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P. D. Loprinzi

University of Mississippi

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The effects of physical exercise on parahippocampal function

PD Loprinzi

Exercise & Memory Laboratory, Department of Health, Exercise Science and Recreation Management,
The University of Mississippi, University, MS, USA

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Objective: The objective of this study was to examine the effects of physical exercise on parahippocampal function. *Methods:* Studies were identified using electronic databases, including PubMed, PsychInfo, Sports Discus, and Google Scholar. In total, 28 articles met the inclusionary criteria. Among these, 20 were among humans and 8 in animal models. Among the 20 human studies that examined some aspects of the parahippocampal gyrus, 5 evaluated the entorhinal cortex and 1 evaluated the perirhinal cortex. Among the 20 human studies, 3 evaluated neural activity (or BOLD-signal changes), 14 evaluated brain volume (gray or white matter), 2 examined fractional anisotropy, 1 examined glucose metabolism, and 1 examined functional connectivity between the parahippocampal gyrus and a proximal brain tissue. Among the 8 animal studies, 4 evaluated the entorhinal cortex, with the other 4 examining the perirhinal cortex. *Results:* The results demonstrated that, among both animal and human models, exercise had widespread effects on parahippocampal function. These effects, included, for example, increased neural excitability in the parahippocampal gyrus, increased gray/white matter, reduced volume of lesions, enhanced regional glucose metabolism, increased cerebral blood flow, augmented markers of synaptic plasticity, and increased functional connectivity with other proximal brain structures. *Conclusion:* Exercise appears to have extensive effects on parahippocampal function.

Keywords: BDNF, cardiorespiratory fitness, exercise, gray matter, memory, physical activity, sedentary behavior, synaptic plasticity, white matter

Introduction

The hippocampus plays a critical role in subserving memory function (10). Among many other factors, recent work highlights the role of exercise behavior on memory, providing evidence to suggest that both acute and chronic exercise can improve hippocampal-dependent memory function (24). Within the hippocampus, exercise may help induce neuronal excitability, increase markers of synaptic plasticity, augment tissue volume, and preserve tissue mass over time (24). The interested reader is referred elsewhere for excellent reviews on this topic (11, 14, 23).

Corresponding address: Exercise & Memory Laboratory, Department of Health, Exercise Science and Recreation Management, The University of Mississippi
229 Turner Center, University, MS 38677, USA
Phone: +1 662 915 5561; Fax: +1 662 915 5521; E-mail: pdloprin@olemiss.edu

In addition to the hippocampus, the parahippocampal gyrus also plays an important role in memory function. The parahippocampal gyrus, positioned just inferior to the hippocampus, has a distinctive, but interactive role with the hippocampus, in influencing memory (27). Detailed anatomy and role of the parahippocampal gyrus in cognitive function, including memory function, can be found elsewhere (2). Briefly, the entorhinal, perirhinal, and parahippocampal cortices comprise the parahippocampal gyrus; in the mouse model, the comparable divisions include the entorhinal, perirhinal, and postrhinal cortices (7). The anterior portion of the parahippocampal gyrus consists of medial and lateral entorhinal cortices, whereas the posterior component consists of the parahippocampal cortex (29).

Cognitively processed information is collected through the perirhinal (originating from anterior brain structures) and parahippocampal cortices (originating from posterior brain structures), processed to the entorhinal cortex and then reaches the hippocampus for further processing. Importantly, the parahippocampal gyrus does not just funnel information to the hippocampus. Regions within the parahippocampal gyrus perform extensive processing. For example, the medial entorhinal cortex facilitates the processing of spatial information, whereas the lateral entorhinal cortex processes object-recognition information (29). The perirhinal cortex appears to play a critical role in recognition memory (6). Furthermore, the parahippocampal cortex is involved in episodic memory relating to associative memory, source memory, and processing of emotional stimuli (2).

Although previous reviews have detailed the effects of exercise on hippocampal functioning (14, 24), an area in need of integration is the potential effects of exercise on parahippocampal function. Thus, the purpose of this paper was to review the literature to discuss the potential effects that exercise behavior may have on parahippocampal functioning.

