Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
doi:10.1093/gerona/glu162

Cardiovascular Fitness and Cognitive Spatial Learning in Rodents and in Humans

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The association between cardiovascular fitness and cognitive functions in both animals and humans is intensely studied. Research in rodents shows that a higher cardiovascular fitness has beneficial effects on hippocampus-dependent spatial abilities, and the underlying mechanisms were largely teased out. Research into the impact of cardiovascular fitness on spatial learning in humans, however, is more limited, and involves mostly behavioral and imaging studies. Herein, we point out the state of the art in the field of spatial learning and cardiovascular fitness. The differences between the methodologies utilized to study spatial learning in humans and rodents are emphasized along with the neuronal basis of these tasks. Critical gaps in the study of spatial learning in the context of cardiovascular fitness between the two species are discussed.

Key Words: Exercise—Spatial learning—Cardiovascular fitness—Hippocampus—Navigation.

Received December 12, 2013; Accepted August 6, 2014

Decision Editor: Rafael de Cabo, PhD

THE effect of cardiovascular fitness on cognition was first shown in the 1970's when better cognitive reaction times in old active men were observed compared to old sedentary men (1). Dozens of studies performed since then concluded that in humans, cardiovascular fitness improves executive functions that rely mostly on frontal regions of the brain (2). During the last 10 years, studies have begun looking into the effects of cardiovascular fitness on hippocampus-dependent cognitive learning and memory, a process focused on information processing rather than prefrontal cortex-dependent executive functions. In rodents, research has repeatedly shown a positive effect for cardiovascular fitness on hippocampus-dependent spatial learning and the underlying anatomical, cellular, and molecular mechanisms of this effect were thoroughly studied (3). In contrast, similar research in humans has been more constrained. This is due to the limited access to deep brain regions such as the hippocampus, outside the setting of brain surgery, or in freely moving humans. These facts hinder investigators from obtaining mechanistic insights on the impact of cardiovascular fitness on hippocampus-dependent spatial learning in humans.

Here, we point out current knowledge on the link between cardiovascular fitness and spatial learning, discuss the possible underlying mechanisms and clarify methodological differences between research in rodents and humans and as a consequence, the critical gaps between the two disciplines. Specific recommendations to address the hypothesis of whether cardiovascular fitness correlates with enhanced spatial learning in humans are suggested.

Cardiovascular Fitness: Definition and Practice

Cardiovascular fitness is the ability of body organs to consume, transport, and utilize oxygen (4). The maximal volume of oxygen the body can consume and use during exercise is termed VO_2 max. Fit people have a higher VO_2 max, which enables them to use oxygen more efficiently. Regular aerobic endurance training produces numerous metabolic and cardiovascular effects, including a decrease in resting heart rate, increased heart rate variability (5), increased resting and exercise stroke volume, an increase in arteriovenous oxygen difference (6) and increased blood pumping efficiency and oxygen utilization in tissues (7). In order to develop and maintain cardiovascular fitness in humans, aerobic exercise is typically performed at a frequency of 3–5 days per week, at an intensity of 60–90% of the maximal heart rate, and duration of 20–60 min over several months (8).

Spatial Learning

Spatial learning is the process in which information about the environment is encoded to facilitate navigation

through space and recall the location of motivationally relevant stimuli (9). This form of learning is critically dependent on the integrity of the hippocampus and surrounding regions such as the medial entorhinal cortex (MEC; Figure 1; [10]). The cognitive map theory (11) proposes that the hippocampus and other parahippocampal regions in rodents represent content and locations within the environment, providing the basis for spatial memory and navigation. When it comes to humans, the theory also suggests lateralization of hippocampal function with the right hippocampus encoding spatial relationships, and the left hippocampus storing relationships between linguistic entities (12). Moreover, one or both hippocampi incorporate temporal information derived from the frontal lobes, which serves to timestamp each individual visit to a location, thus providing the basis for a spatio-temporal contextual or episodic memory system (13). In addition, unlike rodents, humans can represent spatial information symbolically as is the case with maps used for navigation (14).

