Exercise training increases size of hippocampus and improves memory

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19. Next Section

Abstract

The hippocampus shrinks in late adulthood, leading to impaired memory and increased risk for dementia. Hippocampal and medial temporal lobe volumes are larger in higher-fit adults, and physical activity training increases hippocampal perfusion, but the extent to which aerobic exercise training can modify hippocampal volume in late adulthood remains unknown. Here we show, in a randomized controlled trial with 120 older adults, that aerobic exercise training increases the size of the anterior hippocampus, leading to improvements in spatial memory. Exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1 to 2 y. We also demonstrate that increased hippocampal volume is associated with greater serum levels of BDNF, a mediator of neurogenesis in the dentate gyrus. Hippocampal volume declined in the control group, but higher preintervention fitness partially attenuated the decline, suggesting that fitness protects against volume loss. Caudate nucleus and thalamus volumes were unaffected by the intervention. These theoretically important findings indicate that aerobic exercise training is effective at reversing hippocampal volume loss in late adulthood, which is accompanied by improved memory function.

- aging
- brain
- cognition
- plasticity
- MRI

Deterioration of the hippocampus precedes and leads to memory impairment in late adulthood (1, 2). Strategies to fight hippocampal loss and protect against the development of memory impairment has become an important topic in recent years from both scientific and public health perspectives. Physical activity, such as aerobic exercise, has emerged as a promising low-cost treatment to improve neurocognitive function that is accessible to most adults and is not plagued by intolerable side effects often found with pharmaceutical treatments (3). Exercise enhances learning and improves retention, which is accompanied by increased cell proliferation and survival in the hippocampus of rodents (4–6); effects that are mediated, in part, by increased production and secretion of BDNF and its receptor tyrosine kinase trkB (7, 8).

Aerobic exercise training increases gray and white matter volume in the prefrontal cortex (9) of older adults and increases the functioning of key nodes in the executive control network (10, 11). Greater amounts of physical activity are associated with sparing of prefrontal and temporal brain regions over a 9-y period, which reduces the risk for cognitive impairment (12). Further, hippocampal and medial temporal lobe volumes are larger in higher-fit older adults (13, 14), and larger hippocampal volumes mediate improvements in spatial memory (13). Exercise training increases cerebral blood volume (15) and perfusion of the hippocampus (16), but the extent to which exercise can modify the size of the hippocampus in late adulthood remains unknown.

To evaluate whether exercise training increases the size of the hippocampus and improves spatial memory, we designed a single-blind, randomized controlled trial in which adults were randomly assigned to receive either moderate-intensity aerobic exercise 3 d/wk or stretching and toning exercises that served as a control. We predicted that 1 y of moderate-intensity exercise would increase the size of the hippocampus and that change in hippocampal volume would be associated with increased serum BDNF and improved memory function.

Previous SectionNext Section

Results

Aerobic Exercise Training Selectively Increases Hippocampal Volume.

One hundred twenty older adults without dementia (Table 1) were randomly assigned to an aerobic exercise group (n = 60) or to a stretching control group (n = 60). Magnetic resonance images were collected before the intervention, after 6 mo, and again after the completion of the program. The groups did not differ at baseline in hippocampal volume or attendance rates (Table 2 and *SI Results*). We found that the exercise intervention was effective at increasing the size of the hippocampus. That is, the aerobic exercise group demonstrated an increase in volume of the left and right hippocampus by 2.12% and 1.97%, respectively, over the 1-y period, whereas the stretching control group displayed a 1.40% and 1.43% decline over this same interval (Fig. 1*A*). The moderating effect of aerobic exercise on hippocampal volume loss was confirmed by a significant Time × Group interaction for both the left [$F(2,114) = 8.25$; $P < 0.001$; $\eta_p 2 = 0.12$] and right [$F(2,114) = 10.41$; $P < 0.001$; $\eta_p 2 = 0.15$] hippocampus (see Table 2 for all means and SDs).

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Table 1.

Characteristics for the aerobic exercise and stretching control groups

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Table 2.