Methods

Studies were identified using electronic databases, including PubMed, PsychInfo, Sports Discus, and Google Scholar. Articles were retrieved till June 1, 2018 (no restriction was placed on how far back the study was published). The search terms (and their combinations) included exercise, physical activity, sedentary behavior, cardiorespiratory fitness, parahippocampal, entorhinal, perirhinal, and postrhinal. To be eligible for inclusion in this review, the studies had to be published in English; employ a cross-sectional, prospective, or experimental design; include a measure of physical activity, exercise, cardiorespiratory fitness, or sedentary behavior as the independent variable; and the outcome variable could be neural activity, functional neural connectivity across brain regions (had to isolate one of these brain regions: entorhinal, perirhinal, or postrhinal), a growth factor protein measure, or a brain volume measure in either the entorhinal, perirhinal, or postrhinal structure. To provide a comprehensive assessment on this topic, human and animal studies were eligible. In total, 28 articles met these criteria. Among these, 20 were among humans and 8 in animal models.

Results

Table I displays the extraction table for the 20 human studies. Among these, 3 were conducted among children/adolescents, with 17 among adults (7 among older adults). Regarding the

Table I. Extraction table of the evaluated human studies

Study	Subjects	Study design	Exercise protocol	Parahippocampal region of interest	Outcome measure	Findings	Speculated mechanisms
Jahn et al. (21)	13 healthy adults (21–35 years)	Experimental	Stand, walk, run, and lie down; and imagined doing these activities	Parahippocampal	Neural activity	Walking and imagined walking were associated with neural activation in the parahippocampal region	Movement and non-movement neuronal excitability
Erickson et al. (12)	299 adults ($M_{age} = 78$ years)	Prospective exercise assessed at baseline, with MRI 9-years later	Self-reported physical activity	Entorhinal cortex	Gray matter (GM) and white matter (WM)	Greater walking distance was associated with greater GM in the entorhinal cortex. Greater GM volume with physical activity reduced the risk of cognitive impairment twofold	Proliferation and survival of new neurons. Reduction in β-amyloid deposits, reduced τ formation
la Fougere et al. (22)	16 healthy adults (51–73 years)	Experimental	Walking or imagined walking for 10 min	Parahippocampal gyri	BOLD-signal changes	Actual walking and imagined walking increased neural activity in the parahippocampal gyri	Parahippocampal gyri play an important role in navigation
Holzschneider et al. (16)	106 adults (40–55 years)	Cross-sectional and prospective	6-month cycling training	Parahippocampal gyrus	Brain activity	Cross-sectionally, higher cardiorespiratory fitness was associated with greater neuronal activity in the parahippocampal gyrus. Longitudinally, changes in fitness were associated with changes in brain activity in other regions (medial frontal gyrus, cuneus)	Angiogenesis, neurogenesis, long-term potentiation, brain-derived neurotrophic factor production, insulin-like growth factor-1
Mittal et al. (25)	29 high-risk psychosis (27 matched controls) adolescents	Cross-sectional	Accelerometry	Parahippocampal gyri	Parahippocampal volume	Total level of physical activity was positively associated with parahippocampal volume	Neurogenesis and attenuated apoptosis

Burzynska et al. (8)	88 healthy low-fit older adults (60–78 years)	Cross-sectional	Accelerometry	Parahippocampus	White matter hyperintensities (WMH) and fractional anisotropy (FA)	Higher moderate-to-vigorous physical activity was associated with lower WMH (i.e., lower volume of lesions). Light-intensity physical activity was associated with higher FA in the temporal lobe. Higher sedentary behavior was associated with lower FA of parahippocampal white matter	Higher-intensity physical activity may reduce arterial stiffness and blood pressure, preserve arterial elasticity, blood flow, and reduce formation of arteriosclerotic lesions. Exercise may increase BDNF, which has a neuroprotective role in white matter
Demirakca et al. (9)	95 participants (19–82 years)	Cross-sectional	Self-reported physical activity	Parahippocampal gyrus	Gray matter (GM) and white matter (WM)	Physical activity was associated with greater GM in the parahippocampal gyrus. Younger and older adults did not differ in the relationship between physical activity and GM	Not discussed
Schlaffke et al. (30)	13 martial artists and 13 endurance athletes (19–47 years)	Cross-sectional	Self-report of sport status	Parahippocampal gyrus	Gray matter (GM)	Endurance athletes showed higher GM	Repetitive action of endurance exercise; neurogenesis, cell survival, synaptogenesis, changes in vasculature
Tian et al. (36)	Adults 80+ years	Cross-sectional	Fitness (CRF) assessed from 400 m walk	Parahippocampal and entorhinal cortex	Mean diffusivity (MD). Increased MD suggests the loss of microstructural integrity in gray matter	Higher cardiorespiratory fitness was associated with lower MD in the entorhinal cortex	Preserved structural integrity by improved oxygen transport and utilization of the cerebral vascular system and increased oxidative capacity

