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Exercise: An Active Route to Healthy Aging

Aerobic Exercise Training Increases Brain Volume in Aging Humans

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Background. The present study examined whether aerobic fitness training of older humans can increase brain volume in regions associated with age-related decline in both brain structure and cognition.

Methods. Fifty-nine healthy but sedentary community-dwelling volunteers, aged 60–79 years, participated in the 6-month randomized clinical trial. Half of the older adults served in the aerobic training group, the other half of the older adults participated in the toning and stretching control group. Twenty young adults served as controls for the magnetic resonance imaging (MRI), and did not participate in the exercise intervention. High spatial resolution estimates of gray and white matter volume, derived from 3D spoiled gradient recalled acquisition MRI images, were collected before and after the 6-month fitness intervention. Estimates of maximal oxygen uptake (VO_2) were also obtained.

Results. Significant increases in brain volume, in both gray and white matter regions, were found as a function of fitness training for the older adults who participated in the aerobic fitness training but not for the older adults who participated in the stretching and toning (nonaerobic) control group. As predicted, no significant changes in either gray or white matter volume were detected for our younger participants.

Conclusions. These results suggest that cardiovascular fitness is associated with the sparing of brain tissue in aging humans. Furthermore, these results suggest a strong biological basis for the role of aerobic fitness in maintaining and enhancing central nervous system health and cognitive functioning in older adults.

BEGINNING in the third decade of life the human brain shows structural decline, which is disproportionately large in the frontal, parietal, and temporal lobes of the brain (1). This decline is contemporaneously associated with deterioration in a broad array of cognitive processes (2). Given the projected increase in the number of adults surviving to advanced age, and the staggering costs of caring for older individuals who suffer from neurological decline, identifying mechanisms to offset or reverse these declines has become increasingly important.

Cardiovascular exercise has been associated with improved cognitive functioning in aging humans (3,4). These effects have been shown to be the greatest in higher order cognitive processes, such as working memory, switching between tasks, and inhibiting irrelevant information, all of which are thought to be subserved, in part, by the frontal lobes of the brain (3). However, very little is known about the structural brain changes, if any, which underlie these benefits in humans. Previous research with nonhuman animals has shown that chronic aerobic exercise can lead to the growth of new capillaries in the brain (5,6), increase the length and number of the dendritic interconnections between neurons (7), and even increase cell production in the hippocampus (8). These effects likely result from increases in growth factors such as brain-derived neurotrophic factor (7,9) and insulin-like growth factor (10,11), among others (12). The end result of these structural changes is a better interconnected brain that is more plastic and adaptive to change (8,13). Given that cardiovascular exercise has similar effects on human cognitive function that might be predicted from the structural changes in nonhuman animals, it seems likely that similar structural changes would be engendered in human brain tissue following chronic exercise, but research examining the impact of exercise on brain structure has overwhelmingly relied upon nonhuman animals, due to the highly invasive methods typically required to assess changes in brain structure.

With the advent of noninvasive in vivo brain imaging technologies such as structural and functional magnetic resonance imaging (MRI), it is possible to address questions about changes in the underlying brain structure of humans. In one such study (14), we found that older adults with a lifelong history of cardiovascular exercise had better preserved brains than did age-matched sedentary counterparts. Interestingly, the structural preservation was greatest in the frontal and parietal regions of the brain, which are thought to subserve aspects of higher order cognition, such as working memory, task switching, and the inhibition of irrelevant information. However, owing to the cross-sectional nature of that study, it is conceivable that a number of factors influence both brain volume and aerobic fitness. It is even possible that the relationship is reversed. That is, those older

Table 1. Demographic Information on Aerobic Exercising and Nonaerobic Exercising Control Older Adults

Measured Variable	Exercise	Control	*t* Test
Initial VO_2	23.3 (2.4)	23.6 (2.7)	$t(58) < 1$, NS
Change in VO_2	16.1% (1.9)	5.3% (1.3)	$t(58) = 2.05$, $p < .025$
Age	65.5 y	66.9 y	$t(58) < 1$, NS
Sex	53% women	57% women	$t(58) < 1$, NS
Education	13.5 y	14 y	$t(58) < 1$, NS
MMSE	29 (1.2)	29.4 (1.4)	$t(58) < 1$, NS
Hypertensive	30%	26.7%	$t(58) < 1$, NS
HRT (women)	43.3%	53.3%	$t(58) < 1$, NS

Notes: All values except the change in VO_2 outcome represent participant characteristics at the onset of study participation.

HRT includes participant's self-report of either opposed or unopposed estrogen therapy, and participants included in the hypertensive category were those who were diagnosed as hypertensive prior to their participation in the study.

Standard errors are in parentheses.

MMSE = Mini-Mental State Examination score; NS = not significant; HRT = hormone replacement therapy.

adults who have relatively well preserved brains may be differentially able to maintain participation in a physically active lifestyle, through better preserved cognitive abilities or some other set of genetic or environmental variables that affect both somatic and brain health.

