

## Review

# Exercise and Hippocampal Memory Systems

Michelle W. Voss,<sup>1,\*</sup> Carmen Soto,<sup>2</sup> Seungwoo Yoo,<sup>3</sup> Matthew Sodoma,<sup>1</sup> Carmen Vivar,<sup>2</sup> and Henriette van Praag<sup>3</sup>

**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.**

## 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 aerobic **physical activity (PA)**; see [Glossary](#), and its wide accessibility at any age, 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 toward 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-up 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

## Highlights

A sedentary lifestyle increases the risk of memory deterioration and Alzheimer's disease. Unfortunately, there is no treatment for memory decline. However, PA benefits rodent hippocampus-dependent memory through cellular mechanisms likely conserved in humans.

Translating the promise of PA 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 PA-induced memory improvement.

<sup>1</sup>Department of Psychological and Brain Sciences, University of Iowa, Iowa City, IA, USA

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

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

\*Correspondence:  
[michelle-voss@uiowa.edu](mailto:michelle-voss@uiowa.edu) (M.W. Voss).

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.

### 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 [12]. This means aerobic training intensity could not be optimally personalized to starting fitness levels, and makes it 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 supplemental information I–III online 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, 11 meta-analyses of RCTs with primarily older adults used nine unique terms for overlapping memory constructs (e.g., memory, short-term memory, and verbal memory immediate; see supplemental information IV online). 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 [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 preadolescents [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. 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 trisynaptic hippocampal circuit [29]. The dentate gyrus

### Glossary

**Adult neurogenesis:** the adult brain contains two regions that can generate new 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 [136], while the time-course of hippocampal neurogenesis remains under investigation [43,44].

**Blood oxygen level-dependent (BOLD) signal:** 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 s after neuronal activity onset.

**Brain-derived neurotrophic factor (BDNF):** 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:** 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

processes spatial and 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 ambiguous 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 area 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 area CA3 and dentate gyrus. Activity spanning both regions may reflect projections of pattern separated information from the dentate gyrus to area 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 findings. Studies using a cross-sectional design, also suggest greater PA [38] and higher fitness [39] correlate with better discrimination. Furthermore, 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, in association with changes in functional connectivity during the test phase between hippocampal (dentate gyrus/area CA3) and cortical regions involved in recall. These findings suggest 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 in adult mammals, 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 area 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 lesions 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).

rapidly and obligatorily binding elements of experience across dimensions of space and time and their interactions.

**Pattern completion:** 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 that allows accurate generalization in the presence of noise or complexity of external environments [30,137].

**Pattern separation:** 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 (Figures 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:** slow rhythmic oscillatory activity (4–8 Hz frequency) of the local field potential primarily found in the hippocampal structure. It is associated with voluntary movement, spatial navigation, and memory processes (by coordinating neuronal ensembles within the medial temporal lobe) in animals and humans (for review, see [60]).

Table 1. Comparison of aerobic exercise training paradigms across species.

SUBJECTS	CONTROL	EXERCISE REGIMEN	REGION EVALUATED	FINDINGS	REF
· Male PGC-1α null mice · 5, 6 and 13 weeks old	· Housed without wheels · 30 days	· Voluntary wheel running · 30 days	· Hippocampus	· FNDC5 regulates BDNF · ↑ FNDC5 through increase of PGC-1α, ERRα	129
· Male young adults · 25-30 years old	· No exercise · 12 weeks · n=4	· Cycle ergometer 12 weeks, 3 days/week, 4 times × 4 min/day >90% peak aerobic capacity · Treadmill walking 12 weeks, 2 days/week, 45 min/session 70% peak aerobic capacity · n=6	· Plasma	· ↑ Irisin in plasma	130
· Male C57BL/6 mice, Swiss mice and AD mouse model (APP/PS1 ΔE9) · 2.5-3 months old	· No exercise · 5 weeks · n=100	· Swimming · 5 weeks, 5 days/week, 1 hour/day · n=101	· Hippocampus	· ↑ Novel object recognition · ↑ Contextual fear conditioning · ↑ Synaptic plasticity (fEPSP) · ↑ Hippocampal FNDC5 mRNA, FNDC5/irisin and BDNF	131
· Ex vivo cortical slices (n=5) · 16-66 years old (60% female) · Postmortem brain tissue · 68-100 years old (>50% female) Control (n=11), Early AD (n=7), Late AD (n=7)	· n=11	· N/A	· Hippocampus · Cortex · CSF	· ↓ Hippocampal irisin (protein) in late AD · ↓ Irisin CSF in AD and LBD · ↓ FNDC5 mRNA and FNDC5/irisin by Aβ0 · Recombinant irisin stimulate cAMP-PKA-CREB pathway	
· Male C57BL/6 mice · 4 weeks old	· Sedentary · 4 weeks · n=32	· Voluntary wheel running · 4 weeks · n=32	· Dentate gyrus · Frontal cortex · Plasma	· ↑ Muscle CTSB (mRNA and protein) · ↑ Plasma CTSB · ↑ Hippocampal CTSB (mRNA) · ↑ Behavioral performance in MWM (probe)	132
· Young adults · 19-34 years old (56% female)	· Treadmill walking · 16 weeks, 2 sessions/week, 10-25 min/session · 50% maximum heart rate · n=23	· Treadmill running · 16 weeks, 3 sessions/week, 45-75 min/session · 70-90% maximum heart rate · n=20	· Hippocampus · Plasma	· ↑ CTSB plasma · Positive correlation between CTSB level and late complex-object recall score	
· Male C57BL/6 mice · 7 weeks old	· Sedentary · 2 weeks · n=23	· Voluntary wheel running · 2 weeks · n=23	· Entorhinal cortex · Dentate gyrus · CA1 · CA3	· ↑ DG CBV · Correlation between DG CBV and neurogenesis	64
· Young adults · 21-45 years old (82% female)	· Within-subject design	· Aerobic training · 12 weeks, 4 sessions/week, 40 min/session · n=11	· Entorhinal cortex · Dentate gyrus · CA1 · Subiculum	· ↑ DG CBV · Correlation between DG CBV and VO2 max, and cognition · ↑ 1st-trial learning of new declarative memories	
· Older adults with MCI (49% female) · 65-95 years old	· Attending 2 education classes about health promotion · 6 months · n=25 amnestic MCI · n=25 MCI	· 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 amnestic MCI · n=25 MCI	· Medial temporal lobe including entorhinal cortex · Whole brain cortical atrophy	· ↑ Group x 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	163
· Older adults (62% female) · 55-80 years old	· Stretching and toning · 48 weeks, 3 sessions/week, 40 min/session · n=60	· Walking on indoor track · 48 weeks, 3 sessions/week, 40 min/session · 50-75% HRR · n=60	· Hippocampus · Caudate nucleus · Thalamus	· ↑ Anterior hippocampal volume · Correlation between increased VO2 max and an increase of hippocampal volume · Relationship between changes in BDNF and in hippocampal volume	66