Table I. Extraction table of the evaluated human studies *(Continued)*

Study	Subjects	Study design	Exercise protocol	Parahippocampal region of interest	Outcome measure	Findings	Speculated mechanisms
Bracht et al. (5)	33 young healthy adults	Cross-sectional	Accelerometry	Parahippocampal Singuli (PHC)	Fractional anisotropy (FA) and myelin water fraction (MWF); markers of myelination	Positive correlation between physical activity and right PHC	Physical activity may induce remodeling of myelination of the brain. Neurotransmitter release promotes myelin induction. Exercise increases gray matter volume in hippocampus, which may impact plasticity of white matter microstructure
Tian et al. (37)	146 adults ($M_{\text{age}} = 69$ years)	Prospective	Fitness (CRF)	Perirhinal cortex	White matter	Higher midlife CRF was associated with greater white matter	Growth factor production
Tozzi et al. (38)	38 healthy adults (45 years)	Experimental	16-week intervention (twice weekly, 20–40 min/day)	Parahippocampal region	Functional connectivity and local efficiency. A decrease in local efficiency implies a strengthening of functional connections between brain structures	Exercise decreased local efficiency (i.e., increased functional connectivity) in the parahippocampal lobe to the supramarginal gyrus, precentral area, and superior temporal gyrus and temporal pole. Changes in mood from exercise were correlated with these functional connectivity changes	Exercise-induced mood changes may alter functional connectivity from the parahippocampus to other brain structures that are involved in motor function (precentral area), emotional regulation (temporal gyrus and temporal pole), and the ability to re-orient attention to relevant information (supramarginal gyrus)
Whiteman (41)	33 young adults	Cross-sectional	Fitness (CRF)	Entorhinal cortex	Gray matter (GM)	Positive association between CRF and GM. Furthermore, GM was positively associated with memory performance	Growth factor production

Esteban-Cornejo et al. (13)	101 overweight or obese children (8–11 years)	Cross-sectional	Fitness test battery	Parahippocampal gyrus	Gray matter (GM)	Cardiorespiratory fitness was associated with greater parahippocampal gyrus GM. There was no statistically significant association between parahippocampal GM and academic achievement	Increased cell proliferation and survival via BDNF and IGF-1
Muller et al. (26)	22 healthy seniors (63–80 years)	Experimental	Dance or sport group intervention (18 months)	Parahippocampal region	BDNF and parahippocampal volume	The dancing intervention increased parahippocampal volume. Verbal memory improved after 18 months. Increases in BDNF may have mediated the effects	Neurotrophic factor production (BDNF, IGF-1), brain reserve
Shimada et al. (31)	24 older adult women (75–83 years)	Experimental	3-month intervention of biweekly 90-min sessions. Exercise group engaged in aerobic exercise, strength training and physical therapy	Posterior entorhinal cortex	Glucose metabolism	The exercise intervention increased regional glucose metabolism during a bout of walking	Exercise-facilitated cerebral glucose metabolism
Train the Brain Consortium (39)	113 MCI subjects (65–89 years)	Experimental	7 months of multi-domain training (combined physical and cognitive training)	Parahippocampal region	Gray matter and various markers of cognition	The multidomain training increased cerebral blood flow in the parahippocampal region	Cerebral blood perfusion