Research in Rodents: The Neuroanatomical Basis for Spatial Learning

The relation of spatial learning to the location of environmental cues is achieved in part by hippocampal place cells, which fire action potentials whenever an animal is in a certain place in the local environment. Neighboring place cells fire at different locations such that, throughout the hippocampus, the entire environment is represented in the activity of the local cell population (15). Grid cells in layers II and III of the MEC (Figure 2) exhibit similar spatial firing with each cell having multiple firing fields that form a grid, which encompasses the entire environment explored by the animal, with a similar precision to that of place cells (10). Head-direction cells are informed by the vestibular system and fire selectively with respect to head orientation (16). Conjunction cells exhibit traits of grid cells and head direction cells by firing in a grid pattern solely when an animal is directing its head in a specific direction (17). Border cells (Figure 2) are entorhinal cells that fire when an animal is close to the borders of the proximal environment (18). In addition, parahippocampal regions also harbor spatial view cells (19), which are independent of specific directionality, and only respond to specific objects (20). The combined effects of the above cells enable the representation of the entire environment of the rodent. The rodent hippocampus is commonly divided into several subregions: Cornu amonis (CA)1, CA3, dentate gyrus (DG), and the hilus (21; Figure 1). These subregions are crucial for the encoding of novel spatial environments in the hippocampus (22). Importantly, spatial learning sharpens and stabilizes place fields (23), allowing better representation of the surroundings (Figure 2).

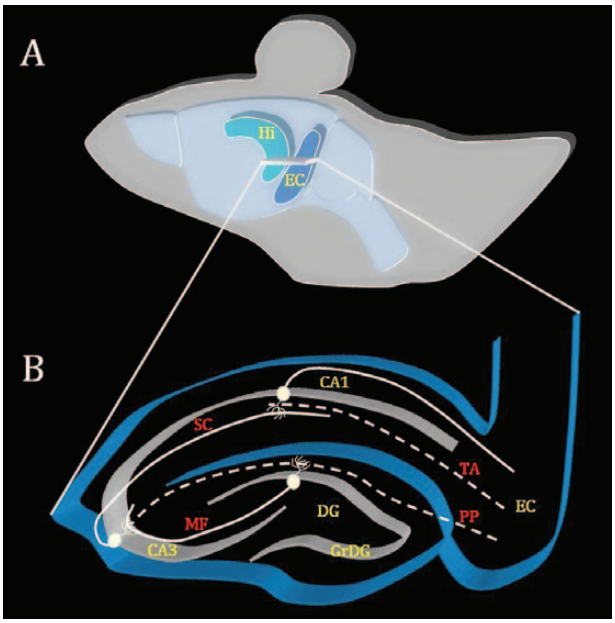

Figure 1. The mouse hippocampus neuroanatomy. (**A**) An illustration of the mouse brain and the entorhinal cortex–hippocampal subregions of the mouse brain. (**B**) Detailed diagram of the entorhinal cortex–hippocampal circuitry from A. The main input of the hippocampus comes from the entorhinal cortex through the perforant path to the dentate gyrus and the CA3 directly. From the dentate gyrus information is transferred through the mossy fibers to area CA3, from there it will be transferred to CA1 area through the schaffer collateral, and back to the entorhinal cortex. CA1 also receives direct input from the entorhinal cortex through the temporoammonic pathway. DG = dentate gyrus, EC = entorhinal cortex, GrDG = granular layer of dentate gyrus, Hi = hippocampus, MF = mossy fibers, PP = perforant path, SC = Schaffer collateral, TA = temporoammonic pathway.

Cardiovascular Fitness and Spatial Learning in Rodents

The impact of cardiovascular fitness on spatial learning and memory in rodents has been thoroughly investigated using various types of tasks including the Morris water maze (24–28), Y-maze (29), radial arm maze (30), and place learning-set task (31). As this topic has been extensively reviewed elsewhere (27) (see Table 1), it is suffice to say that while numerous studies have indicated that cardiovascular fitness improves spatial learning and memory, no physiological measurements (eg VO_2 max) were tested to indicate that the mice had better cardiovascular fitness. This is probably due to lack of adequate measurement techniques for rodents.