To address this issue, we randomly assigned 59 older adults to participate in either a cardiovascular exercise group or a nonaerobic exercise control group for a 6-month period. We scanned these participants in a high-resolution structural MRI protocol immediately before and after participation in the exercise program. We then compared changes in regional brain volume from preintervention to postintervention for aerobic exercisers and nonaerobic exercise control participants using an optimized voxel-based morphometric technique which can assess tissue volume in a point-by-point fashion throughout the brain (see Methods). We additionally analyzed high-resolution brain scans of 20 younger adults; these scans were collected at the same intervals as those from the older adults. The younger adults did not participate in an exercise intervention, and served largely as methodological controls as we did not expect to see any appreciable change in the volume of younger adult brains within the 6-month time frame of the study.

Methods

Participants

Fifty-nine older (60–79 years) and 20 younger (18–30 years) right-handed, neurologically intact adults took part in the 6-month study. All participants were screened for neurological defect (e.g., possible dementia, self-report of neurological disease such as multiple sclerosis, brain tumor, and Parkinson's disease) and appropriateness for testing in an MRI environment (e.g., no metallic implants that could interfere with testing, no claustrophobia). Older adults were additionally required to obtain physician approval for participation in an exercise program before beginning any phase of the study. Older participants were randomly assigned by the project coordinator during recruitment to participate in either an aerobic exercise program or a nonaerobic stretching and toning exercise program.

Participant characteristics are documented in Table 1. The only significant difference between the aerobic and nonaerobic training group participants was in the maximal oxygen uptake (VO_2) change measure (i.e., the cardiovascular improvement from pre- to post-training). The Institutional Review Board at the University of Illinois approved this research. Written informed consent was obtained from all participants.

Exercise Intervention Protocols

The aerobic exercise intervention was designed to improve cardiorespiratory fitness with an exercise intensity prescription derived from peak heart rate (HR) responses to baseline graded exercise testing. Intensity levels began at 40%–50% HR reserve increasing (15) to 60%–70% HR reserve over the course of the trial. Intensity levels and exertion were recorded in daily exercise logs and monitored by trained exercise leaders. Participants in the older nonaerobic exercise control group followed the same activity schedule and format as the aerobic exercise group did, but engaged in a program of whole-body stretching and toning designed for individuals 60 years old or older. As the individual's level of flexibility increased, stretches with increasing levels of difficulty were incorporated into the program. Participants in both the aerobic and control exercise groups attended three 1-hour exercise training sessions per week for the 6-month period of the intervention. Compliance in the exercise sessions was excellent, exceeding 85% for all participants. Each group participated in their sessions at separate geographical locations around campus to reduce the probability of any crossover effects occurring between the groups.

Assessment of Cardiorespiratory Fitness

Participants completed a graded exercise test on a motor-driven treadmill. Peak oxygen uptake (VO_{2peak}) was measured from expired air samples taken at 30-second intervals until the highest VO_{2peak} was attained at the point of volitional exhaustion. The aerobic fitness training group showed a significant 16.1% in increase in VO_{2peak}, whereas the older control participants showed a nonsignificant 5.3% change in VO_{2peak} across the 6-month intervention.

Imaging Protocols and Analyses

We acquired a high-resolution T1 weighted structural image for each participant, 1 week prior to the intervention and within 1 week after cessation of the exercise program. Twenty-two of the older adults and eight of the younger adults were scanned in a 1.5 Tesla GE Signa MRI scanner ($1 \times 1 \times 1.3$ mm; Niskayuna, NY) at both times 1 and 2 and the remaining older and younger adults were scanned in a 3 Tesla Siemens Allegra MRI scanner ($1 \times 1 \times 1.3$ mm; Malvern, PA) at both times 1 and 2. None of the results reported in this study were significantly impacted by the scanner type used to acquire the MRI images.

Our voxel-based morphometry analyses largely followed those methods described elsewhere (16), with the exception that we adapted our protocol to include a highly optimized