Table I. Extraction table of the evaluated human studies *(Continued)*

Study	Subjects	Study design	Exercise protocol	Parahippocampal region of interest	Outcome measure	Findings	Speculated mechanisms
Siddarth et al. (32)	35 non-demented adults (45–75 years)	Cross-sectional	Self-report of sedentary behavior	Parahippocampal, entorhinal cortex	Brain volume	Higher levels of sitting were associated with lower volume in the parahippocampal and entorhinal cortex	Higher amounts of sitting may reduce neurogenesis, synaptic plasticity, neurotrophin production, angiogenesis, and increase inflammation. Sedentary behavior is also associated with diabetes, hypertension, and obesity, which may influence brain volume
Siddarth et al. (33)	29 adults 60+ years with memory complaints	Cross-sectional	Accelerometry	Parahippocampal cortex	Brain volume	Higher physical activity was associated with greater parahippocampal volume. Physical activity was also associated with greater attention, information-processing and executive function, but not for memory recall	BDNF, synaptic plasticity, and reduced amyloid β levels
Szulc-Lerch et al. (35)	28 children (M_{age} = 11.5 years)	Experimental	12-weeks of exercise training; two 90-min group based aerobic sessions and two 30-min home sessions per week	Parahippocampal cortex	Brain volume	Exercise was associated with increased cortical thickness in the left parahippocampal gyrus	Exercise-induced neural synaptic plasticity

MCI: mild cognitive impairment

Table II. Extraction table of the evaluated animal studies

Study	Subjects	Exercise protocol	Parahippocampal region of interest	Outcome measure	Findings	Speculated mechanisms
Ishida et al. (19)	Male Wistar rats	1–2 h running on a treadmill or 0.5–3 h swimming in pool	Entorhinal cortex	Dark neurons	After running, dark neurons appeared in the entorhinal cortex. Dark neurons may reflect the early histopathological state of neuronal damage	Dark neurons induced by stressful exercise might reflect mild neuronal damage. Enhanced HPA axis activation
Stranahan et al. (34)	Adult rats	2 months of voluntary running	Entorhinal cortex	Density of dendrites	Running increased the density of dendritic spines	Regulation of actin cytoskeleton
Griffin et al. (15)	78 male Wistar rats	7 days of running, 1 h/day	Perirhinal cortex	BDNF	Running increased BDNF expression in the perirhinal cortex. Running also increased spatial and non-spatial memory	BDNF may facilitate MAPkinase pathway, which may influence recognition memory
Hopkins and Bucci (17)	32 long Evans rats	4 weeks of voluntary exercise, every other day	Perirhinal cortex	BDNF	Exercise increased BDNF in the perirhinal cortex, which was associated with improved object recognition memory. Results did not persist at the 2-week follow-up period	The effects of exercise on BDNF and object recognition memory appear to occur through pathways separable from the anxiolytic pathways from exercise
Hopkins et al. (18)	Long Evans rats; adolescent and adult rats	4 weeks of voluntary exercise	Perirhinal cortex	BDNF	When tested immediately after the 4-week training, adult rats had increased BDNF and improved recognition memory. This effect disappeared 2 weeks later. In adolescent rats, 2–4 weeks after exercise, memory and BDNF were retained	Apparent interaction between exercise, development, and memory. Cognitive enhancement may be transient when occurring during adulthood, but the neuroplastic effects may have lasting functional consequences in adolescence

(Continued)

Table II. Extraction table of the evaluated animal studies *(Continued)*

Study	Subjects	Exercise protocol	Parahippocampal region of interest	Outcome measure	Findings	Speculated mechanisms
Jacotte-Simancas et al. (20)	48 male Sprague–Dawley albino rats	20 days of wheel access	Perirhinal cortex	Neuron density	Physical exercise reversed the severe memory deficits induced by traumatic brain injury. Physical exercise increased the density of mature neurons in the perirhinal cortex. Positive association was observed between neurogenesis and memory	Neuroprotective effects may be mediated by a reduction of oxidative stress and apoptosis-related mechanisms
Vivar et al. (40)	Adult male C57Bl/6 mice	Wheel running for 1 month	Entorhinal cortex	Connectivity	Innervation from the entorhinal cortex was increased with running. Within the entorhinal cortex, afferent input (to the hippocampus) and short-term synaptic plasticity increased	Increased contribution of these areas to new neuron circuitry may explain, in part, the improved spatial memory function often observed with exercise
Pan et al. (28)	90 male spontaneous hypertensive rats	26 days of physical exercise occurring 3 days after transient middle cerebral artery occlusion	Entorhinal cortex	Markers of neuronal cell proliferation and synaptic plasticity	Physical exercise increased NeuN, Nestin, Ki67, MBP, SYN, PSD-95, and Bcl2 expression	Enhancement of cell proliferation and suppression of neuronal apoptosis