Comparison of aerobic exercise training paradigms across species, animal models (yellow), human (light blue) and human only (dark 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; Aβ0, 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; ERRα, 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-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; VO2 max, Maximal oxygen consumption.

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 [52] mice. 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.

**Box 1. PA Effects on Spatial Memory and Wayfinding**

In rodents, PA improves hippocampus-dependent spatial memory in paradigms including the Morris water maze, Y maze, and 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. [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 [140]. 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 $\beta$ 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 [141]. This suggests some components of spatial navigation may be more sensitive than others to early effects of pathology on spatial memory. More studies across species could examine the slope and shape of learning curves as common metrics for reporting PA effects on learning and memory.

**PA Influences Hippocampal Memory by Rewiring Neuronal Networks**

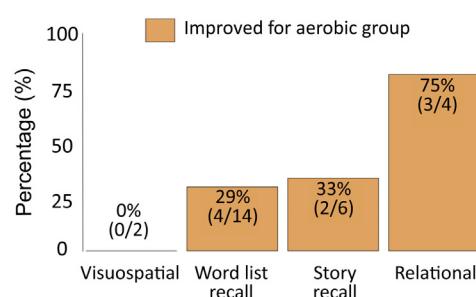
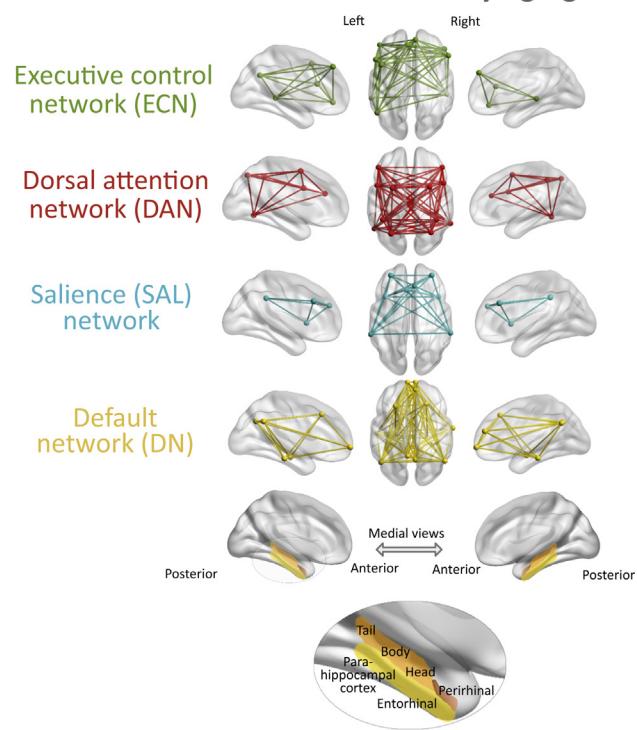
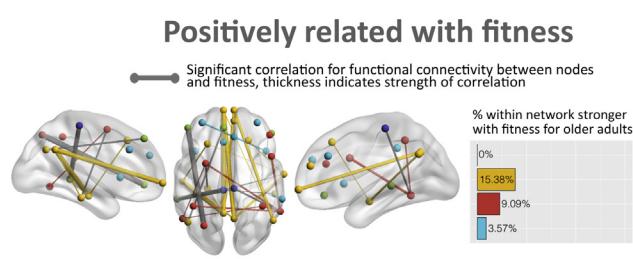
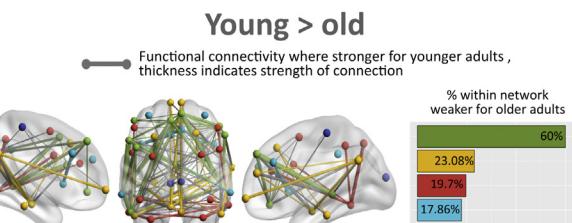
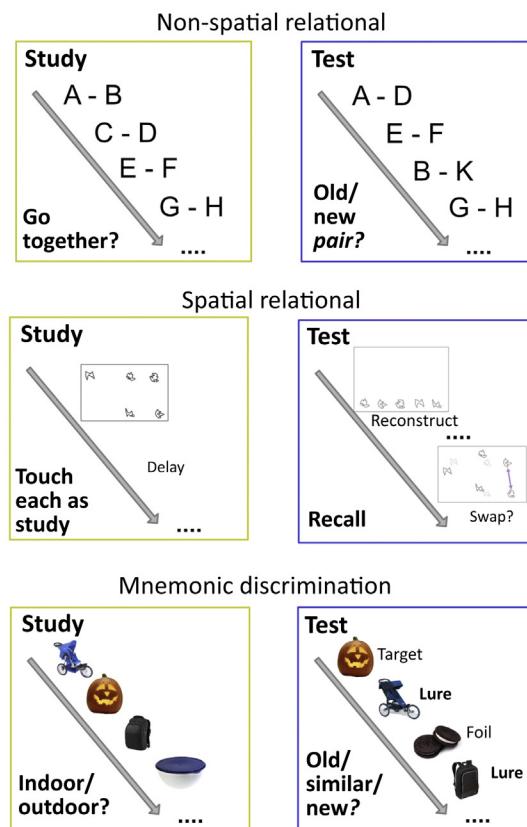
From a functional perspective, increased dentate gyrus neuron production brings several benefits. It may contribute to maintenance of spine and synapse density, and help prevent hippocampal shrinkage in healthy aging [56]. In addition, although adult-born granule cells account for a small percentage 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 noninvasive 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 40 older adults [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

