



Physical Exercise Habits Correlate with Gray Matter Volume of the Hippocampus in Healthy Adult Humans

Citation

Killgore, William D. S., Elizabeth A. Olson, and Mareen Weber. 2013. "Physical Exercise Habits Correlate with Gray Matter Volume of the Hippocampus in Healthy Adult Humans." *Scientific Reports* 3 (1): 3457. doi:10.1038/srep03457. <http://dx.doi.org/10.1038/srep03457>.

Published Version

doi:10.1038/srep03457

Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:11879356>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)



OPEN

Physical Exercise Habits Correlate with Gray Matter Volume of the Hippocampus in Healthy Adult Humans

SUBJECT AREAS:
REGENERATION AND
REPAIR IN THE NERVOUS
SYSTEM
COGNITIVE AGEING
BRAIN

William D. S. Killgore, Elizabeth A. Olson & Mareen Weber

Social, Cognitive and Affective Neuroscience Lab, McLean Hospital, Harvard Medical School.

Received
7 October 2013

Accepted
20 November 2013

Published
12 December 2013

Correspondence and
requests for materials
should be addressed to
W.D.S.K. (Killgore@
mclean.harvard.edu)

Physical activity facilitates neurogenesis of dentate cells in the rodent hippocampus, a brain region critical for memory formation and spatial representation. Recent findings in humans also suggest that aerobic exercise can lead to increased hippocampal volume and enhanced cognitive functioning in children and elderly adults. However, the association between physical activity and hippocampal volume during the period from early adulthood through middle age has not been effectively explored. Here, we correlated the number of minutes of self-reported exercise per week with gray matter volume of the hippocampus using voxel-based morphometry (VBM) in 61 healthy adults ranging from 18 to 45 years of age. After controlling for age, gender, and total brain volume, total minutes of weekly exercise correlated significantly with volume of the right hippocampus. Findings highlight the relationship between regular physical exercise and brain structure during early to middle adulthood.

The human brain is in a constant state of morphological change. Throughout the lifespan new neurons may be formed while others will die¹, some dendrites will branch while others retract², and new synapses are created while others are eliminated^{3,4}. This dynamic remodeling of gray matter occurs against the backdrop of the more protracted process of axonal myelination, which forms the bulk of cerebral white matter⁵. While much of this remodeling is scripted by genetic factors⁶ and follows a fairly well-characterized developmental course from infancy through old age⁷⁻⁹, there is growing evidence that the organization and development of some cerebral systems is not purely hard-wired and can be significantly influenced by many non-genetic factors, including cognitive activity¹⁰, nutrition^{11,12}, and even physical exercise¹³⁻¹⁵.

Within the animal literature, physical exercise appears remarkably effective at facilitating some aspects of neural plasticity, particularly within the hippocampus, the brain region where the most significant expression of neurogenesis during adulthood has been observed¹⁶. Greater levels of physical exercise have been shown to increase the formation of new neurons^{17,18} and to expand dendritic complexity within the dentate gyrus of adult rodents¹⁹. Moreover, the beneficial effects of exercise on brain structure and function appear to translate to humans as well. For instance, adolescents with higher physical fitness levels also show greater gray matter volume within the hippocampus and achieve better scores on cognitive tests than their peers with poorer aerobic capacity^{14,20}. Similarly, physically fit elderly individuals also show larger volumes of the hippocampus and demonstrate correspondingly better memory performance²¹. Perhaps most importantly, older adults who are randomly assigned to engage in a regular aerobic exercise program show significant increases in hippocampal and cortical volumes and improved cognitive performance after a year relative to matched elderly participants in a non-exercise control group^{13,15}, suggesting a causal role of aerobic activity on remodeling critical brain tissues and connections. The underlying mechanisms associated with these changes still remain to be elucidated, but likely include increased blood flow and oxygenation to the hippocampus²², as well as increased production of brain neurotrophic factors and their receptors^{23,24}. At present, the evidence for the beneficial effects of physical exercise on increasing brain volume and enhancing cognition within developing children and older adults is quite convincing. However, there is a dearth of information regarding the association between physical exercise and brain structure within the years comprising early to middle adulthood. This lack of data for this age range is concerning, as it is perhaps the period of greatest vocational productivity, family investment, and effortful contribution to society during the human lifespan.

Here, we examined the correlation between physical exercise and gray matter volume within the hippocampus among healthy adults in the second through fifth decades of life. Participants underwent structural magnetic resonance imaging (MRI) and completed questionnaires about their exercise habits, including the frequency and



duration of typical workouts during a given week. Using voxel-based morphometry (VBM), the exercise variables were entered into a series of multiple regression analyses to predict gray matter volume within the hippocampus, after controlling for age, gender, and total brain volume. It was hypothesized that the number of minutes of exercise per week would be positively correlated with left and right hippocampal volumes.

Results

Exercise levels. Overall, 46 (75%) of participants indicated that they engaged in some regular form of exercise, while 15 (25%) did not. The ratio of men (72.7%) to women (78.6%) who exercised routinely was not significantly different, $\chi^2 = 0.28$, $p = .60$. Participants reported working out an average of 3.16 *Sessions Per Week* ($SD = 2.31$), with the frequency ranging from 0 to 7 workouts during a typical week. On average, participants reported that they worked out 45.00 *Minutes Per Session* ($SD = 36.40$), with sessions ranging from 0 to 120 minutes in duration. Finally, the mean calculated total *Minutes Per Week* of exercise per individual was 189.06 ($SD = 189.45$), and ranged from 0 to 840 minutes.