Means (SD) for both groups at all three time points

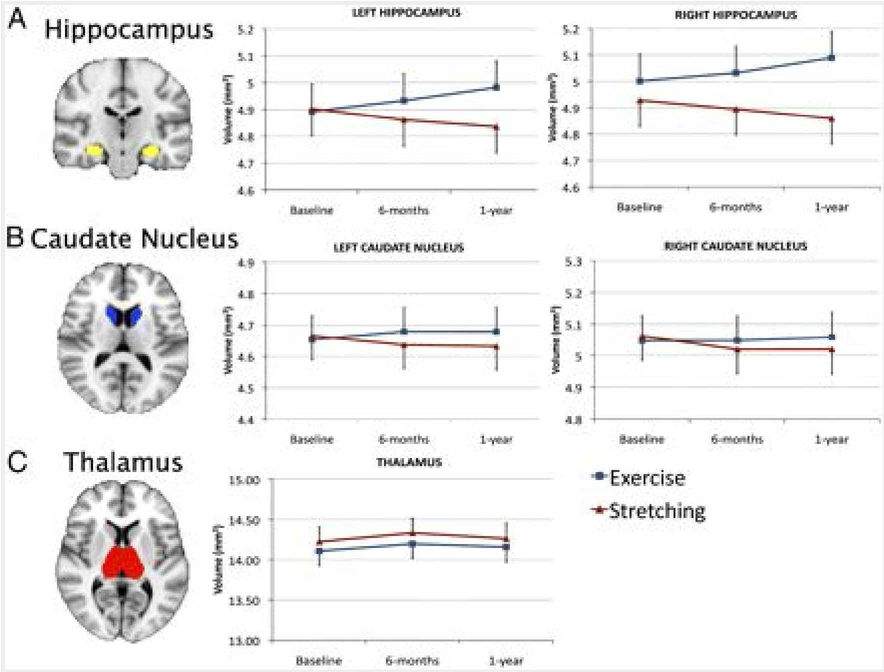

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Fig. 1.

(*A*) Example of hippocampus segmentation and graphs demonstrating an increase in hippocampus volume for the aerobic exercise group and a decrease in volume for the stretching control group. The Time × Group interaction was significant ($P < 0.001$) for both left and right regions. (*B*) Example of caudate nucleus segmentation and graphs demonstrating the changes in volume for both groups. Although the exercise group showed an attenuation of decline, this did not reach significance (both $P > 0.10$). (*C*) Example of thalamus segmentation and graph demonstrating the change in volume for both groups. None of the changes were significant for the thalamus. Error bars represent SEM.

As can be seen in Fig. 2, we found that aerobic exercise selectively increased the volume of the anterior hippocampus that included the dentate gyrus, where cell proliferation occurs (4, 6, 8), as well as subiculum and CA1 subfields, but had a minimal effect on the volume of the posterior section. Cells in the anterior hippocampus mediate acquisition of spatial memory (17) and show more age-related atrophy compared with the tail of the hippocampus (18, 19). The selective effect of aerobic exercise on the anterior hippocampus was confirmed by a significant Time × Group × Region interaction for both the left [$F(2,114) = 4.05$; $P < 0.02$; $\eta_{p}2 = 0.06$] and right [$F(2,114) = 4.67$; $P < 0.01$; $\eta_{p}2 = 0.07$] hippocampus. As revealed by *t*tests, the aerobic exercise group showed an increase in anterior hippocampus volume from baseline to after intervention [left: $t(2,58) = 3.38$; $P < 0.001$; right: $t(2,58) = 4.33$; $P < 0.001$] but demonstrated no change in the volume of the posterior hippocampus (both $P > 0.10$). In contrast, the stretching control group demonstrated a selective decline in volume from baseline to after intervention for the anterior hippocampus [left: $t(2,58) = −3.07$; $P < 0.003$; right: $t(2,58) = −2.45$; $P < 0.01$] but no significant change in volume for the posterior hippocampus (both $P > 0.20$).

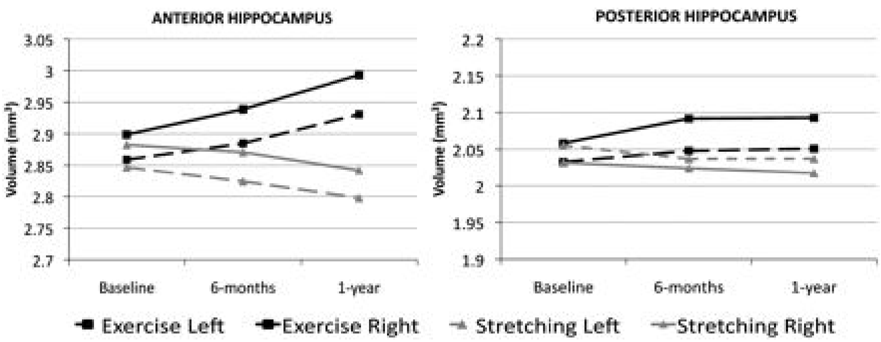

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Fig. 2.

The exercise group showed a selective increase in the anterior hippocampus and no change in the posterior hippocampus. See Table 2 for Means and SDs.