**Key Figure**

Human PA and Fitness Affect Hippocampal Memories and Networks.

**(A) Memory outcomes after training****(C) Association networks affected by aging****(B) Sensitive memory outcomes across age groups and designs**

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 preadolescents [21], adolescents [28], college-age adults [25], cognitively unimpaired older adults (Table 1) [66,68–70], and 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.

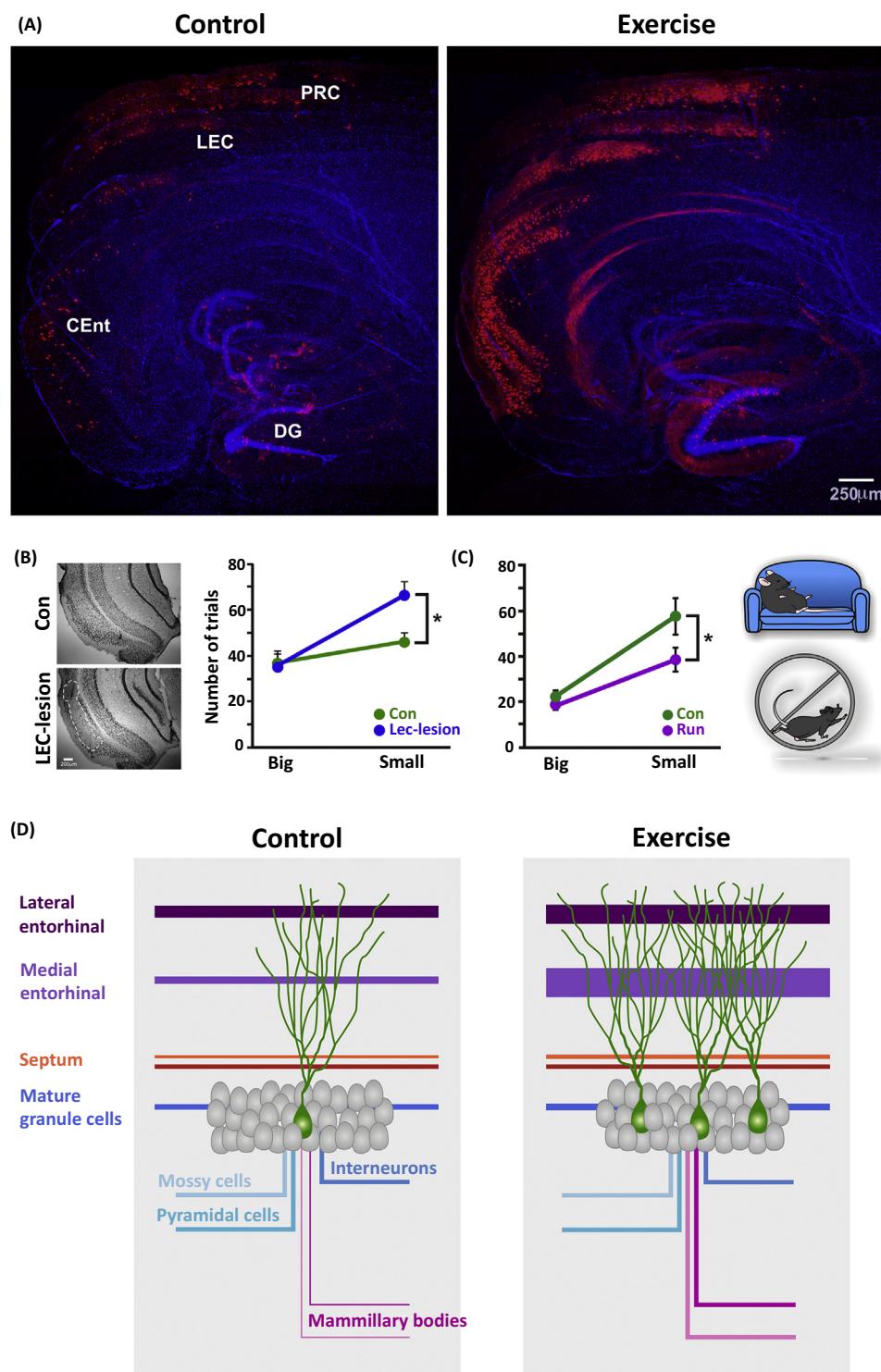
In addition to regional structural growth and metabolic support, studies using neuroimaging with humans have also shown that moderate intensity PA [73–75] and fitness [25,76–78] strengthen functional connectivity of a hippocampal–cortical brain network known as the **default network** (Figure 1C). Functional 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 time series. 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 its functional connectivity can predict later cognitive impairment [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