Total hippocampal volume correlations. We correlated the extracted hippocampal volumes with each of the exercise measures, controlling for age and gender. The number of exercise *Sessions Per Week* was not significantly correlated with either left (partial $r = .204$, $p = .120$) or right (partial $r = .143$, $p = .279$) hippocampal volume. The number of *Minutes Per Session* was marginally correlated with the volume of the left (partial $r = .245$, $p = .061$) and right (partial $r = .254$, $p = .052$) hippocampus, but only at a non-significant trend level. However, when these two variables were combined, there was a significant correlation between the number of *Minutes Per Week* of exercise and the volume of both left (partial $r = .310$, $p = .017$) and right (partial $r = .305$, $p = .019$) hippocampus (see Figure 1).

As a control region, we extracted the volume estimates from the right and left thalamus, which have previously been found to be unrelated to physical exercise¹⁵. As expected, the number of exercise *Sessions Per Week* was not correlated with either left (partial $r = .132$, $p = .320$) or right (partial $r = -.031$, $p = .814$) thalamic volume estimates. Similarly, the number of *Minutes Per Session* was also not correlated with left (partial $r = .173$, $p = .189$) or right (partial $r = .018$, $p = .895$) thalamus. Finally, the number of *Minutes Per Week* of exercise was also unrelated to the volume of the thalamus on either the left (partial $r = .218$, $p = .097$) or right (partial $r = .079$, $p = .552$).

Voxel-wise hippocampal correlations. To further explore the association between exercise variables and hippocampal volume, we conducted a voxel-wise analysis of gray matter volume within two search territories defined by the hippocampal ROIs. These analyses were corrected for multiple comparisons within the volume of the hippocampus. For this analysis, there were no correlated voxels within either the left or right hippocampus for *Sessions Per Week* or *Minutes Per Session*. Additionally, no voxels survived correction for multiple comparisons within left hippocampus for the number of exercise *Minutes Per Week*. There was, however, a cluster of 21 voxels within the right hippocampus (MNI: $x = 27$, $y = -7$, $z = -21$; $T_{57} = 3.38$; $p = .072$, FWE corrected) where the gray matter volume showed a significant correlation with the number of *Minutes Per Week* of exercise (see Figure 2). There were no voxels within either hippocampus showing a negative correlation between physical exercise and gray matter volume.

As a control region, the left and right thalamus were also examined using a voxel-wise analysis constrained to the anatomically defined ROIs, with appropriate small volume correction for multiple comparisons. As expected, no voxels within either thalamus were found to correlate with *Sessions Per Week*, *Minutes Per Session*, or *Minutes Per Week* of exercise.

Exploratory voxel-wise whole brain correlations. To provide additional information beyond the a priori hypothesized ROIs, we also conducted a series of exploratory whole-brain voxel-wise correlational analyses. Applying an FWE cluster correction ($p < .05$) across the entire brain, we found that neither the number of exercise *Sessions Per Week* nor the number of *Minutes Per Session* of exercise were associated with any gray matter volume differences. However, as evident in Figure 3, we did find that the number of *Minutes Per Week* of exercise was positively correlated with larger gray matter volume within a cluster of 1047 voxels located within the left posterior insula (MNI: $x = -51$, $y = -21$, $z = 12$; $T_{57} = 4.23$; $p = .015$, cluster-wise FWE). For this analysis, there were no clusters showing negative correlations with any of the exercise variables.

Discussion

Better aerobic fitness has been reliably associated with increased hippocampal volume and improved cognitive functioning in developing children¹⁴ and elderly adults¹⁵, but almost no data are available concerning this relationship in healthy early to middle aged adults. We therefore examined the association between self-reported exer-