The Basis for Neurocognitive Representation of Spatial Information in Humans

There are important differences between humans and rodents' spatial representations. Humans, unlike rodents, have evolved mechanisms to represent spatial information symbolically (33), enabling humans to acquire spatial information from means other than direct experience. Cognitive maps constructed from symbolic sources differ

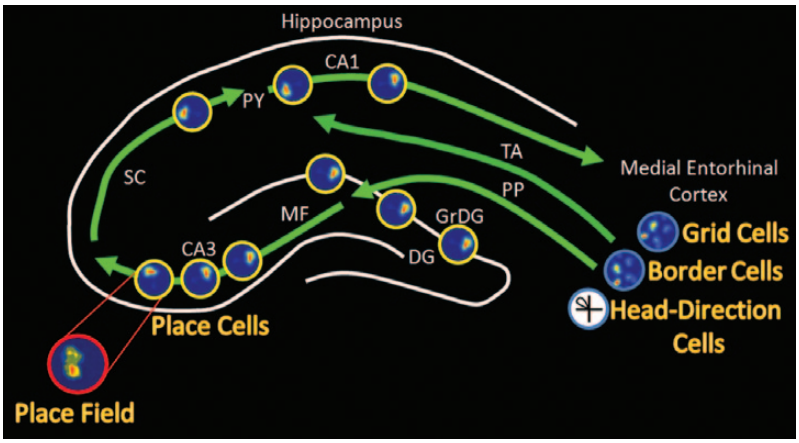

Figure 2. Schematic anatomical representation of the hippocampal-medial entorhinal cortex (MEC) circuitry that plays crucial role in spatial navigation in mouse. Spatial information about the environment is transported from the grid, border, and head-direction cells located in the MEC to place cells in the hippocampus by the perforant path (PP) and temporoammonic path (TP). In the dentate gyrus (DG), information from place cells in the granular cells of the dentate gyrus (GrDG) is transported to place cells in the CA3 by the mossy fiber (MF), and from there by the schaffer collateral (SC) to place cells located between the pyramidal (PY) cells of the CA1. Each of these hippocampal place cells fire in high frequency when the mouse is located in the place field of the relevant place cell. Blue = cells in the medial entorhinal cortex, yellow = place cell, red = place field, green = axonal projections.

from those derived from direct navigational experience in some ways (14) and yet in other ways are similar (34). The environments used to assess spatial learning in humans include virtual environments (VE), real-world environments, and computer-screen tasks. Learning from a VE is similar to learning from navigation, since the interface preserves many of the visual–spatial characteristics that are experienced during real navigation. In a VE, the learner builds up a spatial representation over time through movement within the VE. Studying whether people form the same types of spatial representations in a VE compared with real environments has yielded mixed results. Witmer and *coworkers* found that VE training is useful in a building navigation task but does not produce the same level of performance as map or real-world training (35). Bliss et al. found no difference between map and VE training in a similar task but did not compare performance to real-environment training (36). Philbin et al. found map training to be superior to VE training (37). Other studies have shown evidence for learning and successful navigation solely within a VE (38,39). Richardson et al. found that although individuals are able to acquire a substantial amount of spatial knowledge from a VE, important differences in spatial representations are found between real environments and VEs. The existence of a VE alignment effect suggests that the visual flow input, specifying movement in a desktop VE is sufficient for translational but not for rotational updating. Second, a large alignment effect is found after learning the environment from a map. Indeed, map learning leads to superior performance only when aligned with the initial orientation of a map. The resulting representation is precise, yet inflexible. Thus, cognitive processes necessary for maintaining orientation in a real environment are used, at least in part, when operating in a virtual one (40).

While rodents certainly exhibit maze shortcuts between two previously visited locations (41), this flexibility is extended in humans with symbolic representations, as the activities involved in building such representations bear little resemblance to the direct experience of navigating through an environment. A map often uses symbols that depict an environment more vast and complex than what can be experienced from a single vantage point. Thus, humans demonstrate an ability to construct cognitive maps from both cartographic maps and spatial descriptions (14).

In a recent study, Ekstrom et al. (33) found using the taxi driver task (see below) that 30% of the view cells in the human parahippocampus are location-dependent, while 70% are location-independent. The anatomical distribution of place- and view-responsive cells reveal a dissociation between the hippocampus and the parahippocampal region, with the hippocampus specialized for place and the parahippocampal region specialized for view (42). Thus, the parahippocampal region extracts allocentric spatial information primarily from salient visual landmarks to form a coarse representation of space. The hippocampus combines visual and spatial features, possibly via inputs from the parahippocampal region, with context to compute the flexible map-like representation of space underlying navigation.