study design, 7 employed an experimental design, 2 utilized a non-experimental prospective design, and 11 employed a cross-sectional design. Among the 20 studies that examined some aspects of the parahippocampal gyrus, 5 evaluated the entorhinal cortex and 1 evaluated the perirhinal cortex. Among the 20 studies, 3 evaluated neural activity (or BOLD-signal changes), 14 evaluated brain volume (gray or white matter), 2 examined fractional anisotropy, 1 examined glucose metabolism, and 1 examined functional connectivity between the parahippocampal gyrus and a proximal brain tissue. The studies ranged from a cross-sectional assessment of physical activity (either self-report or via accelerometry) to a 16-week (biweekly) exercise intervention.

Among the three studies evaluating neuronal activity, all demonstrated evidence suggesting that walking (21, 22) or cardiorespiratory fitness (16) was associated with greater neural activity within the parahippocampal gyrus or entorhinal cortex. Among the 14 studies evaluating brain volume, all (8, 9, 12, 13, 25, 26, 30, 32, 33, 35–37, 41), with the exception of one (39), demonstrated that higher cardiorespiratory fitness, greater exercise engagement, or less sedentary behavior (32) were associated with greater parahippocampal volume [or a reduced volume of white matter hyperintensities (8) or loss of microstructural integrity (36)]. Among the two studies evaluating fractional anisotropy (5, 8), both studies demonstrated a positive association between objectively measured physical activity and fractional anisotropy. The single study (31) evaluating parahippocampal glucose metabolism demonstrated that a 3-month exercise intervention increased regional glucose metabolism during a bout of walking. Finally, the single study (38) evaluating functional connectivity demonstrated that a 16-week exercise intervention increased functional connectivity in the parahippocampal lobe to the supramarginal gyrus, precentral area, superior temporal gyrus, and temporal pole.

Table II displays the extraction table for the eight animal studies (15, 17–20, 28, 34, 40). All eight animal studies employed an experimental design. One study (19) employed an aversive exercise protocol (to induce stress; acute high-intensity treadmill exercise and swimming), whereas the other seven employed a running protocol ranging from 7 to 26 days of exercise. Of the eight studies, four evaluated the entorhinal cortex, with the other four examining the perirhinal cortex. One study evaluated the presence of dark neurons (reflect early histopathological state of neuronal damage), two examined dendritic/neuron density, three focused on brain-derived neurotropic factor (BDNF) levels, one evaluated functional connectivity, and the other examined various synaptic plasticity markers (NeuN, Nestin, Ki67, MBP, SYN, PSD-95, and Bcl2).

In the study employing an aversive exercise protocol (19), strenuous exercise (1–2 h of high-intensity exercise; 0.5–3 h of swimming) increased dark neurons in the entorhinal cortex. Among the two studies evaluating dendritic/neuronal density (20, 34), they demonstrated evidence of exercise-induced increases in dendritic density in the entorhinal and perirhinal cortex. Among the three studies investigating changes in BDNF (15, 17, 18), all three demonstrated increases in BDNF in the perirhinal cortex from exercise. Regarding the functional connectivity study (40), innervation from the entorhinal cortex was increased with running, and within the entorhinal cortex, afferent input (to the hippocampus) and short-term synaptic plasticity increased. Finally, for the study examining various synaptic plasticity markers (28), physical exercise increased NeuN, Nestin, Ki67, MBP, SYN, PSD-95, and Bcl2 expression in the entorhinal cortex.

