Published in final edited form as:

Trends Cogn Sci. 2019 April ; 23(4): 318–333. doi:10.1016/j.tics.2019.01.006.

Exercise and hippocampal memory systems

Michelle W. Voss¹, Carmen Soto², Seungwoo Yoo³, Matthew Sodoma¹, Carmen Vivar², and Henriette van Praag³

¹Department of Psychological and Brain Sciences, University of Iowa

²Laboratory of Neurogenesis and Neuroplasticity. Department of Physiology, Biophysics and Neuroscience, Center for Research and Advanced Studies of the National Polytechnic Institute, Mexico City.

³Department of Biomedical Science, Charles E. Schmidt College of Medicine, and Brain Institute, Florida Atlantic University, Jupiter, FL 33458, USA

Abstract

No medications prevent or reverse age-related cognitive decline. Physical activity (PA) enhances memory in rodents, but findings are mixed in human studies. As a result, exercise guidelines specific for brain health are absent. Here, we re-examine results from human studies, and suggest the use of more sensitive tasks to evaluate PA effects on age-related changes in the hippocampus, such as relational memory and mnemonic discrimination. We discuss recent advances from rodent and human studies into the underlying mechanisms at both the central and peripheral levels, including neurotrophins and myokines that could contribute to improved memory. Finally, we suggest guidelines for future research to help expedite well-founded PA recommendations for the public.

Keywords

physical activity; hippocampus; neurogenesis; aging; pattern separation; relational memory; growth factors; myokines

The elephant in the room: can we recommend exercise for memory?

The growing aging population together with an increase in sedentary lifestyle is an urgent public health concern, particularly after the fourth and fifth decades of life. If the pace of increased life expectancy [1] and inactivity [2] continues, an unprecedented percentage of future generations may live with cognitive impairment. By delaying cognitive decline, we may be able to compress our time with dementia or perhaps escape it altogether. Given the health benefits of **physical activity** (PA, see Glossary), and its wide accessibility at any age,

Correspondence: michelle-voss@uiowa.edu (M.W. Voss).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

determining how PA may sustain cognition during aging would have enormous societal and economic impact.

Human and animal studies show PA benefits brain function and cognition, and could counteract age-related cognitive decline [3]. However, a recent National Academies report [4] affirms that while PA appears promising, evidence from human studies is inconclusive towards preventing cognitive decline and insufficient to recommend exercise for reducing the risk of dementia. Their resolution was based on the inconsistency of cognitive benefits in randomized controlled trials (RCTs), and the lack of correspondence between cognitive change, and changes in intervention-induced biomarkers of brain dysfunction. The report called for more intervention studies with long-term follow-ups assessing clinical outcomes.

While valuable, this approach will require decades of lead time before a new recommendation can be considered. In this review, we re-examine evidence that has accumulated from animal models and human PA studies to unravel the mixed results from RCTs. We focus on cross-species approaches to identify possible changes in the hippocampus, a brain area crucial for memory formation [5, 6]. Determining how PA counteracts the trajectory of early memory decline will also provide prevention strategies for cognitive aging and Alzheimer's disease (AD). Specifically, rodent models are utilized to evaluate components of human **episodic memory** vulnerable to aging, such as relational memory, **pattern separation**, and spatial navigation, as well as the underlying cellular and molecular mechanisms. By examining the effects of PA on memory function across different species and timescales, we hope to elucidate the process of change and identify relevant biomarkers of PA effectiveness for long-term brain health during human aging.

The mixed effects of PA on human cognitive function

The National Academies [4] and the National Academy of Medicine [7] reports point out that long-term prospective studies consistently show that PA reduces cognitive decline and dementia risk [8, 9]. Yet, several well-powered RCTs such as the LIFE [10] and MAX [11] trials failed to demonstrate PA benefits on cognition in older adults. However, in these studies **cardiorespiratory fitness** was not measured [e.g., 12]. This means aerobic training intensity could not be optimally personalized to starting fitness levels, and it is difficult to precisely verify fitness adaptations at a group or individual level. Indeed, fitness change may be a critical indicator of whether cognitive changes are expected, and the wide variation in fitness response can overshadow training group effects (see SI I-III and Table 1). Another source of discrepancy between results from observational and experimental designs may be a lack of consistent and precise cognitive outcome measures. For example, eleven meta-analyses of RCTs with primarily older adults used 9 unique terms for overlapping memory constructs (e.g., memory, short-term memory and verbal memory immediate; see SI IV). Therefore, relevant information may be masked when grouping across tasks with different levels of sensitivity and precision at different phases of aging and disease progression.

To better understand the effects of aerobic PA on memory, we summarize effects from the meta-analysis reports at the task level. We focused specifically on neuropsychological tests predicting cognitive impairment and dementia such as word list and story recall, and a more

general decline in visuospatial memory in complex figure tasks. We also included tasks assessing constituent processes in episodic memory such as relational memory and pattern separation, as well as wayfinding (Box 1). These processes may identify early memory dysfunctions, as they rely on the hippocampal circuitry and deteriorate early in AD [13-15]. We counted the number of results consistent with a hypothesis in favor of PA (improved) or against the hypothesis (declined), relative to null effects [e.g., 8]. Positive results for cognitively normal middle-aged and older adults were proportionally highest in relational memory tasks, and there were no negative effects for any task (Figure 1A, Key Figure). Evidence that PA improves middle-aged and older adults' performance on relational memory tasks is consistent with data from cross-sectional studies with older adults [16-18], and with both item and spatial relational tasks (Figure 1B) in pre-adolescents [19-23] and young adults [24-26]. Albeit, some studies with smaller sample sizes of young adults observed null effects [16, 17, 27, 28], which may be due to lack of statistical power. Although, PA has shown improved pattern separation and wayfinding (Box 1) in animal models and young adults, it appears that no RCTs in middle-aged or older adults have focused on these tasks, which represents an important future direction.

PA improves pattern separation in rodents and humans

The ability to discriminate among ambiguous or similar experiences is a crucial feature of episodic memory, and therefore pattern separation is regarded as a critical function of the hippocampal network. It is considered that in the hippocampal network, the feed-forward projections from a smaller number of entorhinal cortex neurons, project via the perforant pathway, onto a larger population of dentate gyrus cells, providing an anatomical basis for the concept of pattern separation. Information is then processed from the dentate gyrus to area CA3 for **pattern completion** and then to area CA1 for encoding, forming the 'tri-synaptic hippocampal circuit' [29]. The dentate gyrus also affects spatial or episodic memories through pattern separation [30, 31]. This theory has been supported by testing rodents with lesions in select hippocampal subfields (area CA1, area CA3 or dentate gyrus) on tasks requiring discrimination among similar stimuli. For example, animals with dentate gyrus damage have deficits in their ability to distinguish between two similar objects, with one covering a baited food well, whereas CA1-lesioned rats can [32]. In addition, dorsal dentate gyrus-lesioned rats, but not dorsal CA1- and CA3-lesioned rats, are impaired in detecting novel object locations [33]. More recently, following a neurotoxic dentate gyrus lesion, rats could not learn new scene stimuli but were able to retrieve learned familiar scenes [34]. Newly-formed scene memories in the lesion group were also easily disrupted by presenting similar versions of the new scene. Thus, the integrity of the dentate gyrus is critical for pattern separation.

In humans, studies using functional magnetic resonance imaging (fMRI) with the **blood oxygen level-dependent (BOLD) signal** show area CA3 and dentate gyrus activity is elevated during pattern separation performance [35-37] while CA1, subiculum and parahippocampal cortices including the entorhinal cortex showed a bias toward pattern completion [37]. Limits in fMRI spatial resolution make it difficult to reliably distinguish between the CA3 and dentate gyrus. Activity spanning both regions may reflect projections of pattern separated information from the dentate gyrus to CA3. A small but growing

number of studies with humans suggest pattern separation, evaluated with mnemonic discrimination tasks (Figure 1B), is a critical process for evaluating PA effects on hippocampal function. Specifically, an intervention study with young adults showed that 6 weeks of high-intensity training, which increases fitness, improved discrimination [27]. However, the small sample and lack of control group limit the finding. Studies using a cross-sectional design, also suggest greater PA [38] and higher fitness [39] correlate with better discrimination. Further, this correlation appears strongest when fitness and circulating **brain-derived neurotrophic factor** (BDNF) are high [40]. Moreover, a single PA session improved object discrimination in young adults, further linked to changes in **functional connectivity** during the test phase between hippocampal (dentate gyrus/CA3) and cortical regions involved in recall, suggesting PA can induce rapid functional changes that affect performance, without structural alterations [41]. Yet, a voxel-based morphometry study in young adults also found higher fitness was associated with greater right entorhinal volume, which was related to mnemonic discrimination [42]. Thus, rapid functional changes appear in similar systems that are enhanced structurally with greater fitness, suggesting mechanisms linking rapid and accumulated effects could help understand how regular PA can improve memory. However, further studies in middle-aged and older adults are needed to elucidate these mechanisms.