Methods to Assess Spatial Learning in Humans and their Neural Basis

In this section, we present important technical details of the major methodologies utilized in studies that assess cardiovascular fitness and spatial learning in humans and discuss the neural basis for the relevance (or irrelevance) of the task to spatial learning.

Table 1. Summary of Methodologies Utilized in the Study of the Effects of Cardiovascular Fitness on Spatial Learning in Rodents.

Cognitive Task	Exercise Type	Exercise Length (wk)	Species	Gender	Age	# of Rodents	Effect on Spatial Ability	Ref.
Morris water maze	Voluntary	4	C57bl/6 mice	Males	3 and 19 mo of age	33	Positive	(27)
		6	C57bl/6 mice	Females	3 mo of age	70	Positive	(26)
		1	Sprague Dawley Rats	Males	3 mo of age	28	Positive	(28)
	Forced	12	Wistar rats	Males	?	16	Positive	(24)
		8	C57bl/6 and DBA mice	Males	3 mo of age	40	Positive	(25)
		1	Wistar rats	Males	4 mo of age	12	No effect	(32)
Y maze	Voluntary	2	C57bl/6 mice	Males	10 wk old	80	Positive	(29)
Radial arm maze	Voluntary	7	Long Evans Hooded rats	Females	5 mo of age	21	Positive	(30)
Whishaw design	Forced	Acute/Chronic	F344 rats	Males	12 wk of age	70	Positive	(31)

The viewpoint shift task.—In this task, participants observe a virtual courtyard from one of two possible fixed viewpoints. Different objects are sequentially presented and participants are then asked to memorize the position of these objects with respect to distinct textures in the courtyard. Five objects are sequentially shown for 3 s each with an interstimulus interval of 1 s. A short distractor phase follows and participants are subsequently asked to retrieve the objects' positions from the same or different prespective (43). Representation by place cells in the hippocampus is associated with object information and environmental layout (44). As each object is presented, it can be added to a single coherent representation of the spatial layout, from which 'scenes' from a specific viewpoint can be generated (45). Thus, the hippocampus and especially place cells have a pivotal role in tasks that require the retrieval of spatial information as in the viewpoint shift task.

The path integration task.—Path integration is the ability to keep track of changes in orientation and position during movement through monitoring self-motion without reference to external cues. Therefore, path integration is a crucial ability for the formation of cognitive maps (46) and has been shown to be associated with hippocampal function. In this task, participants see a computerized uniform surface without landmarks. The participants passively move forward, turn, move further, and stop. Then, they are asked to point back to their starting location using a joystick. For each trial, the pointing error is determined. The ability to path-integrate by linear and angular self-motion in the environment is mediated by grid cells, head-direction cells, and conjunctive cells within the MEC. This information is not determined by environmental stimuli, but by self-motion (47), even though there is less use of vestibular cues, and more use of visual cues as the participant sits in front of a computer screen (48).

Dots fixation task.—In this task one to three dots appear at randomly selected locations on a computer screen for 500 ms. Next, a fixation-cross appears for 3 s. At the end of the delay, a single red test dot is presented either at the same location as one of the previous black dots (match), or at a new location (nonmatch). Subjects are required to indicate as quickly and accurately as possible whether the red test dot matches any of the previously presented black dots (49). This task does not seem to involve the hippocampus or the MEC (50).

The 3D rotation task.—In this task, participants are required to perform mental rotation of three-dimensional (3D) objects. Participants have to match corners and edges of the 3D objects to the corresponding parts of their equivalent unfolded two-dimensional counterparts. Following this, complex geometrical shapes are shown and participants are asked to count the number of surfaces for each shape (51).

Although this task is considered to assess spatial capabilities, imaging studies show no relevancy to hippocampus-dependent spatial learning and memory (52).

The above-mentioned tasks were utilized in studies reviewed herein. Below, we discuss the potential use of two tasks that assess spatial learning in humans but were not yet implicated in cardiovascular fitness research. This is due to the high potential of these tasks to clearly delineate the possible role of cardiovascular fitness on spatial learning in humans.

