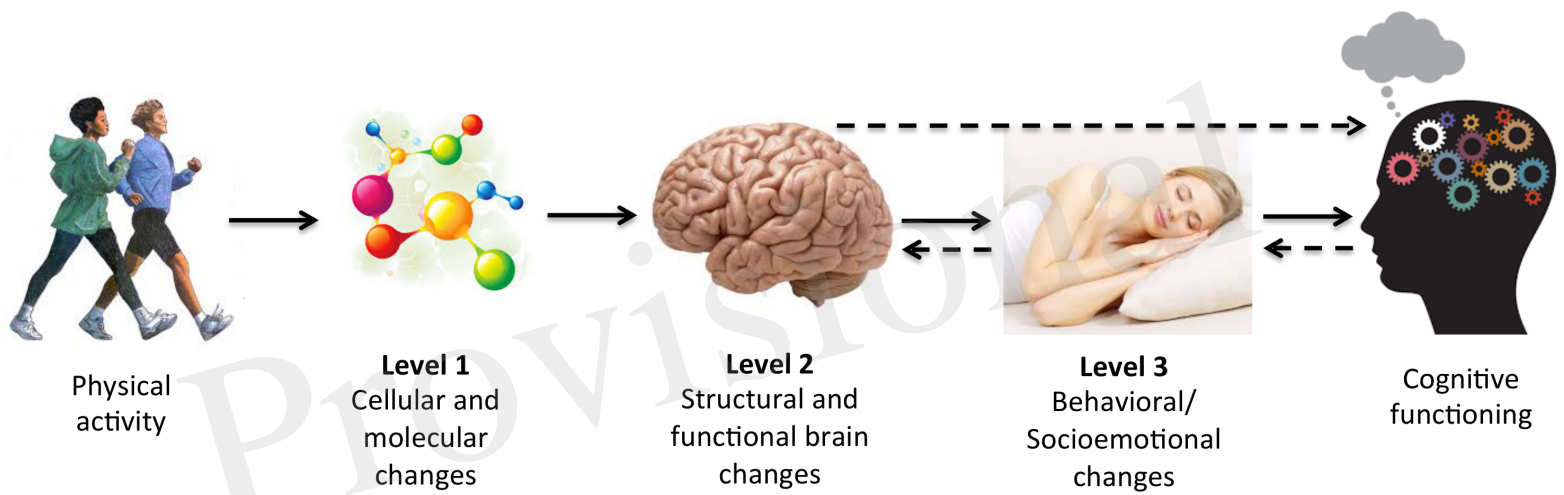


Figure 02.TIFF

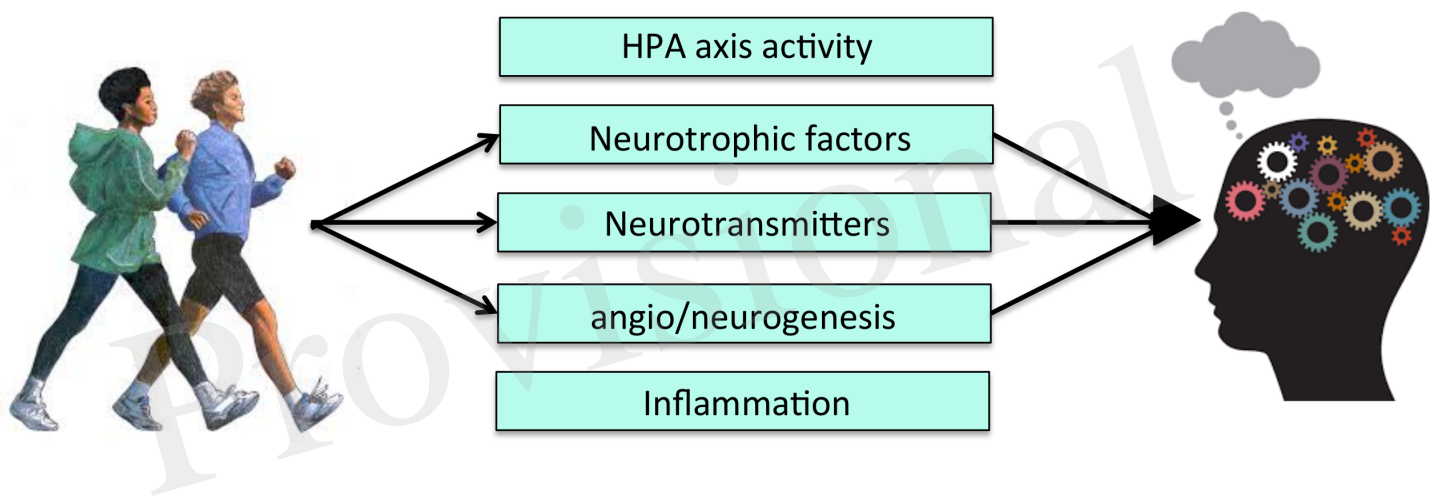


Figure 03.TIFF

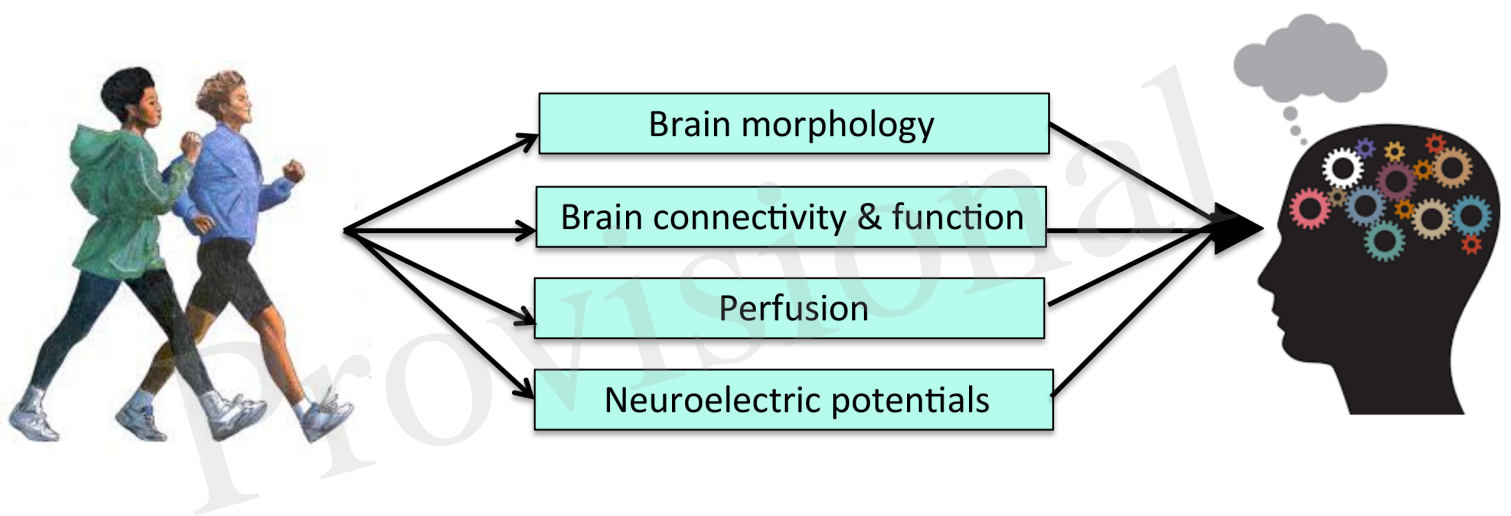


Figure 04.TIFF