In the dentate gyrus of the hippocampus, new neurons are born throughout adulthood in mammals, including humans, a process called **adult neurogenesis** [43, 44]. It has been suggested, that these new neurons play a key role in pattern separation. For example, mice with ablated hippocampal neurogenesis exhibited reduced spatial memory for similar, but not discrete, spatial locations in the radial arm maze task. These mice also showed performance deficits in the touchscreen-based pattern separation task [45]. Similarly, genetic suppression of adult neurogenesis impaired discrimination between similar contexts and disrupted normal population coding in CA3 [46]. Moreover, in transgenic mice in which tetanus toxin blocked the output of developmentally-born granule cells onto area CA3, while adult-born granule cells were intact, enhanced contextual discrimination in a highly similar context in comparison to control mice was observed, suggesting a key role of adult-born granule cells for pattern separation [47]. This concept is further supported by research showing that lesion of the lateral entorhinal cortex, a major input to adult-born granule cells results in deficient performance in the touchscreen task [48] (Figure 2A,B).

Unfortunately, in humans, PA effects on adult neurogenesis cannot be assessed *in vivo*. However, studies in multiple mouse and rat strains have shown that voluntary wheel running and forced treadmill training increase adult neurogenesis in the dentate gyrus throughout life in both sexes [49] and in the presence of AD-like pathology (Box 2). Use of viral vectors to birth-date the adult-born granule cells showed that PA increased their dendritic arborization and cell body area at 7 days-old [50]. In 21-day-old adult-born neurons, PA increased motility of dendritic spines and accelerated their maturation in both young [51] and middle-aged mice [52]. This running-induced enhancement of adult-born neuron morphology and number is associated with improved stimulus [53] and object discrimination in mice [54] (Figure 2C). Consistently, in a Bax conditional knockout mouse, which specifically prevents programmed cell death of adult-born neurons, thereby upregulating adult neurogenesis, there

was greater discrimination and rapid contextual encoding between two similar environments [55]. Altogether, these findings suggest adult hippocampal neurogenesis is important in pattern separation and can be facilitated by PA.

PA influences hippocampal memory by rewiring neuronal networks

From a functional perspective, increased dentate gyrus neuron production brings several benefits. It may contribute to maintenance of spine and synapse density, and help prevent hippocampal shrinkage in healthy aging [56]. In addition, although adult-born granule cells account for a small percentage of the total population of dentate gyrus cells, they have enhanced excitability, lower thresholds to induce long-term potentiation (LTP), and enhanced LTP compared to developmentally-born granule cells [57]. Moreover, PA modifies synaptic plasticity in adult-born neurons. Specifically, voluntary running increases short-term synaptic plasticity from the lateral entorhinal cortex onto adult-born neurons, evoked selectively by lateral perforant pathway stimulation [58]. PA also alters the network of adult-born neurons, augmenting the innervation from entorhinal cortex and areas important for spatial memory and **theta rhythm** generation, such as caudomedial entorhinal cortex, medial septum and supra- and medial mammillary nuclei [58] (Figure 2A,D). Indeed, evidence from animal models and preliminary results in humans show that physical movement induces synchronized neuronal firing at theta rhythm in hippocampal circuits [59, 60]. PA also modifies the expression of genes important for synaptic transmission in the lateral entorhinal cortex [61], a cortical area preferentially innervating adult-born granule cells [48, 62]. Thus, PA could coordinate the activity of neural ensembles to favor memory processes and enhance integration of adult-born neurons into the existing hippocampal-entorhinal circuitry that otherwise deteriorate with aging [63].

Mapping PA and fitness effects on human hippocampal networks

In humans, repeated non-invasive imaging is possible for tracking change throughout the brain. Some imaging methods can also be used in rodents to link imaging markers in humans to plausible biological substrates. In a first proof-of-concept study, exercise-induced increases in cerebral blood volume were observed with MRI in the dentate gyrus of young mice and middle-aged humans [64] (Table 1). More recently, a training study with older adults (N=40) [65] reported increased fitness was associated with improved hippocampal cerebral blood volume. Effects were strongest in the whole hippocampus, but cerebral blood volume changes accounted for increased anterior hippocampal volume [see also, 66, 67]. Thus, in agreement with animal models, exercise-induced changes in human hippocampal volume may couple with increased resting metabolic state or vascular density or both [see also, 68]. However, a study in young to middle-age adults found that anterior hippocampal volume changes from 6 weeks of training that improved fitness increased markers of myelination rather than cerebral blood volume [67]. Using multiple MRI modalities, they also found both fitness and hippocampal volume changes were absent after a 6-week break, further supporting the link between fitness and hippocampal adaptations, as well as the importance of long-term PA.

It is also worth emphasizing that PA effects on hippocampal volume are broader than maintenance or reversal of aging. Benefits have been shown in pre-adolescents [21], adolescents [28], college-age adults [25], cognitively unimpaired older adults [Table 1, 66, 68-70], older adults with mild cognitive impairment and AD [71, 72]. Thus, similar to animal models, PA effects on hippocampal structure are seen across the lifespan, suggesting an intrinsic adaptive benefit offering protection and resilience during aging.

In addition to regional structural growth and metabolic support, studies using neuroimaging with humans have also shown that moderate intensity PA [73-75] and fitness [25, 76-78] strengthen functional connectivity of a hippocampal-cortical brain network known as the **default network** (Figure 1C). Functional connectivity in this context refers to the extent to which the resting BOLD activity across network regions is coupled over time, typically quantified by the correlation strength of their timeseries. The default network spans cortical association regions including the medial and lateral surfaces of the temporal, parietal, and prefrontal cortices. While other association networks also show reduced functional connectivity with aging, the default network uniquely mirrors the spatial topography of structural connections of the medial temporal lobe and the cortical spread of AD pathology [79], and functional connectivity has been observed to predict risk of later cognitive impairment [e.g., 80]. For instance, Figure 1C illustrates association networks that we and others have shown to have reduced functional connectivity with aging [76, 81]. Although all the networks contain long-range cortical connections, more than any other network, the hippocampal-cortical default network is both affected by aging and protected with fitness. The extent to which alterations of the hippocampus are critical to this functional pattern needs to be examined. Especially given that most training effects on hippocampal structure and metabolism have been strongest in the anterior hippocampus, whereas the default network primarily includes the posterior hippocampus and parahippocampal cortex.

Notably, from longitudinal studies, long-distance cortical functional connectivity changes have been observed after 1-year [73] and in relation to fitness [75, 76], but not after shorter training periods (e.g., 6 months) unless fitness is improved [78]. It is also worth emphasizing that fitness relations with default network functional connectivity most often include the prefrontal cortex [25, 76, 77], which may counteract age-related reductions in functional connectivity between posterior and prefrontal cortices [82] and could help explain broader cognitive benefits of aerobic exercise to executive function [73, 77]. The underlying mechanisms in such long-range network effects measured with fMRI are expected to be multidimensional, reflecting integrative effects on neurotransmitter function, neurotrophic support for long-term potentiation and synaptic plasticity, vascular perfusion and reactivity (see outstanding questions). Complementary methods at the cellular and molecular level are also critical to clarifying potential mechanisms and informing potential signaling pathways from exercising muscles to the brain.

Cellular and molecular PA mechanisms

Trophic factors are closely associated with PA benefits for brain function [83]. BDNF plays an important role in synaptic plasticity, neurite outgrowth, neurogenesis and cell survival [84]. Knockdown or deficits in BDNF/tyrosine receptor kinase B (TrkB) signaling impairs

memory function [85]. In rodents, PA upregulates hippocampal BDNF/TrkB mRNA and protein expression after both short (2-7 days) and long (1-8 months) periods, across a range of intensities, exercise and housing conditions [86, 87, for review, see 88]. A meta-analysis reported a large PA effect on BDNF mRNA (effect size=1.82, 13 studies, 17 effects) and protein (effect size=1.25, 10 studies) in the rodent hippocampus [89].

Conversely, blocking hippocampal TrkB receptors abolishes benefits of exercise on learning and memory [90] and selectively ablating TrkB in adult hippocampal progenitor cells precludes running-induced neurogenesis [91], suggesting that BDNF may mediate, in part, the beneficial effects of PA on memory processes.

Utilizing BDNF as a biomarker for PA effects on the brain across species is complicated by several factors. While the neurotrophin can easily be measured in both the rat and mouse brain, blood serum and plasma levels in mice are too low to detect [92, 93]. In rats, peripheral BDNF can be assayed but shows no change after acute running [94] or a decrease after several weeks of exercise in adult [95] and aged [96] subjects. In humans, BDNF cannot be measured non-invasively in the brain, but it can be measured in the blood. It has been estimated the brain contributes 70-80% of circulating plasma BDNF during exercise [97]. In addition, BDNF is both stored and released from platelets [98].

Recently, a meta-analytic review found human BDNF in either serum or plasma increases acutely after a single session of PA and that this effect intensified with training [99]. It is worth noting there are conflicting proposals about how PA intensity affects BDNF signaling. Several studies have found higher intensities acutely elicit more serum BDNF [100], improved memory [101], and increased functional connectivity in hippocampal-cortical and reward systems [102], possibly stimulated by increased sympathetic activation [103]. On the other hand, it has been argued that lower intensities, avoiding a stress response, are optimal for rapid increases in hippocampal BDNF mRNA in rats [104], and can acutely improve pattern separation coupled with increased hippocampal functional connectivity in humans [41]. Critically, only one of these studies included older adults [102], so it will be important to determine how these proposals generalize to aging.