The Blitz3D virtual environment task.—Participants in this task watch or move along a VE town (53) while visiting all the available landmarks within a maze. Next, snapshots of buildings from the same viewpoints as those encountered during navigation are shown to the participants next to a second building. This is done in order to test participants' ability to retrieve information about spatial relationships between pairs of buildings (54). fMRI-based evidence indicated a dissociation between the contributions of the retrosplenial cortex and the hippocampus during navigation in this task. Both of these dissociated areas are active during this task, and head-direction cells are less dominant in virtual reality task compared with place cells. However, they both seem to be involved in spatial learning in the VE tasks.

Taxi driver task.—In this task, subjects navigate at a constant moving velocity in a virtual town that consist of six unlabeled nontarget buildings and three labeled target stores. During a single session, subjects make seven deliveries of passengers to each target shop in a random order. Upon delivery of the passenger, subjects are told whether they have found the correct shop, along with a 'virtual' payment for delivering passengers. Subjects explore the city until they locate another passenger, at which point the cycle repeats (48). While in this task, vestibular cues, encoded by head-direction cells are not utilized, visual cues, represented by place cells; view cells and conjunctive cells are being utilized.

As discussed above, a variety of methodologies have been utilized to assess spatial learning in humans, and these methods seem to differ significantly in their neural basis. Moreover, not all the methods are fully compatible with navigation in reality. For example, the path integration and taxi driver tasks do not involve head-direction cells, which pose a major disadvantage of a computerized spatial task. More importantly, not all the methods are related to spatial learning, as in the case of the dots fixation task and the 3D rotational tasks, which do not involve the hippocampus or the MEC.

With respect to the translational value of the methods used to assess spatial learning, there is a fundamental and important difference between methods used in rodents to those used in humans. Spatial learning tasks commonly used with rodents (e.g., the Morris water maze) integrate multisensory inputs utilized in spatial navigation. This includes visual, olfactory, vestibular, and motor inputs. In contrast, most methods used to assess spatial learning in humans lack some or several of these aspects. For example, any method that uses a computer screen as an interface will lack head-direction inputs to the hippocampus. Other tasks such as the dots-fixation task do not seem to rely on the hippocampus at all. This indicates that although spatial tasks used for rodents are highly translational to real-world situations for humans, spatial tasks used for humans cannot translate into mechanistic insights gained in rodents research.

Cardiovascular Fitness and Spatial Learning in Humans

Older adults with higher fitness levels show greater preservation of hippocampal volume, which is associated with more accurate and faster spatial memory and fewer episodes of forgetting (55). Using the 3D rotation task, Hotting and *coworkers* observed no difference in spatial reasoning between endurance and nonendurance training (51). More recently, Nagamatsu and *coworkers* (49). found, using the dots fixation task, that both aerobic, balance and tone exercises improve spatial memory in older adults with probable mild cognitive impairment (49). The relationship between aerobic fitness and hippocampal volume in elderly humans was also studied using the dots fixation task by Erickson and colleagues. In their study, the authors showed that cardiovascular fitness is a causative factor in increasing hippocampal volume and is effective in reversing hippocampal volume loss in late adulthood, which is accompanied by improved spatial memory functions (56,57).

Using the viewpoint shift and the path integration tasks, cardiovascular fitness was shown to modulate brain activation in a manner associated with spatial learning, however, overall spatial learning performance did not correlate with cardiovascular fitness (58).

The most critical drawback of most studies in humans that try to link cardiovascular fitness and hippocampal-dependent spatial learning is that the tasks they utilize do not involve the hippocampus. These include the dots fixation and the 3D mental rotation tasks. Nevertheless, the data collected thus far (summarized in Table 2), does suggest a link between cardiovascular fitness and spatial learning and memory. Research in this field is far from being complete, and the stage is set for stronger evidence.

Cardiovascular Fitness and Aging

Aging-related cognitive decline (59) is correlated with hippocampal changes including (1) reduced hippocampal neurogenesis, (2) altered brain microvasculature (60), (3) reduction in synaptic plasticity (61), and (4) altered inflammatory balance. These aging-related deleterious consequences can be delayed or partially reversed by physical exercise.

Neurogenesis, the formation of new neurons occurs in the subventricular zone surrounding the lateral ventricles and in the sub granular zone of the hippocampal DG.

Table 2. Summary of Methodologies Utilized in the Study of the Effects of Cardiovascular Fitness on Spatial Learning in Humans.