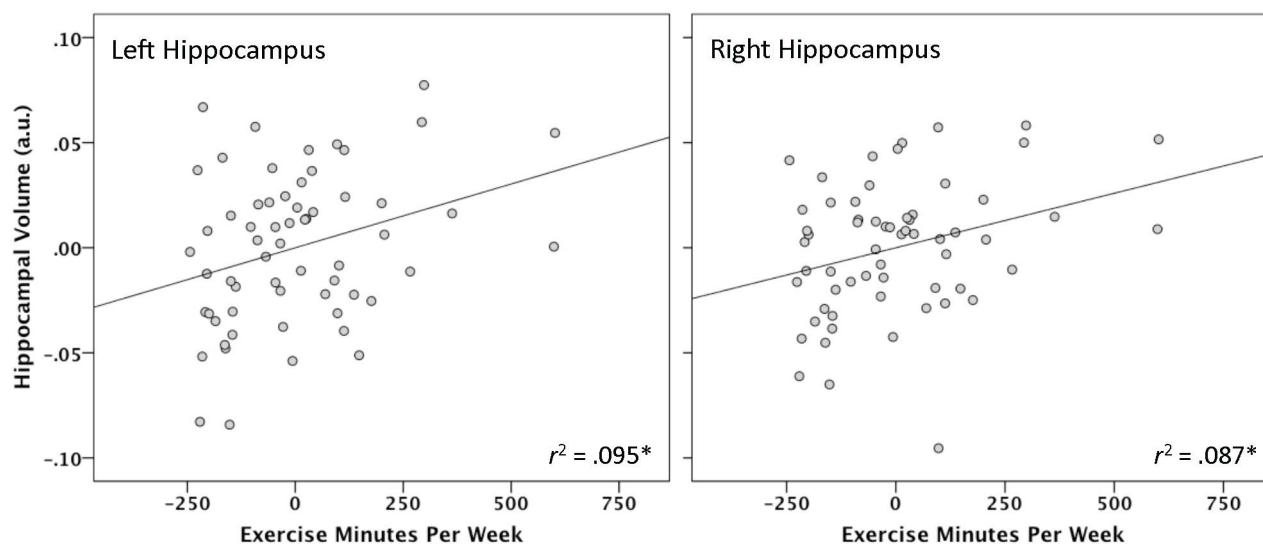


Figure 1 | Partial correlation plots showing the positive association between the residualized values for the mean number of minutes of exercise per week and the residualized modulated volume data extracted from each hippocampus after controlling for age and gender (* $p < .05$).

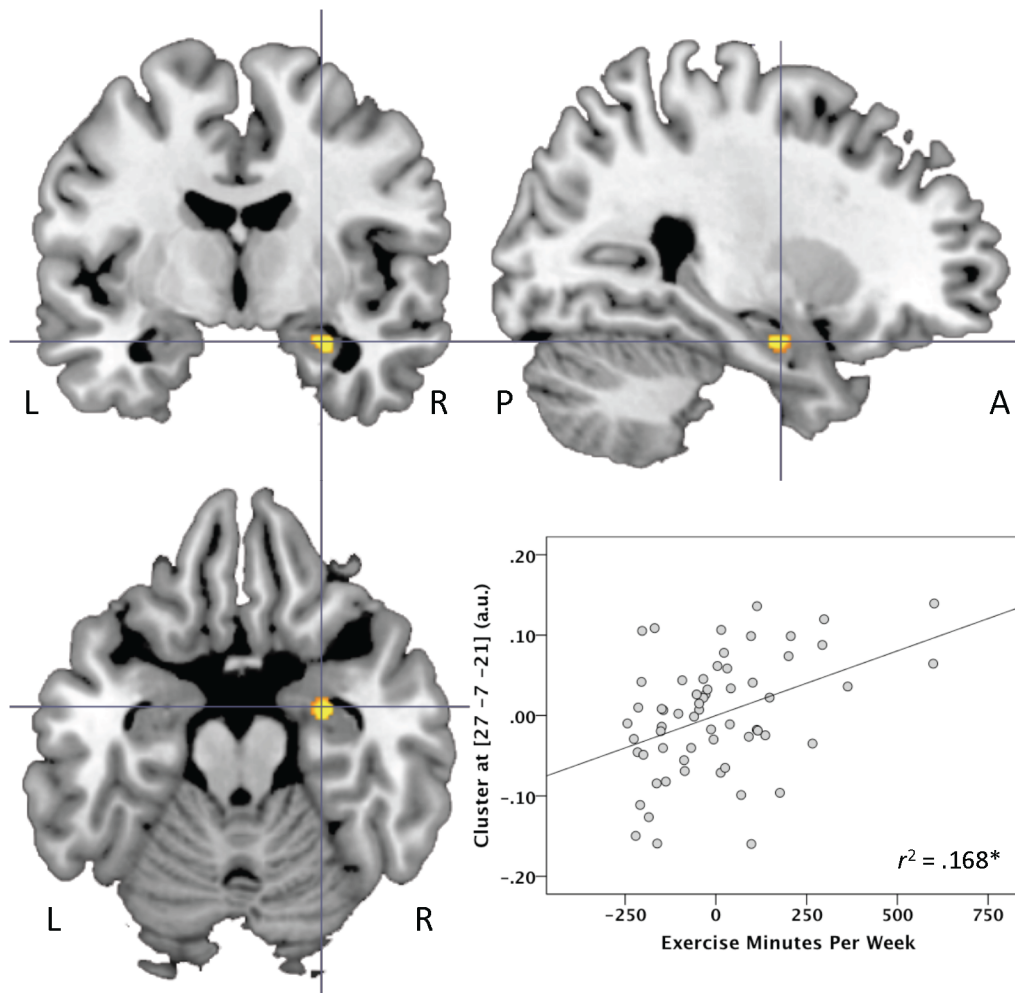


Figure 2 | The figure shows the coronal (upper left), sagittal (upper right), and axial (lower left) slices highlighting the location of a cluster of 21 voxels within the right hippocampus (MNI: $x = 27, y = -7, z = -21$) where the tissue volume showed a significant correlation with the number of *Minutes Per Week* of exercise, after small volume correction for multiple comparisons ($*p < .10$, FWE). For visualization purposes, the scatterplot (lower right) shows the significant association between the residualized values for the mean number of minutes of exercise per week and the mean extracted data from the significant cluster in the hippocampus after controlling for age and gender.

cise levels and gray matter volume of the hippocampus among adults ranging in age from 18 to 45. First, using a standardized atlas-based extraction of non-linearly modulated normalized VBM gray matter volume estimates, we found that the total gray volume measures within the left and right hippocampal regions were significantly positively correlated with the total number of minutes of weekly physical exercise, but not with the number of workouts per week or the number of minutes of exercise per workout session when considered individually. On the other hand, volume estimates for the left and right thalamus, which served as control regions, were unrelated to exercise variables. Second, to provide better spatial localization and statistical control, we conducted a voxel-wise analysis of gray matter volume within each hippocampal ROI, correcting for family-wise error within the search territories, and found that a small region of the right anterior hippocampus was significantly positively correlated with the number of minutes of exercise reported per week, but not with the frequency of workouts or typical session duration. Finally, we conducted an exploratory whole-brain VBM analysis correlating each of the exercise variables with gray matter volume. After correcting for multiple comparisons, only a single region of the left posterior insula showed a positive association between weekly total minutes of exercise and gray matter volume. These findings are consistent with the association between physical exercise and hippocampal volume that is well established in developmental and geriatric

samples, but the present data further extend that work by showing that these associations are robust even during the developmentally stable period of early to middle adulthood and may include other regions such as the posterior insula.