With respect to training, independent meta-analyses have reported that >2 weeks of aerobic training increased resting circulating BDNF measured in either serum or plasma [99, 105]. Following a year of training, elevated serum BDNF was correlated with hippocampal volume [66] and default network functional connectivity [106]. In contrast, several cross-sectional studies have reported a negative relationship between fitness and serum BDNF [107-110]. The sources of these discrepancies remain unclear. However, there are technical considerations that may preclude human PA studies from yielding consistent results. For instance, the number of platelets may affect peripheral BDNF measurements [111]. In addition, the different ELISA kits used may affect reproducibility of results [112].

In tandem with BDNF, vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1) mediate PA effects. Specifically, VEGF, a potent mitogen of endothelial cells, is increased in the rodent hippocampus during PA [113]. VEGF plays a role in PA-induced angiogenesis [114, 115] and increased neurogenesis [116]. This increment may be

associated with activation of lactate receptor HCAR1 in vessel walls, which mediate PA-induced increases in hippocampal VEGF A and angiogenesis [115]. Thus, VEGF may promote neurotransmission and neurovascular adaptations in response to increased metabolic demand associated with neuronal growth and network integration. IGF-1, on the other hand, is directly taken up from circulation into the cortex and hippocampus [117, 118]. In rodents, blocking peripheral IGF-1 blocks PA-induced increases in hippocampal BDNF [119] and adult neurogenesis [120]. In older humans, higher peripheral IGF-1 levels are associated with better cognition. However, with PA, levels of the growth factor have been shown to be increased, decreased or not changed [121]. The differences between studies may be associated with methodological challenges of these assays [122, 123], and illustrate the need for additional peripheral biomarkers of PA effects on the brain.

Identification of mechanisms underlying indirect activation of central growth factor signaling and neurogenesis via factors released from peripheral organs such as muscle (myokines), liver (hepatokines) and adipose tissue (adipokines) [124, 125], may lead to novel approaches to assess PA effects on cognitive function. An important regulator of muscle physiology is 5' adenosine monophosphate-activated protein kinase (AMPK). AMPK activation blocks energy-consuming processes and promotes ATP synthesis and glucose uptake [126]. AMPK also regulates transcription factors involved in muscle contractile processes such PPAR δ [127] and PGC1 α [128]. In rodents, PA activates AMPK and induces PGC1 α expression in the muscle, elevating FNDC5 protein levels, which is secreted as irisin in circulation. Irisin may induce hippocampal BDNF mRNA expression [129] and is detected in human serum [130]. In addition, FNDC/irisin is neuroprotective in a mouse model of Alzheimer's Disease [131]. Treatment of skeletal muscle cells *in vitro* with AMPK agonist AICAR also led to the identification of the myokine cathepsin B. In turn, administering recombinant cathepsin B to neural progenitor cells increased BDNF gene expression. Blocking cathepsin B during PA also occludes benefits on memory and neurogenesis in mice [132]. Moreover, in humans, 4 months of treadmill training increased plasma cathepsin B levels in association with improved visuospatial configural memory [132]. Recent research also established that β -hydroxybutyrate, a ketone synthesized in the liver and accumulating in the hippocampus during PA, activates BDNF gene promoters via inhibition of HDAC (histone deacetylases) [133]. Thus, the identification of central and peripheral factors may allow us to understand the mechanisms underlying the PA effects on cognitive function, which may also lead to methods for enhancing benefits (Table 1).

PA regimens for brain health

One of the biggest questions about PA is what is the best regimen to improve memory? As in recent general PA guidelines, individual factors such as age, gender, weight, health history, suggest there is not one PA prescription for everyone as to how much or how long we should work out to improve our health [2], and we would agree the same applies to memory. Nevertheless, most of the human studies which investigated the benefits of PA showed that aerobic exercise at or above 60% of individualized maximum heart-rate (three times per week for about an hour each session, for more than three months), increased either brain or cognitive measures that otherwise decline with aging, especially when fitness was improved (see SI I-III). This is consistent with general recommendations for adults to get at least 150

minutes of moderate intensity PA per week [2]. Based on the reviewed evidence across species here, we further emphasize the importance of individually-determined intensity and monitoring fitness improvements for maximizing benefits to the brain and memory (see SI III). Moreover, short-term periods of PA at a broader range of intensities immediately enhances neural plasticity and memory [41, 134, 135]. This is consistent with the general guidelines' suggestion to ideally spread PA throughout the week [2]. In the future, we may even understand how to maintain these benefits over the course of a day, which could perhaps motivate more people to override inactivity one day at a time. It is also clear from reviewed studies that consistent PA for weeks to months is needed for long-lasting improvements in hippocampal structural and functional plasticity, and memory function. Thus, overall, consistency is key, achieved through a lifestyle enriched in PA that gets the heart rate up, regardless of the specific regimen of choice.

Concluding remarks and future perspectives

The complexity of biological networks modified by PA requires model organisms that can isolate PA effects with tight experimental control. Animal models unravel plausible mechanisms that enable or constrain PA effects on memory, informing broader theoretical and biomarker development. Overall, data from animal models and humans indicate PA and fitness benefit functions that depend on intact hippocampal circuitry, such as relational memory and pattern separation. From our view, tasks tapping into these processes represent targeted “stress tests” for hippocampal circuitry, ideal for the next generation of intervention outcomes. The reviewed evidence supports the proposal that these tasks will be most sensitive to early system-level deterioration before advanced memory impairments.

Further, while exercise training designs can examine the outcomes of regular exercise, particularly in humans, they are limited in revealing the process of change. An acute paradigm examines rapid effects on cells and circuits during and acutely after PA, perhaps more directly indicating mechanisms of action. More broadly, the within-subject experimental control of acute and cross-over paradigms in humans brings massive advantages for allowing each individual to be their own control. It is also more feasible, as done in animal studies, to manipulate the system by not only enhancing but also blocking a proposed pathway while observing brain-behavior outcomes. While modifying an effect acutely does not guarantee it is necessary for training gains, converging evidence from acute and short timescales and long-term training could inspire strategies for mimicking or boosting exercise effects on the brain and memory.

With respect to long-term follow-up to clinical outcomes, experimental control in RCTs and clinical significance are difficult to optimize in a single study. Single-site RCTs with intensive biomarker measures are riddled with small and selective samples and many outcomes. Leveraging data-sharing and multi-site experimental studies will accelerate progress and enrich follow-up analyses for clinical outcomes. At the same time, an integrative theoretical model tying together critical biological variables in testable forms is necessary, coupled with the transparency of hypothesis testing with pre-registration. Exciting projects like the *Molecular Transducers of Physical Activity Consortium* (MoTrPAC, <https://www.motrpac.org/>), promise to provide rich datasets for this effort. Such theoretical and

mechanistic advances in understanding aerobic PA effects provide a foundation for further determining how other PA modalities such as resistance exercise could boost memory benefits (Box 3). However, at this time, the data are strongest for aerobic PA to maximize memory protection in late-life, and support the recommendation that future RCTs maintain aerobic PA as a reference arm for comparison of multi-modal or alternative PA types. Moreover, through the complementary use of acute and training designs with long-term follow-up, such a process-based approach, would open the door to more rapid and personalized feedback about how to optimize one's activity patterns for improved brain health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank the National Institute on Aging and the National Institute of General Medicine Sciences (RO1 AG055500, T32 GM108540) for their support of our research and the preparation of this review. Consejo Nacional de Ciencia y Tecnología (INFR-2016 268247) and Miguel Aleman Foundation to C.V.

Glossary

Adult neurogenesis

The adult brain contains two regions that can give rise to adult-born neurons in rodents: the subventricular zone of the lateral ventricles gives rise to new olfactory bulb neurons and the subgranular zone of the hippocampal dentate gyrus produces new granule cells. In humans, olfactory neurogenesis stops at birth [159], while the time-course of hippocampal neurogenesis remains under investigation [43, 44].

Blood oxygen level-dependent (BOLD) signal

A signal detected with fMRI indicating a reduction in deoxyhemoglobin that is known to couple with presynaptic activity of neuronal populations, and peaks approximately 4-6 seconds after neuronal activity onset.

Brain-derived neurotrophic factor (BDNF)

A protein supporting neuronal growth and repair, synaptic function, synaptic plasticity, and cellular homeostasis. BDNF is transcribed and expressed in the brain with high concentrations in the hippocampus, cortex, and hypothalamus. In peripheral tissues it is expressed in muscle, vascular endothelial cells, bone marrow megakaryocytes, and stromal and immune cells.

Cardiorespiratory fitness

Capacity to convert oxygen to physical work. The gold-standard measure is a graded maximal exercise test, which increases workload until exhaustion while measuring expired gases, resulting in a measure of the amount of oxygen one can use per minute per kilogram of body weight (mL/kg/min), to generate physical work. In our review, "fitness" refers specifically to cardiorespiratory fitness.

Default network

A hippocampal-cortical network that fragments with aging, particularly for medial temporal lobe and prefrontal connections (Figure 1C). The “Default” term refers to observations that the network is most active when individuals are not directed to think about anything and presumably revert to a default state, including mind wandering, mental simulation, and recollection of episodic memories.

Episodic memory

Memory for how events, places, and people come together in the episodes of day-to-day life. Proposed to rely on relational binding, the process of rapidly and obligatorily binding elements of experience across dimensions of space and time and their interactions.