Cognitive Task	Exercise Type	Length	Gender	Age Range	# of Participants	Effect on Spatial Ability	Ref.
Virtual environment task	N/A	N/A	Men	19–28	17	N/A	(54)
Dots fixation task	Aerobic	20 min twice a week for 6 mo	Men and women	60–80	158	Positive	(55)
3D rotation task	Aerobic and nonaerobic	Twice a week for 6 mo	Men and women	40–55	68	No effect	(51)
The viewpoint shift and path integration tasks	Aerobic and nonaerobic	Twice a weeks for 6 mo	Men and women	40–55	17	No effects	(58)
Dots fixation task	Aerobic and nonaerobic	Twice a week for 6 mo	Women	70–80	86	Positive	(49)
Dots fixation task	N/A	N/A	Men and women	59–81	165	Positive	(56)
Dots fixation task	Aerobic and nonaerobic	12 mo	Men and women	55–80	120	Positive	(57)

While the former provides new neurons that integrate into the olfactory bulb circuitry, the latter provides neurons that integrate into the DG. Hippocampal neurogenesis contributes to cognitive learning processes while aging reduces the capacity of the hippocampus to generate new neurons (27). Physical exercise, however, counteracts aging-related reduction in neurogenesis by several mechanisms; at the cellular level, exercise enhances hippocampal cell proliferation and neurogenesis in a brain-derived neurotropic factor dependent manner (28). Exercise-induced newly formed neurons are preferentially activated during learning tasks (3) as well as contribute to degradation of previously obtained memories (62). Newly generated neurons exhibit higher long-term potentiation (LTP) compared to older neurons (3), which indicates an additional mechanism by which exercise contributes to hippocampal cognitive learning.

Microvasculature and vascular density decreases in an age-dependent manner. The arterioles supplying the deep white matter have the longest course through the brain, and with aging they often become tortuous. In addition, wall thickness of veins and venules in the periventricular white matter increases with normal aging. Along with a decline in cerebral angiogenesis, a failure of vascular recovery from hypoxia-induced bouts may occur. With aging, lost capillaries are less likely to be replaced, and this may cause chronic hypoperfusion and exacerbate hypoxic events (63). As a result, many brain regions exhibit decreased metabolic support for activated neurons due to decreased blood flow (64). The metabolic impact of reduced blood flow may be exacerbated by altered nutrient transport across the capillary wall. In addition, aging reduces the ability of capillaries to respond to increases in neural activity and other factors that promote angiogenesis implying reduced microvasculature plasticity. This aging-related loss of microvascular plasticity directly affects neuronal plasticity events such as neurogenesis, as neurogenesis is mechanistically linked to capillaries and their growth (65). Trophic factors produced by endothelial cells are important regulators of ongoing neurogenesis and angiogenesis within the adult hippocampus (66). Indeed, angiogenesis, the formation of new blood vessels, is gradually impaired during aging in a mechanism involving reduced expression of angiogenic factors such as vascular endothelial growth factor (67). The previously described changes to brain vasculature ultimately cause microvascular hyperpermeability, which culminates in blood–brain barrier permeability. Age-related increase in blood–brain barrier permeability occurs in aged mice and humans (68). Vascular endothelial growth factor is a potent inducer of vascular permeability in the blood–brain barrier, and as vascular endothelial growth factor expression decreases blood–brain barrier permeability increases. Aging-related pathologies such as hypertension, cerebrovascular ischemia, Alzheimer's disease, or Parkinson's disease further destabilize blood–brain barrier integrity (68). The property of the brain vascular bed to maintain cerebral perfusion despite changes in blood pressure is termed cerebral autoregulation (CA [69]). Although one can hypothesize that microvasculature permeability would affect CA during healthy aging, no evidence supports such effect of aging on CA in the 50–75 age range, and it is unknown whether CA is preserved at more advanced age (>75 years (69)). Further, It is not clear whether exercise affects CA (70,71).