---

**Figure 1.** (A) Bar graph shows the proportion of statistically significant effects in favor of improved memory for aerobic activity groups compared to control groups in training studies with older adults. Ratios indicate absolute number of positive effects relative to all studies. See supplemental information IV and V online for more information. (B) In nonspatial 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 [138]. 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) [39,41,139]. (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. The dentate gyrus and CA subregions 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 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]. Abbreviations: PA, physical activity.

---



Trends in Cognitive Sciences

**Figure 2. Effects of PA on Entorhinal-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 (Figure legend continued on the bottom of the next page.)

**Box 2. PA Effects on AD 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 APPswe/PS1dE9 mice, PA increases synaptic plasticity [142], dendritic arborization [143], cell proliferation, and neuronal differentiation [144]. PA also increases cell proliferation [145] and cell survival [146] in triple transgenic (3xTg) mice with both amyloid and tau [147]. Recently, it was also shown in 5xTG AD mice that running for 3 h per day for 4 months increased neurogenesis and BDNF levels, and prevented age-related decline in mnemonic discrimination [148]. Other PA benefits on cognition have been reported across AD mouse models and behavioral assays, including spatial learning and memory [149], contextual memory [143], novel object recognition [131], and recognition memory [150]. Studies suggest PA reduces A $\beta$  and tau hyperphosphorylation [144,151], with high intensity running potentially having the most impact on reducing pathology via increased clearance [152]. 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 [153]. 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 $\beta$  (A $\beta$ <sub>42</sub>) with either amnestic impairment [154] or early AD [155]. In contrast, cross-sectional studies report favorable relations between sensor-based PA and CSF A $\beta$ <sub>42</sub> [156]. Greater PA is also associated with lower risk of amyloid in the default network (PET PIB) associated with aging [157] or APOE4 [158]. 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.

[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

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 dorsoventral 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 LEC and PRC, and only sparsely in the 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, 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 dentate granule cells (green) under control and exercise conditions [58]. Abbreviations: CEnt, caudomedial entorhinal cortex; Con, control; Run, runner; DG, dentate gyrus; LEC, lateral entorhinal cortex; Lec-lesion, lateral entorhinal cortex lesion; PRC, perirhinal cortex.

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 or chronic running in adult rats [94,95] or a decrease with exercise in aged [96] subjects. In humans, BDNF cannot be measured noninvasively 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 that 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]. In contrast, 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 1 (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, however, 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' AMP-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 as peroxisome proliferator-activated receptor  $\delta$  [127] and peroxisome proliferator-activated receptor  $\gamma$  coactivator PGC1 $\alpha$  [128]. In rodents, PA activates AMPK and induces PGC1 $\alpha$  expression in muscle, elevating levels of fibronectin type III domain-containing protein FNDC5, 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 AD [131]. Treatment of skeletal muscle cells *in vitro* with AMPK agonist AICAR led to the identification of the myokine cathepsin B. Administration of recombinant cathepsin B to neural progenitor cells increased BDNF gene expression. Blocking cathepsin B during PA precluded 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  $\beta$ -hydroxybutyrate, a ketone synthesized in the liver and accumulating in the hippocampus during PA, activates BDNF gene promoters via inhibition of 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, and 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 that investigated the benefits of PA showed that aerobic exercise at or above 60% of individualized maximum heart rate (three times per week for about 1 h each session, for more than 3 months), increased either brain or cognitive measures that otherwise decline with aging, especially when fitness was improved (see supplemental information I-III online). This is consistent with general recommendations for adults to get at least 150 min 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 supplemental information III online). 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 suggestion in the general guidelines 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.