The causal role of exercise in modifying hippocampal neuroplasticity has been well documented in the animal literature²⁵. Numerous studies have demonstrated that increased wheel-running in mice leads to enhanced neurogenesis, cell survival, dendritic complexity, and long-term potentiation within the dentate gyrus^{17,18,26,27}. These neural changes are due, in part, to an increase in the production of brain derived neurotrophic factor (BDNF)²⁴ and its associated receptor tyrosine kinase *trkB*²³. Moreover, exercise and the accompanying brain changes are also associated with enhanced cognition and memory performance in rodents^{28,29}. For instance, wheel-running was associated with enhanced spatial learning and retention in the Morris water maze^{18,29}, and leads to improved discrimination of spatial location among adjacent stimuli with identical physical appearance³⁰. Together these findings suggest a strong link between increased physical activity, hippocampal growth, and cognitive functioning in animal models.

The benefits of exercise on brain structure and cognition extend to humans as well. Accumulating research suggests that physical exercise increases hippocampal volume in humans and leads to concomitant enhancement of cognitive functioning. However, most studies

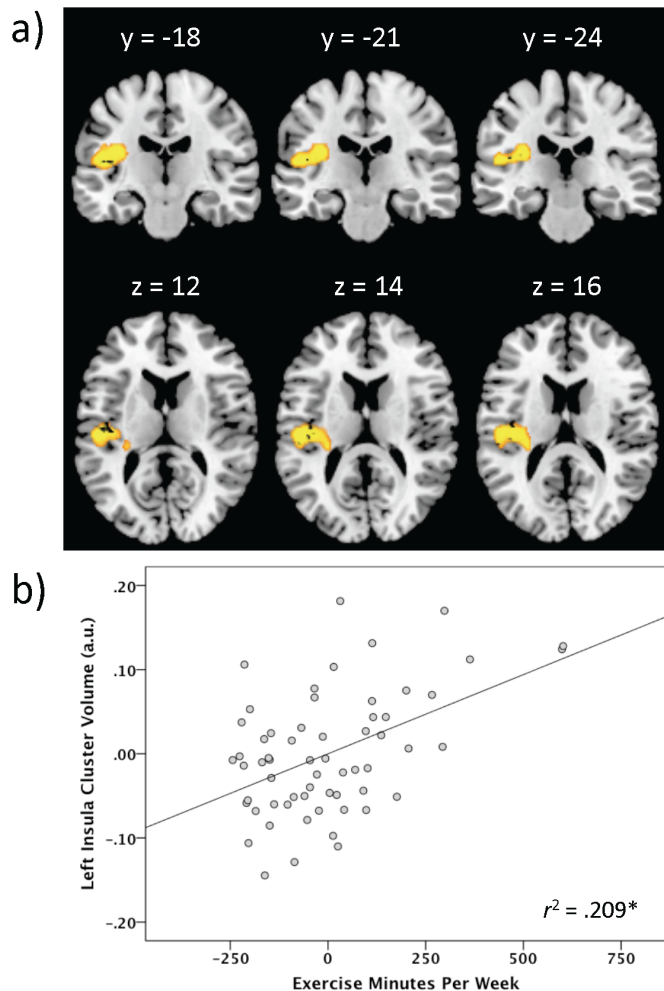


Figure 3 | (a) The figure shows the spatial location of a large cluster of 1047 voxels where there was a significant association between the number of *Minutes Per Week* of exercise and the mean gray matter volume within the left posterior insula (MNI: $x = -51$, $y = -21$, $z = 12$; $*p < .05$ cluster corrected). The top three slices show the cluster in the coronal view and the bottom three slices show it in the axial view. (b) For illustrative purposes only, the scatterplot shows the linear association between the residualized number of *Minutes Per Week* of exercise and the mean gray matter volume within the left posterior insula cluster.

of the effects of exercise on brain structure and function have examined either children, adolescent, or elderly populations. For instance, correlational studies have shown that physical fitness levels among preadolescent children are associated with larger hippocampal volumes, which in turn correlate with greater relational memory performance¹⁴. Similarly, adolescents with higher fitness levels also show larger volumes of the hippocampus, which correlates with greater learning of visuospatial information²⁰. While existing neuroimaging research among children and adolescents is primarily correlational, a growing number of studies have demonstrated a causal connection between exercise and hippocampal volume in older adults. Whereas the hippocampus typically declines in volume at a rate of about 1 to 2% each year after the fifth decade of life in healthy adults³¹, regular aerobic activity may provide a significant protective effect that can eliminate or even reverse this shrinkage of the hippocampus^{15,21} and medial temporal lobe regions³². For example, one year of aerobic exercise training halted this decline in healthy older adults and was associated with an increase in hippocampal volume by approximately 2%, a finding that has also correlated with improved memory performance¹⁵. Aerobic training is also effective at increasing