Pattern completion

The computational process by which incomplete memory formations are reconstructed by partial sensory inputs that are part of the previously stored representations. This process helps to balance perceptual stability which allows accurate generalization in the presence of noise or complexity of external environments [30, 160].

Pattern separation

The computational process by which similar memories are stored and accessible as distinct representations in the brain. Empirical and computational evidence suggest the dentate gyrus enables pattern separation via sparse coding patterns. The behavioral expression of pattern separation processes is more generally referred to as mnemonic discrimination (e.g., Figure 1B and Figure 2B,C).

Physical activity (PA)

Bodily movement produced by the skeletal muscles that increase energy expenditure beyond resting levels. PA varies by type, frequency, duration, and intensity for both lifestyle-related activity and physical exercise that is planned, structured, and to improve physical performance.

Theta rhythm:

A slow rhythmic oscillatory activity (ranging the 4-8 Hz frequency) of the local field potential primarily found in the hippocampal structure. Its role has been known as critical to voluntary movement, spatial navigation, and memory processes (by coordinating neuronal ensembles within the medial temporal lobe) in animals and humans [for review, see 161].

References

1. Kontis V et al. (2017) Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *The Lancet* 389 (10076), 1323–1335.
2. Piercy KL et al. (2018) The Physical Activity Guidelines for Americans. *JAMA*.
3. Duzel E et al. (2016) Can physical exercise in old age improve memory and hippocampal function? *Brain* 139 (3), 662–673. [PubMed: 26912638]
4. Leshner AI et al. (2017) Preventing Cognitive Decline and Dementia: A Way Forward.
5. Scoville WB and Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20 (1), 11–21. [PubMed: 13406589]

6. Eichenbaum H (2010) Memory systems. *Wiley Interdiscip Rev Cogn Sci* 1 (4), 478–90. [PubMed: 26271495]
7. Livingston G et al. (2017) Dementia prevention, intervention, and care. *The Lancet*.
8. Beydoun MA (2014) Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health* 14 (643).
9. Blondell SJ et al. (2014) Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. 14 510.
10. Sink K et al. (2015) Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. *JAMA* 314 (8), 781–90. [PubMed: 26305648]
11. Barnes D et al. (2013) The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. *JAMA Intern Med* 173 (9), 797–804. [PubMed: 23545598]
12. Church TS et al. (2008) Maximal fitness testing in sedentary elderly at substantial risk of disability: LIFE-P study experience. *Journal of aging and physical activity* 16 (4), 408–415. [PubMed: 19033602]
13. Backman L et al. (2005) Cognitive Impairment in Preclinical Alzheimer's Disease: A Meta-Analysis. *Neuropsychology* 19 (4), 520–531. [PubMed: 16060827]
14. Khan UA et al. (2014) Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nat Neurosci* 17 (2), 304–11. [PubMed: 24362760]
15. Leal SL and Yassa MA (2015) Neurocognitive Aging and the Hippocampus across Species. *Trends Neurosci* 38 (12), 800–812. [PubMed: 26607684]
16. Hayes SM et al. (2015) Physical Activity Is Positively Associated with Episodic Memory in Aging. *J Int Neuropsychol Soc* 21 (10), 780–90. [PubMed: 26581790]
17. Hayes SM et al. (2016) Cardiorespiratory Fitness Is Associated With Cognitive Performance in Older But Not Younger Adults. *J Gerontol B Psychol Sci Soc Sci* 71 (3), 474–82. [PubMed: 25528256]
18. Hayes SM et al. (2017) FMRI activity during associative encoding is correlated with cardiorespiratory fitness and source memory performance in older adults. *Cortex* 91, 208–220. [PubMed: 28161031]
19. Raine L et al. (2013) The influence of childhood aerobic fitness on learning and memory. *PLoS One* 8 (9), e72666. [PubMed: 24039791]
20. Hassevoort KM et al. (2017) Macular Carotenoids, Aerobic Fitness, and Central Adiposity Are Associated Differentially with Hippocampal-Dependent Relational Memory in Preadolescent Children. *J Pediatr* 183, 108–114 e1. [PubMed: 28189300]
21. Chaddock L et al. (2010) A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Res* 1358, 172–83. [PubMed: 20735996]
22. Chaddock L et al. (2011) Aerobic fitness and executive control of relational memory in preadolescent children. *Med Sci Sports Exerc* 43 (2), 344–9. [PubMed: 20508533]
23. Monti JM et al. (2012) Aerobic fitness enhances relational memory in preadolescent children: the FITKids randomized control trial. *Hippocampus* 22 (9), 1876–82. [PubMed: 22522428]
24. Schwarb H et al. (2017) Aerobic fitness, hippocampal viscoelasticity, and relational memory performance. *Neuroimage* 153, 179–188. [PubMed: 28366763]
25. Stillman CM et al. (2018) Cardiorespiratory fitness is associated with enhanced hippocampal functional connectivity in healthy young adults. *Hippocampus* 28 (3), 239–247. [PubMed: 29341303]
26. Stillman CM et al. (2016) Physical Activity Is Associated with Reduced Implicit Learning but Enhanced Relational Memory and Executive Functioning in Young Adults. *PLoS One* 11 (9), e0162100. [PubMed: 27584059]
27. Déry N et al. (2013) Adult hippocampal neurogenesis reduces memory interference in humans: opposing effects of aerobic exercise and depression. *Front Neurosci* 7, 66. [PubMed: 23641193]

28. Herting M and Nagel B (2012) Aerobic fitness relates to learning on a virtual Morris Water Task and hippocampal volume in adolescents. *Behav Brain Res* 233 (2), 517–25. [PubMed: 22610054]
29. Amaral DG and Witter MP (1989) The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience* 31 (3), 571–91. [PubMed: 2687721]
30. Yassa MA and Stark CE (2011) Pattern separation in the hippocampus. *Trends Neurosci* 34 (10), 515–25. [PubMed: 21788086]
31. Kesner RP (2007) A behavioral analysis of dentate gyrus function. *Prog Brain Res* 163, 567–76. [PubMed: 17765738]
32. Gilbert PE et al. (2001) Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. *Hippocampus* 11 (6), 626–36. [PubMed: 11811656]
33. Hunsaker MR and Kesner RP (2008) Evaluating the differential roles of the dorsal dentate gyrus, dorsal CA3, and dorsal CA1 during a temporal ordering for spatial locations task. *Hippocampus* 18 (9), 955–64. [PubMed: 18493930]
34. Ahn JR and Lee I (2014) Intact CA3 in the hippocampus is only sufficient for contextual behavior based on well-learned and unaltered visual background. *Hippocampus* 24 (9), 1081–93. [PubMed: 24753165]
35. Lacy JW et al. (2010) Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity. *Learn Mem* 18 (1), 15–8. [PubMed: 21164173]
36. Yassa MA et al. (2011) Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus* 21 (9), 968–79. [PubMed: 20865732]
37. Bakker A et al. (2008) Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science* 319 (5870), 1640–2. [PubMed: 18356518]
38. Bernstein EE and McNally RJ (2018) Examining the effects of exercise on pattern separation and the moderating effects of mood symptoms. *Behavior Therapy*.
39. Suwabe K et al. (2017) Aerobic fitness associates with mnemonic discrimination as a mediator of physical activity effects: evidence for memory flexibility in young adults. *Sci Rep* 7 (1), 5140. [PubMed: 28698596]
40. Whiteman AS et al. (2014) Interaction between serum BDNF and aerobic fitness predicts recognition memory in healthy young adults. *Behav Brain Res* 259, 302–12. [PubMed: 24269495]
41. Suwabe K et al. (2018) Rapid stimulation of human dentate gyrus function with acute mild exercise. *Proc Natl Acad Sci U S A* 115 (41), 10487–10492. [PubMed: 30249651]
42. Whiteman AS et al. (2016) Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: A voxel-based morphometry study. *Neuroimage* 126, 229–38. [PubMed: 26631814]
43. Sorrells SF et al. (2018) Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature* 555 (7696), 377–381. [PubMed: 29513649]
44. Boldrini M et al. (2018) Human Hippocampal Neurogenesis Persists throughout Aging. *Cell Stem Cell* 22 (4), 589–599 e5. [PubMed: 29625071]
45. Clelland CD et al. (2009) A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science* 325 (5937), 210–3. [PubMed: 19590004]
46. Niibori Y et al. (2012) Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. *Nat Commun* 3, 1253. [PubMed: 23212382]
47. Nakashiba T et al. (2012) Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* 149 (1), 188–201. [PubMed: 22365813]
48. Vivar C et al. (2012) Monosynaptic inputs to new neurons in the dentate gyrus. *Nat Commun* 3, 1107. [PubMed: 23033083]
49. Vivar C and van Praag H (2017) Running Changes the Brain: the Long and the Short of It. *Physiology (Bethesda)* 32 (6), 410–424. [PubMed: 29021361]
50. Sah N et al. (2017) Running reorganizes the circuitry of one-week-old adult-born hippocampal neurons. *Sci Rep* 7 (1), 10903. [PubMed: 28883658]
51. Zhao C et al. (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J Neurosci* 26 (1), 3–11. [PubMed: 16399667]