**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 multimodal 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 one can lift a single time as a '1 repetition maximum' (e.g., for each of six exercises, two sets of eight repetitions at 50–80% repetition maximum). A recent meta-analysis reported that, similar to aerobic training, RT does not improve episodic memory assessed with neuropsychological tests [159]. Some data hint that RT could improve relational memory task performance in a female mild cognitive impairment population, when aerobic exercise would not [160]. However, the same study found maintained hippocampal volume after aerobic but not RT [72]. 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 that multimodal training may be more effective for episodic memory (four studies,  $g = 0.48$ ) than aerobic exercise (seven studies,  $g = 0.05$ ) or RT (four studies,  $g = 0.07$ ) (e.g., [163]). Rodent models provide key insights 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 [161]. Whereas both types of PA increased the levels of proteins associated with synaptic plasticity (synapsin 1 and synaptophysin) [161], 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 ( $\beta$ -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 [162]. Across animal and human studies, while direct comparisons are limited, evidence suggests RT could boost but not replace effects of aerobic exercise on memory.

**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.

Furthermore, 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 multisite experimental studies will accelerate progress and enrich

**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 noninvasively and reliably measured in humans?

Are there additional critical signaling pathways mediating or moderating effects of PA on hippocampus-dependent memory, such as stress response pathways including the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal axis? How are they modified by PA dose (intensity, duration), sex, age, medications, and pathology?

How can noninvasive 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?

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 multimodal 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.

### Acknowledgments

We would like to thank the National Institute on Aging and the National Institute of General Medicine Sciences (R01 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 Alemán Foundation to C.V.

### Supplemental Information

Supplemental information associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.tics.2019.01.006>.

### References

1. Kontis, V. *et al.* (2017) Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *Lancet* 389, 1323–1335
2. Piercy, K.L. *et al.* (2018) The physical activity guidelines for Americans. *JAMA* 320, 2020–2028
3. Duzel, E. *et al.* (2016) Can physical exercise in old age improve memory and hippocampal function? *Brain* 139, 662–673
4. Downey, A. *et al.*, eds (2017) *Preventing Cognitive Decline and Dementia: A Way Forward*, National Academies Press
5. Scoville, W.B. and Milner, B. (1957) Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20, 11–21
6. Eichenbaum, H. (2010) Memory systems. *Wiley Interdiscip. Rev. Cogn. Sci.* 1, 478–490
7. Livingston, G. *et al.* (2017) Dementia prevention, intervention, and care. *Lancet* 390, 2673–2734
8. Beydoun, M.A. (2014) Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health* 14, 643
9. Blondell, S.J. *et al.* (2014) Does physical activity prevent cognitive decline and dementia?: a systematic review and meta-analysis of longitudinal studies. *BMC Public Health* 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, 781–790
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, 797–804
12. Church, T.S. *et al.* (2008) Maximal fitness testing in sedentary elderly at substantial risk of disability: LIFE-P study experience. *J. Aging Phys. Act.* 16, 408–415
13. Backman, L. *et al.* (2005) Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology* 19, 520–531
14. Khan, U.A. *et al.* (2014) Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nat. Neurosci.* 17, 304–311
15. Leal, S.L. and Yassa, M.A. (2015) Neurocognitive aging and the hippocampus across species. *Trends Neurosci.* 38, 800–812
16. Hayes, S.M. *et al.* (2015) Physical activity is positively associated with episodic memory in aging. *J. Int. Neuropsychol. Soc.* 21, 780–790
17. Hayes, S.M. *et al.* (2016) Cardiorespiratory fitness is associated with cognitive performance in older but not younger adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 71, 474–482
18. Hayes, S.M. *et al.* (2017) fMRI activity during associative encoding is correlated with cardiorespiratory fitness and source memory performance in older adults. *Cortex* 91, 208–220
19. Raine, L. *et al.* (2013) The influence of childhood aerobic fitness on learning and memory. *PLoS One* 8, e72666
20. Hassevoort, K.M. *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
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, 172–183
22. Chaddock, L. *et al.* (2011) Aerobic fitness and executive control of relational memory in preadolescent children. *Med. Sci. Sports Exerc.* 43, 344–349
23. Monti, J.M. *et al.* (2012) Aerobic fitness enhances relational memory in preadolescent children: the FITKids randomized control trial. *Hippocampus* 22, 1876–1882
24. Schwab, H. *et al.* (2017) Aerobic fitness, hippocampal viscoelasticity, and relational memory performance. *Neuroimage* 153, 179–188
25. Stillman, C.M. *et al.* (2018) Cardiorespiratory fitness is associated with enhanced hippocampal functional connectivity in healthy young adults. *Hippocampus* 28, 239–247