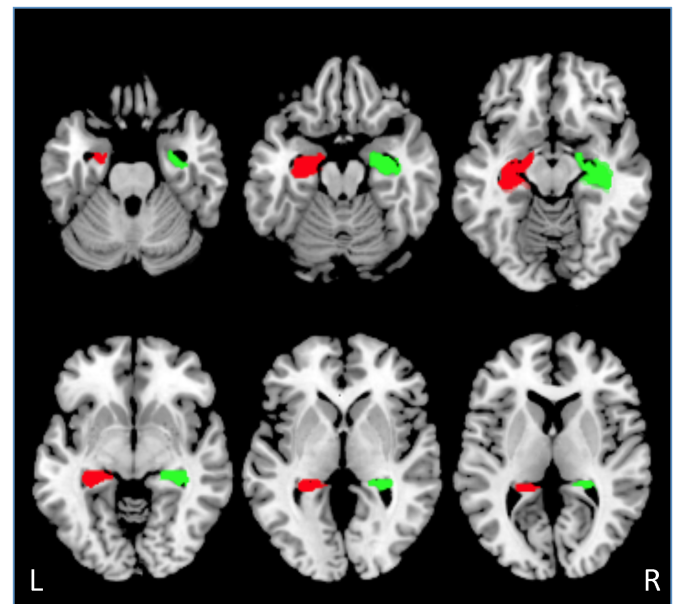


Figure 4 | Axial views showing the left (red) and right (green) hippocampal regions of interest (ROIs) as defined by the Automated Anatomical Labeling (AAL) Atlas⁵⁰ within the Wake Forest University PickAtlas Utility for SPM8⁵¹.

overall brain tissue volume¹³ and is associated with improved cognitive functioning among older adults³³. Thus, the accumulating evidence strongly suggests that regular physical exercise is associated with increased hippocampal volume and enhanced cognitive functioning among developing children and the elderly.

In contrast to the burgeoning literature examining the effects of exercise on brain structure and function in the early and later years of life, studies examining these relationships in healthy younger to middle aged adults are presently few in number. To our knowledge, this is the first study of the association between physical exercise and hippocampal volume among healthy individuals during the second through fifth decades of life, a period when total cortical gray matter volumes are typically much more stabilized and show gradual decline relative to the dynamic reductions that occur during the early and late life periods^{34,35}. We found that the reported number of minutes of exercise per week was significantly correlated with hippocampal volume, particularly within a small region of the right anterior hippocampus. It is noteworthy that the region where exercise appears to correlate with hippocampal volume corresponds roughly to the spatial location of the dentate gyrus, the primary region where hippocampal neurogenesis has been well established to occur¹⁶. Our findings are consistent with other preliminary work showing that regular exercise training was associated with increased cerebral blood volume (CBV) within the dentate gyrus of healthy adults, a finding that was interpreted as evidence of increased neurogenesis²². When considered in light of existing findings, the present results suggest that physical exercise is not only beneficial for supporting brain and cognitive development in children and adolescents and staving off brain degeneration in older age, but may also be associated with improved structure and function within the years of early and middle adulthood. For many, this phase of life represents a period dedicated to intense formal higher education, interpersonal and family investment, sustained work productivity, and professional achievement. It is not difficult to conceive of the potential benefits of maximizing natural brain architecture and cognitive performance through optimized levels of physical exercise and other health-promoting behaviors during this phase of life.

Finally, to contribute to the general body of knowledge and subsequent hypothesis generation, we also conducted an exploratory



corrected whole-brain analysis without a priori hypotheses. In that analysis, we found that physical exercise was positively correlated with gray matter volume within a region of the posterior left insula. Interestingly, several studies have suggested that gray matter volume within the insular region may be specifically affected by physical exercise. The insular cortex is believed to play a role in “cardiovascular control” or “central cardiovascular command,” the regulation of physiological processes such as heart rate and arterial blood pressure³⁶. A recent study suggested that greater aerobic capacity in humans was positively correlated with gray matter density within insular cortex³⁷, although their findings were localized toward the anterior regions and lateralized to the right. Aerobic activity appears to be protective against volume loss in the insula, which is often observed among sedentary non-exercising individuals³⁸. Other findings have also shown greater insular volume in long-term practitioners of Tai Chi Chuan³⁹ and following a year of twice-weekly resistance training⁴⁰. The insular cortex is a complex brain region that plays a number of crucial roles in interoceptive awareness of physiological status⁴¹. The insula has been shown to contribute to a broad spectrum of human affective responses including visceral sensations that can predispose individuals to mood and anxiety disorders^{42,43} and sensations associated with attraction or repulsion to food stimuli^{44–46}. It is conceivable that exercise induced changes in insular gray matter volume could emerge as a profound mediating factor in a number of aspects of human emotional, motivational, and appetitive functions. Future research may explore the potential for these exercise induced neuroplastic effects to contribute to reducing the burden of emotional disorders and obesity.