52. Trinchero MF et al. (2017) High Plasticity of New Granule Cells in the Aging Hippocampus. *Cell Rep* 21 (5), 1129–1139. [PubMed: 29091753]
53. Creer DJ et al. (2010) Running enhances spatial pattern separation in mice. *Proc Natl Acad Sci U S A* 107 (5), 2367–72. [PubMed: 20133882]
54. Bolz L et al. (2015) Running Improves Pattern Separation during Novel Object Recognition. *Brain Plast* 1 (1), 129–141. [PubMed: 29765837]
55. Sahay A et al. (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472 (7344), 466–70. [PubMed: 21460835]
56. Lister JP and Barnes CA (2009) Neurobiological changes in the hippocampus during normative aging. *Archives of neurology* 66 (7), 829–833. [PubMed: 19597084]
57. Schmidt-Hieber C et al. (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 429, 184–187. [PubMed: 15107864]
58. Vivar C et al. (2016) Running rewires the neuronal network of adult-born dentate granule cells. *Neuroimage* 131, 29–41. [PubMed: 26589333]
59. Vanderwolf CH (1969) Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr Clin Neurophysiol* 26 (4), 407–18. [PubMed: 4183562]
60. Rendeiro C and Rhodes JS (2018) A new perspective of the hippocampus in the origin of exercise-brain interactions. *Brain Struct Funct* 223 (6), 2527–2545. [PubMed: 29671055]
61. Guerrieri D and van Praag H (2015) Exercise-mimetic AICAR transiently benefits brain function. *Oncotarget* 6 (21), 18293. [PubMed: 26286955]
62. Woods NI et al. (2018) Preferential Targeting of Lateral Entorhinal Inputs onto Newly Integrated Granule Cells. *J Neurosci* 38 (26), 5843–5853. [PubMed: 29793975]
63. Leal SL and Yassa MA (2018) Integrating new findings and examining clinical applications of pattern separation. *Nat Neurosci* 21 (2), 163–173. [PubMed: 29371654]
64. Pereira A et al. (2007) An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci U S A* 104 (13), 5638–43. [PubMed: 17374720]
65. Maass A et al. (2015) Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol Psychiatry* 20 (5), 585–93. [PubMed: 25311366]
66. Erickson K et al. (2011) Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A* 108 (7), 3017–22. [PubMed: 21282661]
67. Thomas AG et al. (2016) Multi-modal characterization of rapid anterior hippocampal volume increase associated with aerobic exercise. *NeuroImage* 131, 162–170. [PubMed: 26654786]
68. Kleemeyer MM et al. (2016) Changes in fitness are associated with changes in hippocampal microstructure and hippocampal volume among older adults. *Neuroimage* 131, 155–61. [PubMed: 26584869]
69. Rosano C et al. (2016) Hippocampal Response to a 24-Month Physical Activity Intervention in Sedentary Older Adults. *The American Journal of Geriatric Psychiatry*, 1–9.
70. Jonasson LS et al. (2016) Aerobic Exercise Intervention, Cognitive Performance, and Brain Structure: Results from the Physical Influences on Brain in Aging (PHIBRA) Study. *Front Aging Neurosci* 8, 336. [PubMed: 28149277]
71. Vidoni E et al. (2012) Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years. *Neurobiol Aging* 33 (8), 1624–32. [PubMed: 21531480]
72. ten Brinke L et al. (2015) Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. *Br J Sports Med* 49 (4), 248–54. [PubMed: 24711660]
73. Voss M et al. (2010) Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci* 2.
74. Chirles TJ et al. (2017) Exercise Training and Functional Connectivity Changes in Mild Cognitive Impairment and Healthy Elders. *J Alzheimers Dis* 57 (3), 845–856. [PubMed: 28304298]
75. Boraxbekk CJ et al. (2016) Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network-A multimodal approach. *Neuroimage* 131, 133–41. [PubMed: 26702778]

76. Voss M et al. (2016) Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *NeuroImage* 131, 113–125. [PubMed: 26493108]
77. Voss M et al. (2010) Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia* 48 (5), 1394–1406. [PubMed: 20079755]
78. Flodin P et al. (2017) Does Aerobic Exercise Influence Intrinsic Brain Activity? An Aerobic Exercise Intervention among Healthy Old Adults. *Front Aging Neurosci* 9, 267. [PubMed: 28848424]
79. Buckner R et al. (2008) The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124, 1–38. [PubMed: 18400922]
80. Buckley RF et al. (2017) Functional network integrity presages cognitive decline in preclinical Alzheimer disease. *Neurology*.
81. Wig GS (2017) Segregated Systems of Human Brain Networks. *Trends Cogn Sci* 21 (12), 981–996. [PubMed: 29100737]
82. Andrews-Hanna J et al. (2007) Disruption of large-scale brain systems in advanced aging. *Neuron* 56 (5), 924–35. [PubMed: 18054866]
83. Cotman CW and Berchtold NC (2002) Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 25 (6), 295–301. [PubMed: 12086747]
84. Sleiman SF and Chao MV (2015) Downstream Consequences of Exercise Through the Action of BDNF. *Brain Plast* 1 (1), 143–148. [PubMed: 29765838]
85. Heldt SA et al. (2007) Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Mol Psychiatry* 12 (7), 656–70. [PubMed: 17264839]
86. Neeper S et al., Exercise and brain neurotrophins, *Nature*, ENGLAND, 1995, p. 109.
87. Freitas DA et al. (2018) High intensity interval training modulates hippocampal oxidative stress, BDNF and inflammatory mediators in rats. *Physiol Behav* 184, 6–11. [PubMed: 29111230]
88. Voss M et al. (2013) Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci* 17 (10), 525–44. [PubMed: 24029446]
89. Hatchard T et al. (2014) Translating the impact of exercise on cognition: methodological issues in animal research. *Behav Brain Res* 273, 177–88. [PubMed: 25026095]
90. Vaynman S et al. (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci* 20 (10), 2580–90. [PubMed: 15548201]
91. Li Y et al. (2008) TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. *Neuron* 59 (3), 399–412. [PubMed: 18701066]
92. Klein AB et al. (2011) Blood BDNF concentrations reflect brain-tissue BDNF levels across species. *Int J Neuropsychopharmacol* 14 (3), 347–53. [PubMed: 20604989]
93. Radka SF et al. (1996) Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. *Brain Res* 709 (1), 122–301. [PubMed: 8869564]
94. Goekint M et al. (2012) Acute running stimulates hippocampal dopaminergic neurotransmission in rats, but has no influence on brain-derived neurotrophic factor. *J Appl Physiol* (1985) 112 (4), 535–41. [PubMed: 22134693]
95. Yau SY et al. (2012) Effects of voluntary running on plasma levels of neurotrophins, hippocampal cell proliferation and learning and memory in stressed rats. *Neuroscience* 222, 289–301. [PubMed: 22813995]
96. Sakita M et al. (2018) Remodeling of myelinated fibers and internal capillaries in distal peripheral nerves following aerobic exercise in aged rats. *J Appl Physiol* (1985) 125 (4), 1051–1061. [PubMed: 30024334]
97. Rasmussen P et al. (2009) Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol* 94 (10), 1062–9. [PubMed: 19666694]
98. Fujimura H et al. (2002) Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thrombosis and haemostasis* 88 (04), 728–734.

99. Szuhany KL et al. (2015) A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res* 60, 56–64. [PubMed: 25455510]
100. Ferris LT et al. (2007) The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med Sci Sports Exerc* 39 (4), 728–34. [PubMed: 17414812]
101. Griffin É et al. (2011) Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav* 104 (5), 934–41. [PubMed: 21722657]
102. Weng TB et al. (2017) The Acute Effects of Aerobic Exercise on the Functional Connectivity of Human Brain Networks. *Brain Plasticity* 2 (2), 171–190. [PubMed: 29765855]
103. Ivy AS et al. (2003) Noradrenergic and serotonergic blockade inhibits BDNF mRNA activation following exercise and antidepressant. *Pharmacology Biochemistry and Behavior* 75 (1), 81–88.
104. Soya H et al. (2007) BDNF induction with mild exercise in the rat hippocampus. *Biochem Biophys Res Commun* 358 (4), 961–7. [PubMed: 17524360]
105. Dinoff A et al. (2016) The Effect of Exercise Training on Resting Concentrations of Peripheral Brain-Derived Neurotrophic Factor (BDNF): A Meta-Analysis. *PLoS One* 11 (9), e0163037. [PubMed: 27658238]
106. Voss M et al. (2013) Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav Immun* 28, 90–9. [PubMed: 23123199]
107. Huang T et al. (2014) The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scand J Med Sci Sports* 24 (1), 1–10. [PubMed: 23600729]
108. Currie J et al. (2009) Cardio-respiratory fitness, habitual physical activity and serum brain derived neurotrophic factor (BDNF) in men and women. *Neurosci Lett* 451 (2), 152–5. [PubMed: 19133315]
109. Jung SH et al. (2011) Association among basal serum BDNF, cardiorespiratory fitness and cardiovascular disease risk factors in untrained healthy Korean men. *Eur J Appl Physiol* 111 (2), 303–11. [PubMed: 20878177]
110. Cho HC et al. (2012) The concentrations of serum, plasma and platelet BDNF are all increased by treadmill VO(2)max performance in healthy college men. *Neurosci Lett* 519 (1), 78–83. [PubMed: 22617010]
111. Naegelin Y et al. (2018) Measuring and Validating the Levels of Brain-Derived Neurotrophic Factor in Human Serum. *eNeuro* 5 (2).
112. Polacchini A et al. (2015) A method for reproducible measurements of serum BDNF: comparison of the performance of six commercial assays. *Sci Rep* 5, 17989. [PubMed: 26656852]
113. Tang K et al. (2010) Exercise-induced VEGF transcriptional activation in brain, lung and skeletal muscle. *Respir Physiol Neurobiol* 170 (1), 16–22. [PubMed: 19853064]
114. Van der Borght K et al. (2009) Physical exercise leads to rapid adaptations in hippocampal vasculature: temporal dynamics and relationship to cell proliferation and neurogenesis. *Hippocampus* 19 (10), 928–36. [PubMed: 19212941]
115. Morland C et al. (2017) Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. *Nat Commun* 8, 15557. [PubMed: 28534495]
116. Cao L et al. (2004) VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat Genet* 36 (8), 827–35. [PubMed: 15258583]
117. Carro E et al. (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J Neurosci* 20 (8), 2926–33. [PubMed: 10751445]
118. Fernandez AM et al. (2018) Insulin Peptides as Mediators of the Impact of Life Style in Alzheimer's disease. *Brain Plast* 4 (1), 3–15. [PubMed: 30564544]
119. Ding Q et al. (2006) Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience* 140 (3), 823–33. [PubMed: 16650607]
120. Trejo J et al. (2001) Circulating Insulin-Like Growth Factor I Mediates Exercise-Induced Increases in the Number of New Neurons in the Adult Hippocampus. *J Neurosci* 21 (5), 1628–1634. [PubMed: 11222653]
121. Stein AM et al. (2018) Physical exercise, IGF-1 and cognition A systematic review of experimental studies in the elderly. *Dement Neuropsychol* 12 (2), 114–122. [PubMed: 29988330]