Discussion

The motivation for the present paper was a result of: (1) prior work demonstrating unique (when compared to the hippocampus) roles of the parahippocampal gyrus in memory function, (2) research demonstrating that exercise can improve hippocampal-dependent memory, and (3) limited integrative work discussing the role of exercise on parahippocampal function. The main finding of the present review was that, across various animal and human models (children up to older adults), exercise may have extensive effects on parahippocampal function. These effects, included, for example, increasing neural excitability in the parahippocampal gyrus, increasing gray/white matter, reducing the volume of lesions, enhancing regional glucose metabolism, increasing cerebral blood flow, augmenting various markers of synaptic plasticity, and increasing the functional connectivity with other proximal brain structures. Some of the mechanistic explanations for these exercise-induced alterations included, for example, proliferation and survival of new neurons; reduction in β-amyloid deposits and reduced τ formation; angiogenesis, neurogenesis, and synaptogenesis; growth factor production, regulation of actin cytoskeleton, and long-term potentiation; attenuated apoptosis; cerebral blood perfusion; and attenuated cardiovascular disease risk factors. Other notable and interesting observations from the studies evaluated in this review are discussed in the following narrative.

In addition to exercise enhancing the aforementioned parahippocampal functions, some of these exercise-induced modulations also correlated with enhanced memory and cognitive function. For example, in older adults, greater walking distance was associated with greater gray matter in the entorhinal cortex, and greater gray matter volume with physical activity reduced the risk for cognitive impairment twofold (12). This aligns with the findings among younger adults that observed a positive association between cardiorespiratory fitness and gray matter, with gray matter positively associating with memory performance (41). Relatedly, among older adults, an 18-month-dancing intervention increased parahippocampal volume, improved verbal memory performance, and provided suggestive evidence that these effects were mediated by increases in BDNF (26). These findings were also supported by several studies among animal models (15, 17).

Interestingly, research demonstrated that, in addition to actual locomotion, imagined locomotion increased parahippocampal neural activity (21, 22). Future research should continue to investigate this line of inquiry and evaluate if imagined locomotion can also improve memory function. Another interesting observation was that, in addition to physical exercise and cardiorespiratory fitness, higher levels of sedentary behavior were associated with lower parahippocampal volume (8, 32). This aligns with other work evaluating cardiovascular-related outcomes, which suggest that, independent of physical exercise, prolonged sedentary behavior may have negative health consequences (4).

The modality of exercise may also be important to consider in future research. For example, compared to a strength-training intervention, a dancing intervention was effective in increasing parahippocampal volume, verbal memory, and BDNF production (26). Similar findings were observed when comparing individuals who typically engaged in endurance activities when compared to martial artist athletes (30). In addition to the total volume of movement, perhaps the type of movement and rhythm of movement may have unique effects on parahippocampal function. This aligns with hippocampal work demonstrating that running speed alters the frequency of hippocampal gamma oscillations (1).

Another area worthy of continued investigation is whether exercise-induced mood alterations play a contributory role in the exercise–memory link. As reviewed here, Tozzi et al. (38) showed that exercise decreased local efficiency (i.e., increased functional connectivity) in the parahippocampal lobe to the supramarginal gyrus, precentral area, superior temporal gyrus, and temporal pole, and changes in mood from exercise were correlated with these functional connectivity changes. Mood, in theory, could play a mediating role in the exercise–memory link, as, for example, dopamine receptors are found in both the parahippocampal and hippocampal structures. Some work, however, has not demonstrated a mediational role of mood on the exercise–memory relationship (3).

The developmental period should also be carefully considered in future research. As evaluated herein, favorable exercise-induced changes in parahippocampal function occurred across the lifespan. In children, cardiorespiratory fitness (13) and exercise (35) were associated with greater parahippocampal volume. In adult rats, beneficial effects of exercise (improved memory and increased BDNF) were lost after a 2-week detraining period; however, in adolescent rats, these effects were retained after the detraining period (18).

In conclusion, this brief review provides evidence to suggest that, among both animal and human models, exercise may have widespread effects on parahippocampal function. These effects, included, for example, increased neural excitability in the parahippocampal gyrus, increased gray/white matter, reduced volume of lesions, enhanced regional glucose metabolism, increased cerebral blood flow, augmented markers of synaptic plasticity, and increased functional connectivity with other proximal brain structures.

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Conflict of interest

The author declares no conflict of interest.

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