26. Stillman, C.M. *et al.* (2016) Physical activity is associated with reduced implicit learning but enhanced relational memory and executive functioning in young adults. *PLoS One* 11, e0162100
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
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, 517–525
29. Amaral, D.G. and Witter, M.P. (1989) The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience* 31, 571–591
30. Yassa, M.A. and Stark, C.E. (2011) Pattern separation in the hippocampus. *Trends Neurosci.* 34, 515–525
31. Kesner, R.P. (2007) A behavioral analysis of dentate gyrus function. *Prog. Brain Res.* 163, 567–576
32. Gilbert, P.E. *et al.* (2001) Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. *Hippocampus* 11, 626–636
33. Hunsaker, M.R. and Kesner, R.P. (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, 955–964
34. Ahn, J.R. 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, 1081–1093
35. Lacy, J.W. *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, 15–18
36. Yassa, M.A. *et al.* (2011) Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus* 21, 968–979
37. Bakker, A. *et al.* (2008) Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science* 319, 1640–1642
38. Bernstein, E.E. and McNally, R.J. (2018) Examining the effects of exercise on pattern separation and the moderating effects of mood symptoms. *Behav. Ther.* Published online September 21, 2018. <http://dx.doi.org/10.1016/j.beth.2018.09.007>
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, 5140
40. Whiteman, A.S. *et al.* (2014) Interaction between serum BDNF and aerobic fitness predicts recognition memory in healthy young adults. *Behav. Brain Res.* 259, 302–312
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, 10487–10492
42. Whiteman, A.S. *et al.* (2016) Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: a voxel-based morphometry study. *Neuroimage* 126, 229–238
43. Sorrells, S.F. *et al.* (2018) Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature* 555, 377–381
44. Boldrini, M. *et al.* (2018) Human hippocampal neurogenesis persists throughout aging. *Cell Stem Cell* 22, 589–599.e5
45. Clelland, C.D. *et al.* (2009) A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science* 325, 210–213
46. Niibori, Y. *et al.* (2012) Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. *Nat. Commun.* 3, 1253
47. Nakashiba, T. *et al.* (2012) Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* 149, 188–201
48. Vivar, C. *et al.* (2012) Monosynaptic inputs to new neurons in the dentate gyrus. *Nat. Commun.* 3, 1107
49. Vivar, C. and van Praag, H. (2017) Running changes the brain: the long and the short of it. *Physiology (Bethesda)* 32, 410–424
50. Sah, N. *et al.* (2017) Running reorganizes the circuitry of one-week-old adult-born hippocampal neurons. *Sci. Rep.* 7, 10903
51. Zhao, C. *et al.* (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J. Neurosci.* 26, 3–11
52. Trinchero, M.F. *et al.* (2017) High plasticity of new granule cells in the aging hippocampus. *Cell Rep.* 21, 1129–1139
53. Creer, D.J. *et al.* (2010) Running enhances spatial pattern separation in mice. *Proc. Natl. Acad. Sci. U. S. A.* 107, 2367–2372
54. Bolz, L. *et al.* (2015) Running improves pattern separation during novel object recognition. *Brain Plast.* 1, 129–141
55. Sahay, A. *et al.* (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472, 466–470
56. Lister, J.P. and Barnes, C.A. (2009) Neurobiological changes in the hippocampus during normative aging. *Arch. Neurol.* 66, 829–833
57. Schmidt-Hieber, C. *et al.* (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 429, 184–187
58. Vivar, C. *et al.* (2016) Running rewires the neuronal network of adult-born dentate granule cells. *Neuroimage* 131, 29–41
59. Vanderwolf, C.H. (1969) Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr. Clin. Neurophysiol.* 26, 407–418
60. Rendeiro, C. and Rhodes, J.S. (2018) A new perspective of the hippocampus in the origin of exercise-brain interactions. *Brain Struct. Funct.* 223, 2527–2545
61. Guerrieri, D. and van Praag, H. (2015) Exercise-mimetic AICAR transiently benefits brain function. *Oncotarget* 6, 18293
62. Woods, N.I. *et al.* (2018) Preferential targeting of lateral entorhinal inputs onto newly integrated granule cells. *J. Neurosci.* 38, 5843–5853
63. Leal, S.L. and Yassa, M.A. (2018) Integrating new findings and examining clinical applications of pattern separation. *Nat. Neurosci.* 21, 163–173
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, 5638–5643
65. Maass, A. *et al.* (2015) Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol. Psychiatry* 20, 585–593
66. Erickson, K. *et al.* (2011) Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U. S. A.* 108, 3017–3022
67. Thomas, A.G. *et al.* (2016) Multi-modal characterization of rapid anterior hippocampal volume increase associated with aerobic exercise. *Neuroimage* 131, 162–170
68. Kleemeyer, M.M. *et al.* (2016) Changes in fitness are associated with changes in hippocampal microstructure and hippocampal volume among older adults. *Neuroimage* 131, 155–161
69. Rosano, C. *et al.* (2016) Hippocampal response to a 24-month physical activity intervention in sedentary older adults. *Am. J. Geriatr. Psychiatry* 25, 209–217
70. Jonasson, L.S. *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
71. Vidoni, E. *et al.* (2012) Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years. *Neurobiol. Aging* 33, 1624–1632
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, 248–254
73. Voss, M. *et al.* (2010) Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front. Aging Neurosci.* Published online August 26, 2010. <http://dx.doi.org/10.3389/fnagi.2010.00032>