122. Bidlingmaier M et al. (2014) Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. *J Clin Endocrinol Metab* 99 (5), 1712–21. [PubMed: 24606072]
123. Walz JM et al. (2016) Pre-Analytical Parameters Affecting Vascular Endothelial Growth Factor Measurement in Plasma: Identifying Confounders. *PLoS One* 11 (1), e0145375. [PubMed: 26730574]
124. Delezie J and Handschin C (2018) Endocrine Crosstalk Between Skeletal Muscle and the Brain. *Front Neurol* 9, 698. [PubMed: 30197620]
125. Moon HY et al. (2019) Conditioned media from AICAR-treated skeletal muscle cells increases neuronal differentiation of adult neural progenitor cells. *Neuropharmacology* 145 (Pt A), 123–130. [PubMed: 30391731]
126. Hardie DG (2011) AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. *Genes Dev* 25 (18), 1895–908. [PubMed: 21937710]
127. Wang YX et al. (2004) Regulation of muscle fiber type and running endurance by PPARdelta. *PLoS Biol* 2 (10), e294. [PubMed: 15328533]
128. Lin J et al. (2002) Transcriptional co-activator PGC-1 α drives the formation of slow-twitch muscle fibres. *Nature* 418 (6899), 797. [PubMed: 12181572]
129. Wrann C et al. (2013) Exercise induces hippocampal BDNF through a PGC-1 α /FNDC5 pathway. *Cell Metab* 18 (5), 649–59. [PubMed: 24120943]
130. Jedrychowski M et al. (2015) Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. *Cell Metab* 22 (4), 734–40. [PubMed: 26278051]
131. Lourenco MV et al. (2019) Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nature Medicine* 25 (1), 165–175.
132. Moon HY et al. (2016) Running-Induced Systemic Cathepsin B Secretion Is Associated with Memory Function. *Cell Metab* 24 (2), 332–40. [PubMed: 27345423]
133. Sleiman SF et al. (2016) Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body beta-hydroxybutyrate. *Elife* 5.
134. Basso JC and Suzuki WA (2017) The Effects of Acute Exercise on Mood, Cognition, Neurophysiology, and Neurochemical Pathways: A Review. *Brain Plast* 2 (2), 127–152. [PubMed: 29765853]
135. Roig M et al. (2013) The effects of cardiovascular exercise on human memory: a review with meta-analysis. *Neurosci Biobehav Rev* 37 (8), 1645–66. [PubMed: 23806438]
136. Holzschnieder K et al. (2012) Cardiovascular fitness modulates brain activation associated with spatial learning. *Neuroimage* 59 (3), 3003–14. [PubMed: 22027496]
137. Allison SL et al. (2016) Spatial Navigation in Preclinical Alzheimer's Disease. *JAD* 52 (1), 77–90. [PubMed: 26967209]
138. Zhao G et al. (2015) Treadmill exercise enhances synaptic plasticity, but does not alter beta-amyloid deposition in hippocampi of aged APP/PS1 transgenic mice. *Neuroscience* 298, 357–66. [PubMed: 25917310]
139. Lin TW et al. (2015) Running exercise delays neurodegeneration in amygdala and hippocampus of Alzheimer's disease (APP/PS1) transgenic mice. *Neurobiol Learn Mem* 118, 189–97. [PubMed: 25543023]
140. Tapia-Rojas C et al. (2016) Voluntary Running Attenuates Memory Loss, Decreases Neuropathological Changes and Induces Neurogenesis in a Mouse Model of Alzheimer's Disease. *Brain Pathol* 26 (1), 62–74. [PubMed: 25763997]
141. Rodriguez JJ et al. (2011) Voluntary running and environmental enrichment restores impaired hippocampal neurogenesis in a triple transgenic mouse model of Alzheimer's disease. *Curr Alzheimer Res* 8 (7), 707–17. [PubMed: 21453244]
142. Marlatt MW et al. (2013) Prolonged running, not fluoxetine treatment, increases neurogenesis, but does not alter neuropathology, in the 3xTg mouse model of Alzheimer's disease. *Curr Top Behav Neurosci* 15, 313–40. [PubMed: 23670818]
143. Oddo S et al. (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* 39 (3), 409–21. [PubMed: 12895417]

144. Choi SH et al. (2018) Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science* 361 (6406).
145. Liu HL et al. (2011) Treadmill exercise prevents decline in spatial learning and memory in APP/PS1 transgenic mice through improvement of hippocampal long-term potentiation. *Behav Brain Res* 218 (2), 308–14. [PubMed: 21192984]
146. Yuede CM et al. (2009) Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiol Dis* 35 (3), 426–32. [PubMed: 19524672]
147. Cho J et al. (2015) Treadmill Running Reverses Cognitive Declines due to Alzheimer Disease. *Med Sci Sports Exerc* 47 (9), 1814–24. [PubMed: 25574797]
148. Moore KM et al. (2016) A spectrum of exercise training reduces soluble A β in a dose-dependent manner in a mouse model of Alzheimer's disease. *Neurobiol Dis* 85, 218–224. [PubMed: 26563933]
149. Morris JK et al. (2017) Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. *PLoS One* 12 (2), e0170547. [PubMed: 28187125]
150. Baker L et al. (2010) Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 67 (1), 71–9. [PubMed: 20065132]
151. Steen Jensen C et al. (2016) Cerebrospinal Fluid Amyloid Beta and Tau Concentrations Are Not Modulated by 16 Weeks of Moderate- to High-Intensity Physical Exercise in Patients with Alzheimer Disease. *Dement Geriatr Cogn Disord* 42 (3–4), 146–158. [PubMed: 27643858]
152. Law LL et al. (2018) Moderate intensity physical activity associates with CSF biomarkers in a cohort at risk for Alzheimer's disease. *Alzheimers Dement (Amst)* 10, 188–195. [PubMed: 29527551]
153. Okonkwo OC (2014) Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology*.
154. Head D et al. (2012) Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition. *Arch Neurol* 69 (5), 636–43. [PubMed: 22232206]
155. Barha CK et al. (2017) Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. *Front Neuroendocrinol* 46, 71–85. [PubMed: 28442274]
156. Nagamatsu L et al. (2012) Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Arch Intern Med* 172 (8), 666–8. [PubMed: 22529236]
157. Cassilhas RC et al. (2012) Spatial memory is improved by aerobic and resistance exercise through divergent molecular mechanisms. *Neuroscience* 202, 309–17. [PubMed: 22155655]
158. Cassilhas RC et al. (2007) The impact of resistance exercise on the cognitive function of the elderly. (0195–9131 (Print)).
159. Sanai N et al. (2011) Corridors of migrating neurons in the human brain and their decline during infancy. *Nature* 478 (7369), 382–6. [PubMed: 21964341]
160. Wilson DA (2009) Pattern separation and completion in olfaction. *Ann N Y Acad Sci* 1170, 306–12. [PubMed: 19686152]
161. Rendeiro C and Rhodes JS (2018) A new perspective of the hippocampus in the origin of exercise-brain interactions. *Brain Struct Funct*.
162. Watson P et al. (2013) Spatial reconstruction by patients with hippocampal damage is dominated by relational memory errors. *Hippocampus* 23 (7), 570–80. [PubMed: 23418096]
163. Suwabe K et al. (2018) Rapid stimulation of human dentate gyrus function with acute mild exercise. *Proc Natl Acad Sci U S A*.
164. Bernstein EE and McNally RJ (2018) Exploring behavioral pattern separation and risk for emotional disorders. *J Anxiety Disord* 59, 27–33. [PubMed: 30170239]
165. Suzuki T et al. (2013) A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One* 8 (4), e61483. [PubMed: 23585901]

Highlights

- A sedentary lifestyle increases the risk of memory deterioration and Alzheimer's disease. Unfortunately, there is no treatment for memory decline. However, animal studies indicate physical activity benefits hippocampus-dependent memory through biological mechanisms likely conserved in humans.
- Translating the promise for physical activity to human memory improvement or maintenance has been challenging and the best modes of activity and cognitive outcomes remain unclear.
- We propose a cross-species approach to bring insight to sensitive hippocampal memory tasks and a mechanistic foundation for physical activity-induced memory improvement in the long run.