The regional specificity of the intervention was investigated further by examining two regions that served as control: thalamus and caudate nucleus. The volume of the thalamus increased for both the aerobic exercise and stretching groups (Fig. 1*C*), but this increase was not significant [$F(2,114) = 0.65$; $P < 0.52$]. Aerobic exercise did not moderate the increase in thalamic volume, as demonstrated by a nonsignificant Time × Group interaction [$F(2,114) = 0.24$; $P < 0.80$]. The volume of both the left and right caudate nucleus declined (Fig. 1*B*), but only for the stretching group. Aerobic exercise attenuated the loss of volume, although the Time × Group interaction was not significant for either the left [$F(2,114) = 2.25$; $P < 0.11$; $\eta_p2 = 0.03$] or right [$F(2,114) = 1.63$; $P < 0.19$; $\eta_p2 = 0.02$] hemispheres.

Our results demonstrate that the size of the hippocampus is modifiable in late adulthood and that moderate-intensity aerobic exercise is effective at reversing volume loss. Increased volume with exercise occurred in a selective fashion, influencing the anterior hippocampus but not the posterior hippocampus or the thalamus or caudate nucleus.

Changes in Fitness Are Associated with Increased Hippocampal Volume.

The intervention was effective at increasing aerobic fitness levels. The aerobic exercise group showed a 7.78% improvement in maximal oxygen consumption (VO_2 max) after the intervention, whereas the stretching control group showed a 1.11% improvement in VO_2 max (Table 1). This difference between the groups was confirmed by a Time × Group interaction [$F(2,111) = 4.42$; $P < 0.01$; $\eta_p2 = 0.07$]. We examined whether improvements in fitness levels were associated with the magnitude of the change in hippocampal volume. To test this, we ran correlations between change in aerobic fitness levels and change in hippocampal volume, collapsing across both groups of participants. We found that greater improvements in aerobic fitness level over the 1-y interval were associated with greater increases in hippocampal volume for the left ($r = 0.37$; $P < 0.001$) and right ($r = 0.40$; $P < 0.001$) hemispheres, suggesting that larger changes in fitness translate to larger changes in volume (Fig. 3 *A* and *B*). This result is consistent with several rodent studies of exercise on neurogenesis and BDNF (20, 21). Improvements in VO_2 max were correlated with increases in both anterior (left: $r = 0.28$; $P < 0.001$; right: $r = 0.51$; $P < 0.001$) and posterior (left: $r = 0.32$; $P < 0.001$; right: $r = 0.39$; $P < 0.001$) hippocampal regions, indicating that changes in aerobic fitness have a global influence on hippocampal volume. Correlations between changes in VO2 max and change in caudate nucleus and thalamic volumes were not significant (all $r < 0.14$; $P > 0.10$).

