The effects of physical exercise on parahippocampal function

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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).
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
| 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 |
| 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 |
| Study | Participants | Study Design | Measure | Region | Outcome | Notes |
|-------|--------------|--------------|---------|--------|---------|-------|
| 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 |
| 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 ($M_{age} = 69$ 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 |
| Study                                      | Participants                        | Design                  | Intervention                                                                 | Outcome                                                                                                                                      | Findings                                                                                                                                 |
|-------------------------------------------|-------------------------------------|-------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Esteban-Cornejo et al. (13)               | 101 overweight or obese children   | 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 |
| 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 |
| Shimada et al. (31)                       | 24 older adult women (75–83 years)  | Experimental            | 3-month intervention of biweekly 90-min sessions. Exercise group engaged in    | Posterior entorhinal cortex Glucose metabolism                                                                                               | The exercise intervention increased regional glucose metabolism during a bout of walking.                                                                                                         |
| Train the Brain Consortium (39)           | 113 MCI subjects (65–89 years)      | Experimental            | 7 months of multidomain 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                                                                                                             |
| 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 |
| Szulo-Lerch et al. (35) | 28 children (Mage = 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 MAP kinase 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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