Outstanding Questions

- What experimental cognitive tasks are most sensitive to early dysfunction in hippocampal circuits?
- What signaling pathways increase central BDNF expression from PA, and can they be non-invasively and reliably measured in humans?
- Are there additional critical signaling pathways mediating or moderating effects of PA on hippocampal-dependent memory, such as stress response pathways including the hypothalamic-pituitary-adrenal axis and the sympatho-adrenal axis? How are they modified by PA dose (intensity, duration, etc), sex, age, medications, pathology?
- How can non-invasive imaging outcomes be added to animal studies to link changes in biological substrates to testable forms in humans?
- What experimental designs can examine more directly whether, for who, and how PA changes the trajectory of memory decline? For instance, a prospective design could identify “decliners” to enrich a training study, and high-density measurement at training onset and offset could clarify the time-course and durability of PA-dependent changes in hippocampal and memory outcomes.
- Will it be possible to harness peripheral factors as therapeutic interventions for aged or frail individuals who cannot exercise?

Box 1: PA effects on spatial memory and wayfinding

In rodents, PA improves hippocampus-dependent spatial memory in paradigms including the Morris water maze, the Y-maze, and the radial arm maze [89]. These maze tasks test a type of spatial navigation called wayfinding, which is based on coding your position in space and relative to landmarks to build a mental map for finding your way in space. PA also promotes performance in spatial memory tasks with low motor demand, such as contextual fear conditioning and spatial pattern separation [see review 88]. It would be important to see this translate to aging humans because one of the first signs of AD related cognitive decline is difficulty with navigation via wayfinding. However, few studies have examined PA or fitness benefits on wayfinding in older adults. One RCT examined a more general form of spatial working memory as an outcome with older adults. This trial found that aerobic exercise led to 2% increases in hippocampal volume, which were associated with greater gains in fitness and improvements in memory performance [66]. Similar to relational memory, promising trends have been reported for navigation processes in younger age groups. A study with middle-age adults showed preliminary evidence that fitness may enhance activation in regions important for wayfinding during spatial learning in a virtual maze, though these benefits were not seen in performance [136]. Another study, with adolescent males, showed that greater fitness was related to faster learning, but not recall of objects in a virtual environment [28]. With respect to mechanisms, the difference in learning versus recall may be a clue to early disease processes that would be good to target with PA. A study with older adults presenting a preclinical AD biomarker profile (e.g., cerebrospinal fluid A β 42 levels below 500 pg/ml) but without other cognitive symptoms, showed this group was slower to acquire new memories during wayfinding, but showed preserved recall and recognition [137]. This suggests some components of spatial navigation may be more sensitive than others to early effects of pathology on spatial memory. Further, more studies across species could examine the slope and shape of learning curves as common metrics for reporting PA effects on learning and memory with more contact to computational and process models for learning mechanisms.

Box 2. PA effects on Alzheimer's disease pathology

Mice and rats do not naturally develop hallmark AD pathologies of amyloid plaques and tau neurofibrillary tangles. Most animal models express familial AD genes that lead to build-up of amyloid and tau proteins in young adulthood. PA can counteract these processes and enhance neural plasticity in many of the mouse models. For instance, in APP^{swe}/PS1^{dE9} mice, PA increases synaptic plasticity [138], dendritic arborization [139], cell proliferation and neuronal differentiation [140]. PA also increased cell proliferation [141] and cell survival [142] in triple transgenic (3xTg) mice with both amyloid and tau [143]. Recently, it was also shown that in 5xTG AD mice running for three hours per day for four months increased neurogenesis and BDNF levels, and prevented age-related decline in mnemonic discrimination [144]. Other PA benefits on cognition have been reported across AD mouse models and behavioral assays, including spatial learning and memory [145], contextual memory [139], novel object [131] and recognition memory [146]. Studies suggest PA reduces A β and tau hyper-phosphorylation [140, 147], with high intensity running potentially having the most impact on reducing pathology via increased clearance [148]. Data from humans also suggest PA interacts with processes leading to pathology aggregation such as clearance or perhaps resilience to its presence. In humans, pathology is measured *in vivo* with positron emission tomography (PET) using tracers binding to amyloid or tau. No training studies have reported on amyloid or tau brain imaging outcomes. However, one intervention found greater fitness improvements in AD patients were related to increased hippocampal volume and episodic memory [149]. Without PET, proxy biomarkers of brain pathology can be measured from cerebrospinal fluid (CSF). Two small training studies failed to show changes in CSF A β (A β ₄₂) with either amnesic impairment [150] or early AD [151]. In contrast, cross-sectional studies report favorable relations between sensor-based PA and CSF A β ₄₂ [152]. Greater PA is also associated with lower risk of amyloid in the default network (PET PiB) associated with aging [153] or APOE ϵ 4 [154]. Thus, evidence supports PA benefits during periods of amyloid and tau cortical spreading. However, important questions remain about the extent to which PA at this stage is affecting clearance rather than mitigating its source. Just as valuable are preserved benefits on BDNF, neurogenesis, and morphology, as these could be mechanisms for promoting cognitive resilience even without pathology reversal per se.

Box 3: Can lifting weights also improve hippocampal memory?

The recommendation to “be more active” has broad appeal practically. However, different types of PA may be more effective than others or work through complementary mechanisms informing therapeutic strategies. To begin answering these questions, RCTs have examined effects of resistance training and also multi-modal training that combine elements of aerobic, resistance, and flexibility or balance exercise. Instead of individualized heart rate training zones used for aerobic training, resistance training (RT) interventions determine resistance intensity referenced to the most you can lift a single time as a “1 repetition maximum” (e.g. for each of 6 exercises, 2 sets of 8 repetitions at 50% to 80% repetition maximum). A recent meta-analysis reported that, similar to aerobic training, RT does not improve episodic memory assessed with neuropsychological tests [155]. Some data hint resistance training could improve relational memory task performance in a female mild cognitive impairment population, when aerobic exercise would not [156]. However, the same study found maintained hippocampal volume after aerobic but not RT [12]. Overall, the evidence suggests aerobic and RT affect cognition via different pathways, as RT interventions also do not increase resting serum BDNF [105]. Supportive of complementary benefits, the meta-analysis found multi-modal training may be more effective for episodic memory (4 studies, $g=0.48$) than aerobic (7 studies, $g=0.05$) or RT (4 studies, $g=0.07$). Rodent models provide key insight to comparing pathways detectable with biomarkers. Using the ladder climbing model as RT, and treadmill training as aerobic exercise in rodents, 8 weeks of both types of training improved spatial learning and memory [157]. Whereas both types of PA increased the levels of proteins associated with synaptic plasticity (synapsin 1 and synaptophysin) [157], improved memory correlated with activation of distinct signaling pathways, suggesting aerobic and RT elicit distinct molecular mechanisms to improve memory processes. Treadmill training showed increased IGF-1, BDNF, TrkB, and calcium/calmodulin-dependent kinase II (β -CaMKII) in the hippocampus, whereas resistance training increased IGF-1 levels peripherally and in the hippocampus, as well as activation of its receptor signaling pathway (Akt protein) in the hippocampus. The peripheral IGF-1 increment after RT in this study is in agreement with a study in humans, where 24 weeks of RT increased peripheral IGF-1 levels [158]. Across animal and human studies, while direct comparisons are limited, evidence suggests RT could boost- but not replace- effects of aerobic exercise on memory.

Figure 1, Key Figure: Human PA and fitness affect hippocampal memories and networks

(A) Bar graph shows the proportion of statistically significant effects in favor of improved memory for aerobic compared to control groups in training studies with older adults. Ratios indicate absolute number of positive effects relative to all studies. See SI IV-V for more information. (B) In non-spatial relational tasks, letters symbolize items, which could take the form of words, faces, scenes, etc. Participants are tested for memory of relations compared to recombined or novel pairs. The spatial relational reconstruction task requires retrieval of object-location pairs and inter-relations. A signature error involves swapping item identity with correct locations [162]. Mnemonic discrimination tasks test memory precision. Participants incidentally encode objects and are tested on memory for repeats (targets), similar objects (lures), or new objects (foils) [39, 163, 164]. (C) Association networks modified by aging and PA. Network links and bar graphs are colored according to network. Links show connections within each network. Only the default network includes aspects of the hippocampal and medial temporal lobe memory system, as approximated in the oval inset. The figure to the right of the inset illustrates a different view of the relative positioning of medial temporal lobe structures (ph, parahippocampus; erc, entorhinal cortex; prc, perirhinal cortex). The dentate gyrus and CA sub-regions are coiled together along the long

axis of the hippocampus. Young>Old functional connectome indicates the links that were stronger for young adults [76], and the bar graph shows the percentage of links within each network in favor of young adults. The functional connectome below shows links that were stronger with greater fitness, and the bar graph shows the percentage of links within each network having a positive association with fitness. Of all the networks with connections that are weaker for older adults, the hippocampal-cortical default network had the greatest percentage (15.38%) that were stronger with greater fitness [76].