Although the present findings are consistent with a growing number of studies suggesting a link between physical exercise and regional brain tissue volume, several weaknesses should also be considered. Perhaps the major limitation of this work was that exercise frequency and duration were estimated via one-time self-reports, which are likely to introduce some error into the data. Future work should incorporate daily exercise logs or some form of activity monitoring to remove this subjective element. Second, we focused exclusively on the frequency and number of minutes of exercise sessions, but did not further divide these data according to the type of exercise (e.g., aerobic versus resistance training) or general intensity level (e.g., walking versus running). It will be important to explore the effect of exercise type on gray matter volume in subsequent research. Finally, the use of VBM for measuring volumetric data is not without its limitations. While VBM is a valid and widely used methodology that provides exceptional consistency in the treatment of data across participants, it also loses some precision by convolving all datasets to a common template space. Alternative approaches that use expert traced or automated anatomical segmentation and parcellation methods should also be considered in future work. Despite these limitations, we believe that the present findings provide compelling data to suggest that greater levels of physical exercise are associated with larger volume of the hippocampus during the years of early to middle adulthood. The relation between these findings and healthy adult cognition deserve further exploration.

Methods

Participants. Sixty-one healthy right-handed adult volunteers (33 males; 28 females) ranging in age from 18 to 45 ($M = 30.5$ years, $SD = 8.1$) were recruited from the Boston metropolitan area to participate in a larger neuroimaging study. Participants were pre-screened via a detailed telephone questionnaire to exclude any history of Axis I psychiatric disorder, severe medical or neurological illness, moderate to severe head injury, current psychotropic medication use, or other drugs or substances that might affect functional neuroimaging. No attempt was made to select participants based on particular physical exercise habits or physical fitness level. The body mass index (BMI) of the sample ranged from 19.2 to 34.8 ($M = 24.6$, $SD = 3.4$). Participants provided written informed consent and were compensated for their time. This study was approved by the McLean Hospital Institutional Review Board. Separate data from a subset of this sample have been published elsewhere^{47–49}, but the correlations between physical exercise and brain volume are novel and have never before been reported.

Materials and procedure. Upon arrival at the laboratory, participants completed an information questionnaire about their daily routines, which included questions about exercise, diet, height, weight, and sleep habits. For the present report, two questions were of relevance. Participants indicated whether they routinely engaged in regular exercise (“Do you engage in regular exercise? YES, NO”), and if so, estimated the typical weekly frequency of workouts (i.e., “If ‘YES’: How many days per week do you exercise (circle one)? 1 2 3 4 5 6 7”, which was coded as *Sessions Per Week*) and the duration of typical workout sessions (i.e., “If ‘YES’: How many minutes per exercise session (on average): ___”, which was coded as *Minutes Per Session*). From these, we calculated the simple product of *Sessions Per Week* \times *Minutes Per Session* to determine the average *Minutes Per Week* of physical exercise. If participants did not routinely engage in regular exercise (i.e., endorsing “NO” to the question above), their physical exercise total was counted as zero. The threshold and specific nature of physical activity to be defined as “regular exercise” was left to the participant’s discretion. Exercise was not further subdivided by type (e.g., walking; stretching; aerobic; strength) or intensity level. After completion of the questionnaires, participants underwent an MRI scan.

MRI parameters. Structural MRI was collected on a 3.0 Tesla (SIEMENS Tim Trio, Erlangen, Germany) scanner, fitted with a 12-channel head coil. For each participant, a three-dimensional T1-weighted MPRAGE sequence (TR/TE/flip angle = 2.1 s/ 2.25 ms/12°) was obtained over 128 slices in the sagittal plane (256 \times 256 matrix). Slice thickness was 1.33 mm, yielding a voxel size of 1.33 mm \times 1 mm \times 1 mm.

Voxel-based morphometry (VBM). The brain images were analyzed using voxel-based morphometry in SPM8 (Wellcome Department of Imaging Neuroscience Group, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>), using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>). The default settings for a non-linearly modulated normalized VBM were used for preprocessing in VBM8. Essentially, the T1-weighted structural brain images were DARTEL-normalized to the standard stereotaxic space of the Montreal Neurological Institute (MNI) and resliced to 1.5 \times 1.5 \times 1.5 mm. We used the non-linear modulated normalization procedure. Following this procedure, tissue class images are produced in alignment with the MNI template, which are then multiplied by the non-linear component of the Jacobian determinant. Thus, this method applies a proportional scaling directly to the data to control for individual variability in brain size. The images were then segmented into tissue types of gray matter, white matter and cerebrospinal fluid. Data quality checks were also undertaken within VBM8 and no artifacts or outliers were identified. Finally, the normalized gray matter images were spatially smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

Statistical analysis. The analysis proceeded in several stages. First, we tested our a priori hypothesis that the volume of the hippocampus would correlate with physical exercise. This involved using the Region Extraction Tool (REX) to extract the mean values for the left and right hippocampi from the segmented, modulated, normalized gray matter images. The hippocampi were defined using a region of interest (ROI) approach utilizing masks created from the Automated Anatomical Labeling (AAL) Atlas⁵⁰ as implemented in the Wake Forest University PickAtlas Utility for SPM8⁵¹ (see Figure 4). Prior work in this area also included the thalamus as a control region because it was not expected to correlate with exercise¹⁵. Therefore, the same ROI procedure was used to identify and extract values from the left and right thalami, which were used as control regions in the analysis. Extracted mean values for each ROI from each individual were then entered into a partial correlation analysis with each of the three exercise variables (i.e., *Sessions per Week*, *Minutes per Session*, and *Minutes per Week*) in SPSS 20 for Macintosh, controlling for age and gender. Second, a voxel-wise analysis was undertaken in SPM8 to identify the specific regions of the hippocampus that showed the strongest correlation between gray matter volume and the physical exercise variables for each of the three exercise variables, with age and gender controlled. This analysis was constrained to the hippocampal ROIs and was family-wise error (FWE) corrected for voxel-wise multiple comparisons within the ROIs ($p < .10$). Due to the small size of the region of interest and the specific a priori hypotheses based on prior animal and human literature, we tested for significance at a slightly more liberal FWE correction threshold than for an unplanned comparison. Finally, we conducted an exploratory whole-brain voxel-wise analysis, correlating each of the three exercise variables with gray matter volume throughout the brain ($p < .05$, FWE cluster volume corrected).