74. Chirles, T.J. *et al.* (2017) Exercise training and functional connectivity changes in mild cognitive impairment and healthy elders. *J. Alzheimers Dis.* 57, 845–856
75. Boraxbekk, C.J. *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, 133–141
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
77. Voss, M. *et al.* (2010) Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia* 48, 1394–1406
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
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
80. Buckley, R.F. *et al.* (2017) Functional network integrity presages cognitive decline in preclinical Alzheimer disease. *Neurology* 89, 29–37
81. Wig, G.S. (2017) Segregated systems of human brain networks. *Trends Cogn. Sci.* 21, 981–996
82. Andrews-Hanna, J. *et al.* (2007) Disruption of large-scale brain systems in advanced aging. *Neuron* 56, 924–935
83. Cotman, C.W. and Berchtold, N.C. (2002) Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 25, 295–301
84. Sleiman, S.F. and Chao, M.V. (2015) Downstream consequences of exercise through the action of BDNF. *Brain Plast.* 1, 143–148
85. Heldt, S.A. *et al.* (2007) Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Mol. Psychiatry* 12, 656–670
86. Neuner, S. *et al.* (1995) Exercise and brain neurotrophins. *Nature* 373, 109
87. Freitas, D.A. *et al.* (2018) High intensity interval training modulates hippocampal oxidative stress, BDNF and inflammatory mediators in rats. *Physiol. Behav.* 184, 6–11
88. Voss, M. *et al.* (2013) Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn. Sci.* 17, 525–544
89. Hatchard, T. *et al.* (2014) Translating the impact of exercise on cognition: methodological issues in animal research. *Behav. Brain Res.* 273, 177–188
90. Vaynman, S. *et al.* (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur. J. Neurosci.* 20, 2580–2590
91. Li, Y. *et al.* (2008) TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. *Neuron* 59, 399–412
92. Klein, A.B. *et al.* (2011) Blood BDNF concentrations reflect brain-tissue BDNF levels across species. *Int. J. Neuropsychopharmacol.* 14, 347–353
93. Radka, S.F. *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, 122–301
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, 35–41
95. Yau, S.Y. *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
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, 1051–1061
97. Rasmussen, P. *et al.* (2009) Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp. Physiol.* 94, 1062–1069
98. Fujimura, H. *et al.* (2002) Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thrombosis Haemostasis* 88, 728–734
99. Szuhany, K.L. *et al.* (2015) A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J. Psychiatr. Res.* 60, 56–64
100. Ferris, L.T. *et al.* (2007) The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med. Sci. Sports Exerc.* 39, 728–734
101. Griffin, É. *et al.* (2011) Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol. Behav.* 104, 934–941
102. Weng, T.B. *et al.* (2017) The acute effects of aerobic exercise on the functional connectivity of human brain networks. *Brain Plast.* 2, 171–190
103. Ivy, A.S. *et al.* (2003) Noradrenergic and serotonergic blockade inhibits BDNF mRNA activation following exercise and antidepressant. *Pharmacol. Biochem. Behav.* 75, 81–88
104. Soya, H. *et al.* (2007) BDNF induction with mild exercise in the rat hippocampus. *Biochem. Biophys. Res. Commun.* 358, 961–967
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, e0163037
106. Voss, M. *et al.* (2013) Neurobiological markers of exercise-related brain plasticity in older adults. *Brain Behav. Immun.* 28, 90–99
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, 1–10
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, 152–155
109. Jung, S.H. *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, 303–311
110. Cho, H.C. *et al.* (2012) The concentrations of serum, plasma and platelet BDNF are all increased by treadmill VO<sub>2max</sub> performance in healthy college men. *Neurosci. Lett.* 519, 78–83
111. Naegelin, Y. *et al.* (2018) Measuring and validating the levels of brain-derived neurotrophic factor in human serum. *eNeuro* 5, Published online March 22, 2018. <http://dx.doi.org/10.1523/ENEURO.0419-17.2018>
112. Polacchini, A. *et al.* (2015) A method for reproducible measurements of serum BDNF: comparison of the performance of six commercial assays. *Sci. Re.* 5, 17989
113. Tang, K. *et al.* (2010) Exercise-induced VEGF transcriptional activation in brain, lung and skeletal muscle. *Respir. Physiol. Neurobiol.* 170, 16–22
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, 928–936
115. Morland, C. *et al.* (2017) Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. *Nat. Commu.* 8, 15557
116. Cao, L. *et al.* (2004) VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat. Genet.* 36, 827–835
117. Carro, E. *et al.* (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J. Neurosci.* 20, 2926–2933
118. Fernandez, A.M. *et al.* (2018) Insulin peptides as mediators of the impact of life style in Alzheimer's disease. *Brain Plast.* 4, 3–15