Figure 2: Effects of PA on hippocampal circuits and pattern separation in mice.

In mice voluntary wheel running increases the number of new hippocampal neurons and modifies their network. (A) Using viral vectors to trace the structures that project directly to adult-born neurons it was observed that running enhances entorhinal cortex innervation of adult-born dentate granule cells [58]. Control and running afferent circuitry are depicted in a 3D reconstruction of photomicrographs taken throughout the dorso-ventral extent of hippocampal-entorhinal cortex slices derived from young adult male mice. In control conditions, afferent traced cells (labeled with rabies virus expressing MCherry, red) that project directly to new neurons, are observed in the lateral entorhinal cortex (LEC) and perirhinal cortex (PRC), and only sparsely in the caudomedial entorhinal cortex (CEnt). Exercise increases the input from the CEnt and LEC onto the adult-born granule cells. Nuclei are stained with 4',6-diamidino-2-phenylindole (DAPI), blue [58]. (B) LEC input to

new neurons is important for pattern separation. **(B, C)** Mice are trained in the touchscreen to distinguish between two identical stimuli spaced apart (big) closely together (small) to evaluate pattern separation. The ability to differentiate which icon is associated with reward in the more challenging, small separation condition, is **(B)** reduced following LEC lesion [48], and **(C)** enhanced by running [53]. **(D)** Model showing the relative contribution of the regions that directly innervate adult-born granule cells under control and exercise conditions [58].

Table 1.
Comparison of aerobic exercise training paradigms across species, animal models (yellow) and human (blue).

Note ↑ and ↓ indicate an increase and a decrease of each factor, respectively, induced by PA. Most of the studies include hippocampal structures, and observed PA effects on cognitive function and biological markers. Abbreviations: AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; A β , Amyloid- β oligomers; BDNF, Brain-derived neurotrophic factor; CA1, Cornu ammonis 1; CA3, Cornu ammonis 3; CBV, Cerebral blood volume; CSF, Cerebrospinal fluid; CTSB, Cathepsin B; DG, Dentate gyrus; ERR α , Estrogen-related receptor alpha; fEPSP, Field excitatory postsynaptic potential; FNDC5, Fibronectin type III domain-containing protein 5; HRR, Heart rate reserve; IGF-I, Insulin-like growth factor-I; LBD, Lewy body dementia; MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination; MWM, Morris water maze; PGC-1 α , Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; VO2 max, Maximal oxygen consumption.

	SUBJECTS	CONTROL	EXERCISE REGIMEN	REGION EVALUATED	FINDINGS	REF
CROSS-SPECIES REPORTS	<ul style="list-style-type: none">• Male PGC-1α null mice• 5, 6 and 13 weeks old	<ul style="list-style-type: none">• Housed without wheels• 30 days	<ul style="list-style-type: none">• Voluntary wheel running• 30 days	<ul style="list-style-type: none">• Hippocampus	<ul style="list-style-type: none">• FNDC5 regulates BDNF• $\uparrow$ FNDC5 through increase of PGC-1α, ERRα	129
	<ul style="list-style-type: none">• Male young adults• 25-30 years old	<ul style="list-style-type: none">• No exercise• 12 weeks• n=4	<ul style="list-style-type: none">• Cycle ergometer• 12 weeks, 3 days/week, 4 times $\times$ 4 min/day• >90% peak aerobic capacity• Treadmill walking• 12 weeks, 2 days/Week, 45 min/session• 70% peak aerobic capacity• n=6	<ul style="list-style-type: none">• Plasma	<ul style="list-style-type: none">• $\uparrow$ Irisin in plasma	130
	<ul style="list-style-type: none">• Male C57BL/6 mice, Swiss mice and AD mouse model (APP/PS1 E9)• 2.5-3 months old	<ul style="list-style-type: none">• No exercise• 5 weeks• n=100	<ul style="list-style-type: none">• Swimming• 5 weeks, 5 days/week, 1 hour/day• n=101	<ul style="list-style-type: none">• Hippocampus	<ul style="list-style-type: none">• $\uparrow$ Novel object recognition• $\uparrow$ Contextual fear conditioning• $\uparrow$ Synaptic plasticity (fEPSP)• $\uparrow$ Hippocampal FNDC5 mRNA, FNDC5/irisin and BDNF	131
	<ul style="list-style-type: none">• Ex vivo cortical slices (n=5)• 16-66 years old (60% female)	<ul style="list-style-type: none">• n=11	<ul style="list-style-type: none">• N/A	<ul style="list-style-type: none">• Hippocampus• Cortex• CSF	<ul style="list-style-type: none">• $\downarrow$ Hippocampal irisin (protein) in late AD• $\downarrow$ Irisin CSF in AD and LBD• $\downarrow$ FNDC5 mRNA and FNDC5/i irisin by Aβ• Recombinant irisin stimulate cAMP-PKA-CREB pathway	
	<ul style="list-style-type: none">• Postmortem brain tissue• 68-100 years old (>50% female)• Control• Early AD (n=7)• Late AD (n=7)					

	SUBJECTS	CONTROL	EXERCISE REGIMEN	REGION EVALUATED	FINDINGS	REF
	<ul style="list-style-type: none"> Male C57BL/6 mice 4 weeks old 	<ul style="list-style-type: none"> Sedentary 4 weeks n=32 	<ul style="list-style-type: none"> Voluntary wheel running 4 weeks n=32 	<ul style="list-style-type: none"> Dentate gyrus Frontal cortex Plasma 	<ul style="list-style-type: none"> ↑ Muscle CTSB (mRNA and protein) ↑ Plasma CTSB ↑ Hippocampal CTSB (mRNA) ↑ Behavioral performance in MWM (probe) 	132
	<ul style="list-style-type: none"> Young adults 19-34 years old (56% female) 	<ul style="list-style-type: none"> Treadmill walking 16 weeks, 2 sessions/week, 10-25 m in/session 50% maximum heart rate n=23 	<ul style="list-style-type: none"> Treadmill running 16 weeks, 3 sessions/week, 45-75 min/session 70-90% maximum heart rate n=20 	<ul style="list-style-type: none"> Hippocampus Plasma 	<ul style="list-style-type: none"> ↑ CTSB plasma Positive correlation between CTSB level and late complex-object recall score 	
	<ul style="list-style-type: none"> Male C57BL/6 mice 7 weeks old 	<ul style="list-style-type: none"> Sedentary 2 weeks n=23 	<ul style="list-style-type: none"> Voluntary wheel running 2 weeks n=23 	<ul style="list-style-type: none"> Entorhinal cortex Dentate gyrus CA1 CA3 	<ul style="list-style-type: none"> ↑ DG CBV Correlation between DG CBV and neurogenesis 	64
	<ul style="list-style-type: none"> Young adults 21-45 years old (82% female) 	<ul style="list-style-type: none"> Within-subject design 	<ul style="list-style-type: none"> Aerobic training 12 weeks, 4 sessions/week, 40 min/session n=11 	<ul style="list-style-type: none"> Entorhinal cortex Dentate gyrus CA1 Subiculum 	<ul style="list-style-type: none"> ↑ DG CBV Correlation between DG CBV and VO2 max, and cognition ↑ 1st-trial learning of new declarative memories 	
SEPARATE REPORTS IN HUMAN	<ul style="list-style-type: none"> Older adults with MCI (49% female) 65-95 years old 	<ul style="list-style-type: none"> Attending 2 education classes about health promotion 6 months n=25 amnesic MCI n=25 MCI 	<ul style="list-style-type: none"> Multicomponent exercise (Aerobic exercise, muscle strength training, postural balance retraining, dual-task training) 6 months, 2 days/week, 90 min/day 60% maximum heart rate n=25 amnesic MCI n=25 MCI 	<ul style="list-style-type: none"> Medial temporal lobe including entorhinal cortex Whole brain cortical atrophy 	<ul style="list-style-type: none"> ↑ Group × time interaction in MMSE and logical memory I in aMCI group ↓ Whole brain cortical atrophy Association between low total cholesterol levels before the intervention and an improvement of logical memory I Significant relationship between a higher level of BDNF and improved ADAS-cog performance 	165
	<ul style="list-style-type: none"> Older adults (62% female) 55-80 years old 	<ul style="list-style-type: none"> Stretching and toning 48 weeks, 3 sessions/week, 40 min/session n=60 	<ul style="list-style-type: none"> Walking on indoor track 48 weeks, 3 sessions/week, 40 min/session 50-75% HRR n=60 	<ul style="list-style-type: none"> Hippocampus Caudate nucleus Thalamus 	<ul style="list-style-type: none"> ↑ Anterior hippocampal volume Correlation between increased VO2 max and an increase of hippocampal volume Relationship between changes in BDNF and in hippocampal volume 	66