- Spalding, K. L. *et al.* Dynamics of hippocampal neurogenesis in adult humans. *Cell* **153**, 1219–1227; doi:10.1016/j.cell.2013.05.002 (2013).
- Wong, R. O. & Ghosh, A. Activity-dependent regulation of dendritic growth and patterning. *Nat. Rev. Neurosci.* **3**, 803–812; doi:10.1038/nrn941 (2002).
- Cohen-Cory, S. The developing synapse: construction and modulation of synaptic structures and circuits. *Science* **298**, 770–776; doi:10.1126/science.1075510 (2002).
- Hua, J. Y. & Smith, S. J. Neural activity and the dynamics of central nervous system development. *Nat. Neurosci.* **7**, 327–332; doi:10.1038/nn1218 (2004).
- Casey, B. J., Tottenham, N., Liston, C. & Durston, S. Imaging the developing brain: what have we learned about cognitive development? *Trends Cogn Sci* **9**, 104–110; doi:10.1016/j.tics.2005.01.011 (2005).
- Thompson, P. M. *et al.* Genetic influences on brain structure. *Nat. Neurosci.* **4**, 1253–1258. (2001).



7. Giedd, J. N. *et al.* Brain development during childhood and adolescence: a longitudinal MRI study. *Nat. Neurosci.* **2**, 861–863 (1999).
8. Sowell, E. R. *et al.* Mapping cortical change across the human life span. *Nat. Neurosci.* **6**, 309–315; doi:10.1038/nn1008 (2003).
9. Toga, A. W., Thompson, P. M. & Sowell, E. R. Mapping brain maturation. *Trends Neurosci.* **29**, 148–159; doi:10.1016/j.tins.2006.01.007 (2006).
10. May, A. Experience-dependent structural plasticity in the adult human brain. *Trends Cogn Sci* **15**, 475–482; doi:10.1016/j.tics.2011.08.002 (2011).
11. Conklin, S. M. *et al.* Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neurosci. Lett.* **421**, 209–212; doi:10.1016/j.neulet.2007.04.086 (2007).
12. Taki, Y. *et al.* Breakfast staple types affect brain gray matter volume and cognitive function in healthy children. *PLoS ONE* **5**, e15213; doi:10.1371/journal.pone.0015213 (2010).
13. Colcombe, S. J. *et al.* Aerobic exercise training increases brain volume in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* **61**, 1166–1170 (2006).
14. Chaddock, L. *et al.* A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Res.* **1358**, 172–183; doi:10.1016/j.brainres.2010.08.049 (2010).
15. Erickson, K. I. *et al.* Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 3017–3022; doi:10.1073/pnas.1015950108 (2011).
16. Eriksson, P. S. *et al.* Neurogenesis in the adult human hippocampus. *Nat. Med.* **4**, 1313–1317; doi:10.1038/3305 (1998).
17. van Praag, H., Kempermann, G. & Gage, F. H. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* **2**, 266–270; doi:10.1038/6368 (1999).
18. van Praag, H., Shubert, T., Zhao, C. & Gage, F. H. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J. Neurosci.* **25**, 8680–8685; doi:10.1523/JNEUROSCI.1731-05.2005 (2005).
19. Redila, V. A. & Christie, B. R. Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. *Neuroscience* **137**, 1299–1307; doi:10.1016/j.neuroscience.2005.10.050 (2006).
20. Herting, M. M. & Nagel, B. J. Aerobic fitness relates to learning on a virtual Morris Water Task and hippocampal volume in adolescents. *Behav. Brain Res.* **233**, 517–525; doi:10.1016/j.bbr.2012.05.012 (2012).
21. Erickson, K. I. *et al.* Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus* **19**, 1030–1039; doi:10.1002/hipo.20547 (2009).
22. Pereira, A. C. *et al.* An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 5638–5643; doi:10.1073/pnas.0611721104 (2007).
23. Li, Y. *et al.* TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressant treatment. *Neuron* **59**, 399–412; doi:10.1016/j.neuron.2008.06.023 (2008).
24. Vaynman, S., Ying, Z. & Gomez-Pinilla, F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur. J. Neurosci.* **20**, 2580–2590; doi:10.1111/j.1460-9568.2004.03720.x (2004).
25. Cotman, C. W., Berchtold, N. C. & Christie, L. A. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci.* **30**, 464–472; doi:10.1016/j.tins.2007.06.011 (2007).
26. Eadie, B. D., Redila, V. A. & Christie, B. R. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J. Comp. Neurol.* **486**, 39–47; doi:10.1002/cne.20493 (2005).
27. van Praag, H., Christie, B. R., Sejnowski, T. J. & Gage, F. H. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. U. S. A.* **96**, 13427–13431 (1999).
28. Cetinkaya, C. *et al.* Positive effects of aerobic exercise on learning and memory functioning, which correlate with hippocampal IGF-1 increase in adolescent rats. *Neurosci. Lett.* **549**, 177–181; doi:10.1016/j.neulet.2013.06.012 (2013).
29. Gomes da Silva, S. *et al.* Early exercise promotes positive hippocampal plasticity and improves spatial memory in the adult life of rats. *Hippocampus* **22**, 347–358; doi:10.1002/hipo.20903 (2012).