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, 823–833
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, 1628–1634
121. Stein, A.M. *et al.* (2018) Physical exercise, IGF-1 and cognition: A systematic review of experimental studies in the elderly. *Dement. Neuropsychol.* 12, 114–122
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, 1712–1721
123. Walz, J.M. *et al.* (2016) Pre-analytical parameters affecting vascular endothelial growth factor measurement in plasma: identifying confounders. *PLoS One* 11, e0145375
124. Delezic, J. and Handschin, C. (2018) Endocrine crosstalk between skeletal muscle and the brain. *Front Neuro.* 9, 698
125. Moon, H.Y. *et al.* (2019) Conditioned media from AICAR-treated skeletal muscle cells increases neuronal differentiation of adult neural progenitor cells. *Neuropharmacology* 145, 123–130
126. Hardie, D.G. (2011) AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. *Genes Dev.* 25, 1895–1908
127. Wang, Y.X. *et al.* (2004) Regulation of muscle fiber type and running endurance by PPARdelta. *PLoS Biol.* 2, e294
128. Lin, J. *et al.* (2002) Transcriptional co-activator PGC-1 $\alpha$  drives the formation of slow-twitch muscle fibres. *Nature* 418, 797
129. Wrann, C. *et al.* (2013) Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. *Cell Metab.* 18, 649–659
130. Jedrychowski, M. *et al.* (2015) Detection and quantitation of circulating human irisin by tandem mass spectrometry. *Cell Metab.* 22, 734–740
131. Lourenco, M.V. *et al.* (2019) Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat. Med.* 25, 165–175
132. Moon, H.Y. *et al.* (2016) Running-induced systemic cathepsin B secretion is associated with memory function. *Cell Metab.* 24, 332–340
133. Sleiman, S.F. *et al.* (2016) Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body beta-hydroxybutyrate. *eLife* 5, e15092
134. Basso, J.C. and Suzuki, W.A. (2017) The effects of acute exercise on mood, cognition, neurophysiology, and neurochemical pathways: a review. *Brain Plast.* 2, 127–152
135. Roig, M. *et al.* (2013) The effects of cardiovascular exercise on human memory: a review with meta-analysis. *Neurosci. Biobehav. Rev.* 37, 1645–1666
136. Sanai, N. *et al.* (2011) Corridors of migrating neurons in the human brain and their decline during infancy. *Nature* 478, 382–386
137. Wilson, D.A. (2009) Pattern separation and completion in olfaction. *Ann. N. Y. Acad. Sci.* 1170, 306–312
138. Watson, P. *et al.* (2013) Spatial reconstruction by patients with hippocampal damage is dominated by relational memory errors. *Hippocampus* 23, 570–580
139. Bernstein, E.E. and McNally, R.J. (2018) Exploring behavioral pattern separation and risk for emotional disorders. *J. Anxiety Disord.* 59, 27–33
140. Holzsneider, K. *et al.* (2012) Cardiovascular fitness modulates brain activation associated with spatial learning. *Neuroimage* 59, 3003–3014
141. Allison, S.L. *et al.* (2016) Spatial navigation in preclinical Alzheimer's disease. *J. Alzheimers Dis.* 52, 77–90
142. 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, 357–366
143. Lin, T.W. *et al.* (2015) Running exercise delays neurodegeneration in amygdala and hippocampus of Alzheimer's disease (APP/PS1) transgenic mice. *Neurobiol. Learn. Mem.* 118, 189–197
144. 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, 62–74
145. Rodriguez, J.J. *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, 707–717
146. Marlatt, M.W. *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, 313–340
147. Oddo, S. *et al.* (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* 39, 409–421
148. Choi, S.H. *et al.* (2018) Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science* 361, eaan8821
149. Liu, H.L. *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, 308–314
150. Yuede, C.M. *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, 426–432
151. Cho, J. *et al.* (2015) Treadmill running reverses cognitive declines due to Alzheimer disease. *Med. Sci. Sports Exerc.* 47, 1814–1824
152. Moore, K.M. *et al.* (2016) A spectrum of exercise training reduces soluble Abeta in a dose-dependent manner in a mouse model of Alzheimer's disease. *Neurobiol. Dis.* 85, 218–224
153. Morris, J.K. *et al.* (2017) Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. *PLoS One* 12, e0170547
154. Baker, L. *et al.* (2010) Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch. Neurol.* 67, 71–79
155. 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, 146–158
156. Law, L.L. *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
157. Okonkwo, O.C. (2014) Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology* 83, 1753–1760
158. Head, D. *et al.* (2012) Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. *Arch. Neurol.* 69, 636–643
159. Barha, C.K. *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
160. Nagamatsu, L. *et al.* (2012) Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Arch. Intern. Med.* 172, 666–668
161. Cassilhas, R.C. *et al.* (2012) Spatial memory is improved by aerobic and resistance exercise through divergent molecular mechanisms. *Neuroscience* 202, 309–317
162. Cassilhas, R.C. *et al.* (2007) The impact of resistance exercise on the cognitive function of the elderly. *Med. Sci. Sports Exerc.* 39, 401–407
163. Suzuki, T. *et al.* (2013) A randomized controlled trial of multi-component exercise in older adults with mild cognitive impairment. *PLoS One* 8, e61483