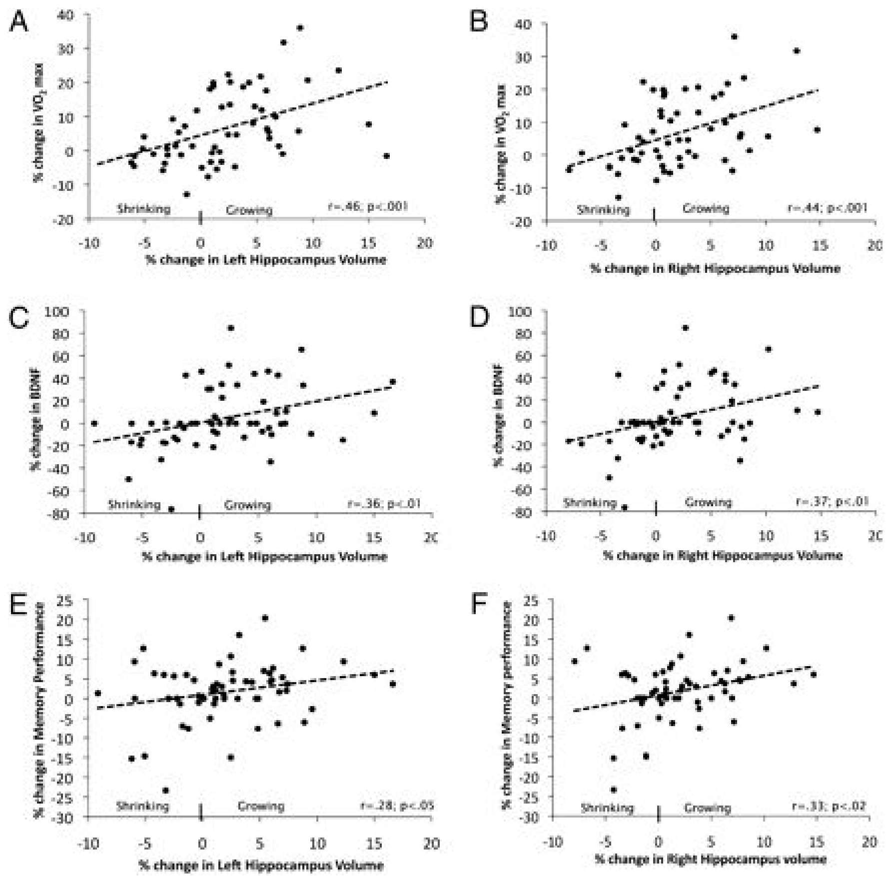

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Fig. 3.

All scatterplots are of the aerobic exercise group only because it was the only group that showed an increase in volume across the intervention. (*A* and *B*) Scatterplots of the association between percent change in left and right hippocampus volume and percent change in aerobic fitness level from baseline to after intervention. (*C* and *D*) Scatterplots of percent change in left and right hippocampus volume and percent change in BDNF levels. (*E* and *F*) Scatterplots of percent change in left and right hippocampus and percent change in memory performance.

We reasoned that if higher physical fitness is protective against the loss of brain tissue, then higher fitness levels at baseline would be predictive of less volume loss over the 1-y period. We examined the participants that declined in volume in the stretching group to test this hypothesis, because the stretching group, and not the aerobic exercise group, showed a decline in hippocampal volume over the 1-y interval. We found results partially consistent with this prediction. That is, higher fitness levels at baseline were associated with less hippocampal volume loss over the 1-y interval, for the right ($r = 0.50$; $P < 0.002$) but not for the left ($r = 0.17$; $P < 0.30$) hippocampus. Further, consistent with our expectations, it was only the right anterior hippocampus ($r = 0.48$; $P < 0.003$) that was protected by higher fitness levels at baseline; the posterior hippocampus was not affected by baseline fitness ($r = 0.21$; $P > 0.20$).

BDNF Is Associated with Changes in Hippocampal Volume.

Exercise increases levels of BDNF in the hippocampus (5, 7, 20), which, along with the trkB receptor, is considered to be a partial mediator of the enhancing effect of exercise on learning and memory (7, 8). BDNF can be measured in serum, and higher serum levels of BDNF are associated with both better memory function and larger hippocampal volumes (22). Here, we examined whether 1 y of aerobic exercise would change circulating levels of BDNF and whether increased hippocampal volume would be correlated with changes in BDNF. The aerobic exercise group did not demonstrate greater changes in serum BDNF levels compared with the stretching group, as indicated by a nonsignificant Time × Group interaction [$F(1,97) = 1.42$; $P < 0.23$; $\eta_p2 = 0.01$]. We reasoned, however, that because BDNF mediates cell proliferation in the dentate gyrus of the hippocampus, increased hippocampal volume could be associated with increased levels of serum BDNF. Because the aerobic exercise group was the only group to show an increase in volume over the 1-y period, we ran a correlation between change in BDNF and change in hippocampal volume for the aerobic exercise group to test this hypothesis. We found that greater changes in serum BDNF were associated with greater increases in volume for the left ($r = 0.36$; $P < 0.01$) and for the right ($r = 0.37$; $P < 0.01$) hippocampus (Fig. 3 *C* and *D*). Further, these effects were selective for the left ($r = 0.30$; $P < 0.03$) and right anterior hippocampus ($r = 0.27$; $P < 0.04$) and only marginal with the left ($r = 0.25$; $P < 0.06$) and right ($r = 0.22$; $P < 0.08$) posterior hippocampus. There were no associations between changes in serum

BDNF and changes in caudate nucleus or thalamus volumes (all $P > 0.50$); nor were there any associations between hippocampal volume and serum BDNF for the stretching control group (all $P > 0.40$). This indicates that exercise-induced increases in BDNF are selectively related to the changes in anterior hippocampal volume resulting from aerobic exercise.

Hippocampal Volume Is Related to Improvements in Spatial Memory.