The above aging-related effects on microvasculature are thought to contribute to aging-related cognitive decline in several ways (66). Physical exercise counteracts these effect by increasing blood vessel density in the adult brain (72) via vascular endothelial growth factor, insulin-like growth factor (IGF), and angiopoietin 1 and 2 (73). Exercise-induced angiogenesis subsequently increases the availability of oxygen and glucose to existing neural circuitry. This increase may subsequently promote optimal function of mature neurons and synaptic connections to accommodate new learning and memory demand through promoting or enhancing mechanisms of memory such as LTP or synaptogenesis (74). Both these changes probably contribute to the increases in

hippocampal volume observed in exercising animals (55). During normal healthy aging cerebral blood flow declines by up to 50% while CA seems to be preserved. However, cerebral blood flow velocity of the middle cerebral artery is increased in exercising men compared with sedentary individuals. Moreover, aerobic activity in elderly subjects is associated with lower vessel tortuosity values and an increase in the number of small-caliber vessels (75).

Aging also correlates with decreases in synapse numbers, but little or no alteration in the structure of the remaining synaptic elements themselves (76). In contrast, physical exercise increases dendritic spine size and quantity, which are associated with LTP induction and are considered to support changes in synaptic strength, directly impacting memory functions (3). In this respect, *N*-methyl-D-aspartate (NMDA) receptor binding sites are more affected by aging than other ionotropic glutamate receptors in mice. Binding affinity to NMDA decreases with age in the cerebral cortex and hippocampus, regions which are important to memory processing (77). Exercise enhances mRNA levels of the NR2B subunit of the NMDA receptor in the DG and increases the capacity for the DG to express LTP in vitro and in vivo in adult animals (78).

Aging-related cognitive decline is also associated with changes in the expression of inflammatory cytokines. In the aging brain, pro-inflammatory cytokines are chronically increased. Higher levels of the pro inflammatory cytokine interleukin (IL)-6 levels are observed in the cortex, hippocampal formation, and cerebellum of aged mice. In contrast, levels of the anti-inflammatory cytokine IL-10 are decreased (79). This perturbation in pro- and anti-inflammatory balance is thought to contribute to age-related neuronal dysfunction, by over activating NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Over activation of these glutamate receptors can induce neurodegenerative processes and amplify neuronal vulnerability through increased intracellular calcium concentration. In addition, proinflammatory cytokines impair the aged brain's ability to maintain hippocampal LTP. inflammation-induced LTP impairment is accompanied by enhanced activity of stress-activated protein kinases and reactive oxygen species. Importantly, inflammation-induced LTP impairment can be reversed by the anti-inflammatory cytokine IL-10, shown to be reduced with aging (79). By reducing the ratio between pro- and anti-inflammatory (including IL-10) cytokines in the hippocampus, exercise reduces the risk of neuroinflammation in aging (79).

Final Conclusions and Future Directions in the Field

Studies in rodents indicate that cardiovascular fitness enhances spatial learning. This field, however, suffers from inconsistent methodologies and animal models, preventing us from directly extrapolating these data into a beneficial effect in humans. Despite this, we can also generalize that almost any kind of aerobic exercise that promotes cardiovascular fitness is beneficial in enhancing spatial learning. One outstanding and unresolved question is the difference between forced and voluntary exercise in promoting spatial learning in rodents. This will have to be carefully assessed, with a need to regulate both running distance, timing of running bouts, and stress levels.

In respect to humans, due to the large variety of tasks designed to tease-out possible effects of cardiovascular fitness on spatial learning, careful interpretation of these studies is required. Similarly to studies with rodents, many factors differ between studies, obscuring a clear conclusion on whether cardiovascular fitness affects spatial learning in humans. The complicated studies conducted to date are far from providing a clear-cut answer to the question of whether cardiovascular fitness enhances spatial learning. This largely stems from the fact that certain tasks considered to be spatial tasks (e.g., the dots fixation task), do not seem to involve the cellular, molecular, and anatomical mechanisms thought to underlie spatial learning. The most reliable and realistic spatial tasks utilized thus far with human subjects, are the Blitz3D VE and the taxi driver tasks. None of these reliable tasks was utilized in research that focuses on the effects of cardiovascular fitness on spatial learning in humans. Whether these highly realistic spatial tasks can reliably show possible effects by cardiovascular fitness on spatial learning in humans is unknown. Thus, it is impossible at this time to determine whether and to what extent cardiovascular fitness affects spatial learning in humans. Mean age, number of volunteers, choice of exercise all play important roles in the outcome, and a standardized protocol has to be described in order to obtain reliable information.

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