30. Creer, D. J., Romberg, C., Saksida, L. M., van Praag, H. & Bussey, T. J. Running enhances spatial pattern separation in mice. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 2367–2372; doi:10.1073/pnas.0911725107 (2010).
31. Raz, N. *et al.* Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb. Cortex* **15**, 1676–1689; doi:10.1093/cercor/bhi044 (2005).
32. Bugg, J. M. & Head, D. Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiol. Aging* **32**, 506–514; doi:10.1016/j.neurobiolaging.2009.03.008 (2011).
33. Colcombe, S. & Kramer, A. F. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol. Sci.* **14**, 125–130 (2003).
34. Jernigan, T. L. *et al.* Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol. Aging* **22**, 581–594 (2001).
35. Whitford, T. J. *et al.* Brain maturation in adolescence: concurrent changes in neuroanatomy and neurophysiology. *Hum. Brain Mapp.* **28**, 228–237; doi:10.1002/hbm.20273 (2007).
36. Lanfranchi, P. A. & Somers, V. K. Arterial baroreflex function and cardiovascular variability: interactions and implications. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **283**, R815–826; doi:10.1152/ajpregu.00051.2002 (2002).
37. Peters, J. *et al.* Voxel-based morphometry reveals an association between aerobic capacity and grey matter density in the right anterior insula. *Neuroscience* **163**, 1102–1108; doi:10.1016/j.neuroscience.2009.07.030 (2009).
38. Gondoh, Y. *et al.* Effects of aerobic exercise training on brain structure and psychological well-being in young adults. *J. Sports Med. Phys. Fitness* **49**, 129–135 (2009).
39. Wei, G. X. *et al.* Can taichi reshape the brain? A brain morphometry study. *PLoS ONE* **8**, e61038; doi:10.1371/journal.pone.0061038 (2013).
40. Liu-Ambrose, T., Nagamatsu, L. S., Voss, M. W., Khan, K. M. & Handy, T. C. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. *Neurobiol. Aging* **33**, 1690–1698; doi:10.1016/j.neurobiolaging.2011.05.010 (2012).
41. Craig, A. D. Interoception: the sense of the physiological condition of the body. *Curr. Opin. Neurobiol.* **13**, 500–505 (2003).
42. Killgore, W. D. S. *et al.* Neural correlates of anxiety sensitivity during masked presentation of affective faces. *Depress. Anxiety*; doi:10.1002/da.20788 (2011).
43. Paulus, M. P. & Stein, M. B. An insular view of anxiety. *Biol. Psychiatry* **60**, 383–387 (2006).
44. Cornier, M. A., Melanson, E. L., Salzberg, A. K., Bechtell, J. L. & Tregellas, J. R. The effects of exercise on the neuronal response to food cues. *Physiol. Behav.* **105**, 1028–1034; doi:10.1016/j.physbeh.2011.11.023 (2012).
45. Evero, N., Hackett, L. C., Clark, R. D., Phelan, S. & Hagobian, T. A. Aerobic exercise reduces neuronal responses in food reward brain regions. *J. Appl. Physiol.* **112**, 1612–1619; doi:10.1152/jappphysiol.01365.2011 (2012).
46. Killgore, W. D. *et al.* Physical exercise and brain responses to images of high-calorie food. *Neuroreport* **24**, 962–967; doi:10.1097/WNR.000000000000029 (2013).
47. Killgore, W. D. & Schwab, Z. J. Sex differences in the association between physical exercise and IQ. *Percept. Mot. Skills* **115**, 605–617 (2012).
48. Killgore, W. D., Schwab, Z. J., Kipman, M., DelDonno, S. R. & Weber, M. Voxel-based morphometric gray matter correlates of daytime sleepiness. *Neurosci. Lett.* **518**, 10–13; doi:10.1016/j.neulet.2012.04.029 (2012).
49. Killgore, W. D. *et al.* Gray matter correlates of Trait and Ability models of emotional intelligence. *Neuroreport* **23**, 551–555; doi:10.1097/WNR.0b013e32835446f7 (2012).
50. Tzourio-Mazoyer, N. *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**, 273–289 (2002).
51. Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19**, 1233–1239 (2003).

Acknowledgments

Funding: This research was supported by a USAMRAA grant (W81XWH-09-1-0730) to WDSK.

Author contributions

W.K. designed the study, conducted the primary neuroimaging and statistical analyses, and wrote major sections of the manuscript. M.W. conducted the initial processing of the neuroimaging data. E.O. and M.W. assisted in the conceptualization and writing of the manuscript. All authors reviewed the manuscript.

Additional information

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Killgore, W.D.S., Olson, E.A. & Weber, M. Physical Exercise Habits Correlate with Gray Matter Volume of the Hippocampus in Healthy Adult Humans. *Sci. Rep.* **3**, 3457; DOI:10.1038/srep03457 (2013).



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported license. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/3.0>