Spatial memory (13, 22) was tested on both exercise and stretching groups at baseline, after 6 mo, and again after the completion of the 1-y intervention to determine whether changes in hippocampal volume translate to improved memory. Both groups showed improvements in memory, as demonstrated by significant increases in accuracy between the first and last testing sessions for the aerobic exercise [$t(2,51) = 2.08$; $P < 0.05$] and the stretching control [$t(2,54) = 4.41$; $P < 0.001$] groups. Response times also became faster for both groups between the baseline and postintervention sessions (all $P < 0.01$), indicating that improvements in accuracy were not caused by changes in speed–accuracy tradeoff. However, the aerobic exercise group did not improve performance above that achieved by the stretching control group, as demonstrated by a nonsignificant Time × Group interaction [$F(1,102) = 0.67$; $P < 0.40$; $\eta_p2 = 0.007$]. Nonetheless, we found that higher aerobic fitness levels at baseline ($r = 0.31$; $P < 0.001$) and after intervention ($r = 0.28$; $P < 0.004$) were associated with better memory performance on the spatial memory task. Change in aerobic fitness levels from baseline to after intervention, however, was not related to improvements in memory for either the entire sample ($r = 0.15$; $P < 0.12$) or when considering each group separately (both $P > 0.05$). Furthermore, changes in BDNF were not associated with improvements in memory function for either group ($r < 0.15$; $P > 0.20$). On the other hand, larger left and right hippocampi at baseline (both $P < 0.005$) and after intervention (both $P < 0.005$) were associated with better memory performance (12). Therefore, we reasoned that increased hippocampal volume after the exercise intervention should translate to improved memory function. In support of this hypothesis, we found that, in the aerobic exercise group, increased hippocampal volume was directly related to improvements in memory performance. The correlation between improvement in memory and hippocampal volume reached significance for left ($r = 0.23$; $P < 0.05$) and right ($r = 0.29$; $P < 0.02$) hemispheres (Fig. 3 *E* and *F*). This indicates that increases in hippocampal volume after 1 y of exercise augments memory function in late adulthood. In contrast, changes in caudate nucleus and thalamus volumes were unrelated to changes in memory performance for either group (all $P > 0.10$).

Previous SectionNext Section

Discussion

Hippocampal volume shrinks 1–2% annually in older adults without dementia (1), and this loss of volume increases the risk for developing cognitive impairment (2). We find results consistent with this pattern, such that the stretching control group demonstrated a 1.4% decline in volume over the 1-y interval. With escalating health care costs and an increased proportion of people aged >65 y, it is imperative that low-cost, accessible preventions and treatments for brain tissue loss are discovered. In this randomized controlled study of exercise training, we demonstrate that loss of hippocampal volume in late adulthood is not inevitable and can be reversed with moderate-intensity exercise. A 1-y aerobic exercise intervention was effective at increasing hippocampal volume by 2% and offsetting the deterioration associated with aging. Because hippocampal volume shrinks 1–2% annually, a 2% increase in hippocampal volume is equivalent to adding between 1 and 2 y worth of volume to the hippocampus for this age group.

On the basis of the several regions we examined, the effect of exercise was rather selective, influencing only the anterior hippocampus and neither the thalamus nor the caudate nucleus. This indicates that exercise does not influence all brain regions uniformly. In fact, research from human cognitive studies and rodents indicates some specificity, such that exercise influences some brain regions and behaviors but has minimal influence on others (3, 5, 9, 12, 20, 21, 23–25). Such selectivity suggests that there are regionally dependent molecular pathways influenced by exercise. In fact, we found here that changes in serum BDNF levels were associated with changes in anterior hippocampal volume; an important link because the hippocampus is rich in BDNF, and BDNF levels increase with exercise treatments in both rodents (5, 7, 20) and humans (26, 27). BDNF is a putative mediator of neurogenesis and contributes to dendritic expansion (28, 29) and is also critical in memory formation (30–32). Our results suggest that cell proliferation or increased dendritic branching might explain increased hippocampal volume and improvements in memory after exercise; however, increased vascularization (15, 16, 33) and dendritic complexity (34) may also be contributing to increased volume.

Aerobic exercise increased anterior hippocampal volume but had little effect on the posterior hippocampus. Neurons in the anterior hippocampus are selectively associated with spatial memory acquisition (17) and show exacerbated age-related atrophy compared with the posterior hippocampus (18, 19). It is possible that regions demonstrating less age-related decay might also be less amenable to growth. Thus, aerobic exercise might elicit the greatest changes in regions that show the most precipitous decline in late adulthood, such as the anterior hippocampus and prefrontal cortex (9). Overall, these data suggest that the anterior hippocampus remains amenable to augmentation.

In sum, we found that the hippocampus remains plastic in late adulthood and that 1 y of aerobic exercise was sufficient for enhancing volume. Increased hippocampal volume translates to improved memory function and higher serum BDNF. We also demonstrate that higher fitness levels are protective against loss of hippocampal volume. These results clearly indicate that aerobic exercise is neuroprotective and that starting an exercise regimen later in life is not futile for either enhancing cognition or augmenting brain volume.