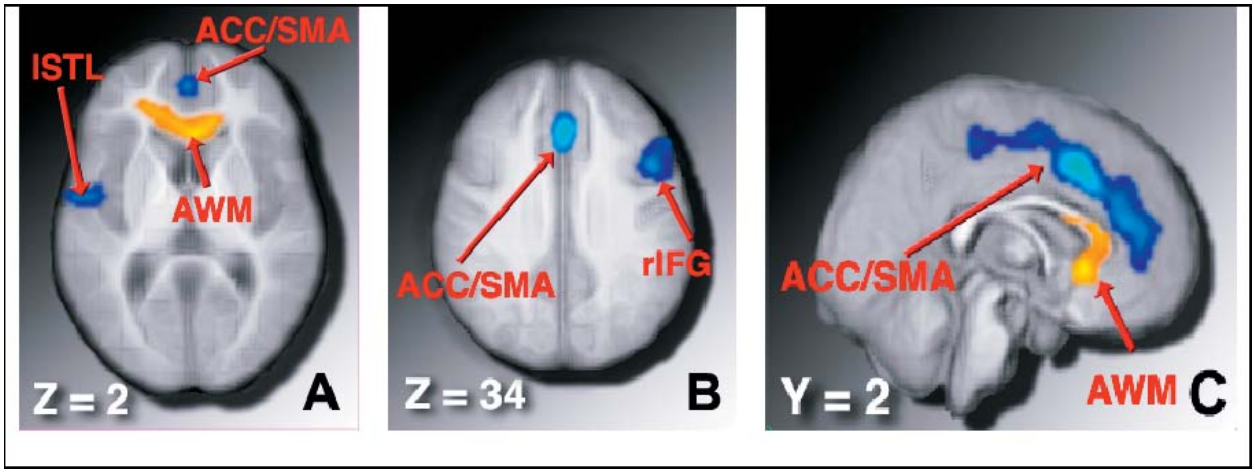

Figure 1. Regions showing a significant increase in volume for older adults who participated in an aerobic fitness training program, compared to nonaerobic (stretching and toning) control older adults. **A** and **B,** Neurologically oriented axial slices through the brain, at +2 and +34 mm, respectively, in stereotaxic space. **C,** Sagittal slice 2 mm to the right of the midline of the brain. *Blue regions:* Gray matter volume was increased for aerobic exercisers, relative to nonaerobic controls. *Yellow regions:* White matter volume was increased for aerobic exercisers, relative to controls. (See also Table 2.)

and robust longitudinal registration approach to perform the initial coregistration between participants' time 1 and time 2 images (17). The registration constrained spatial scaling by the skull to minimize any potential differences in scanner geometry or misregistration due to soft-tissue changes.

First, each participant's images were skull-stripped and segmented into 3D maps of gray matter, white matter, and cerebrospinal fluid, using a semi-automated algorithm that takes into account voxel intensity distributions as well as hidden Markov random fields to estimate tissue volume at each voxel (18). Then, the 3D maps of gray and white matters for each participant were registered to a common space (MNI) using a 12-parameter affine transformation. These segmented images were then used as a priori templates for a second-level segmentation. In addition, a mean image was calculated from all participants, spatially smoothed with a 12 mm full-width at half max kernel, and subsequently used as a study-specific template. The use of study-specific templates has been shown to reduce error associated with misregistration and, therefore, to provide a better estimate of brain volume differences between groups. The second-level analysis then consisted of a resegmentation based on the a priori gray and white matter maps from stage 1 and a realignment to the study-specific template image. These images provide a voxel-by-voxel estimation of the volume of gray matter, white matter, and cerebrospinal fluid contained within the particular voxel. These images were then multiplied by the Jacobian determinant for each participant to preserve original volume and to control for differences in the extent of registration and possible interpolation error. Finally, the percent change in volume was computed at each voxel for each participant. All of these processes were conducted by an experimenter who was blind to the group assignment of each individual.

The maps representing the percent volume change in gray and white matter for each participant were then forwarded to a group analysis, where we compared the changes in volume for aerobic exercising and nonaerobic control older adults in a set of unpaired *t* tests at each voxel. We initially subjected the younger adult data to a simple *t* test against zero to evaluate whether any changes occurred during the 6-month period for younger adults. These analyses yielded three statistical parametric maps for gray and white mater, which described where (a) aerobic exercisers showed a greater increase in volume than stretching and toning controls, (b) nonaerobic controls showed a greater increase in volume than aerobic exercisers, and (c) any change in volume, positive or negative, was present in younger adults. We performed a second set of analyses to examine whether the results of our initial analysis interacted with the two different MRI scanners used in the study. In none of the regions presented in Figure 1 did the scanner used to collect the MRI data interact with the effects of interest. The resulting statistical parametric maps presented in Table 2 were statistically corrected for multiple comparisons at a $p < .05$ level for each cluster (19).

Results

Descriptive information on the participants is presented in Table 1. Participant ages ranged from 60 to 79 years, with a mean of 66.5 years. Overall, the sample was 55% female, and tended to be well educated, with an average 13.8 years of education. The estimated VO_2 scores ranged from 12.6 to

Table 2. Cluster Size, Peak Location, and Statistical Value for Each of the Four Regions Where Aerobically Exercising Older Adults Showed a Significant Increase in Brain Volume

Region	Peak Z	Cluster Size	X (mm)	Y (mm)	Z (mm)
ACC/SMA	5.17	1459	−2	20	38
rIFG	4.01	604	54	14	30
lSTL	3.94	308	−58	−6	8
AWM	4.66	1085	4	26	2

Note: ACC/SMA = anterior cingulate cortex, supplementary motor cortex; rIFG = right inferior frontal gyrus; lSTL = left superior temporal gyrus; AWM = anterior white matter.

49.9. As shown in greater detail in Table 1, groups did not differ at program onset with respect to average VO_2 score, age, sex, years of education, hormone replacement therapy usage, hypertension, or Mini-Mental State Examination score. However, after the intervention the aerobically exercising older adults showed a significant increase in VO_2.

As predicted, no significant changes in either gray or white matter volume were detected for our younger participants. However, when directly comparing the changes in gray matter volume for older exercise and control participants, we found that the previously sedentary aerobic exercising group showed a benefit in brain volume in several regions after participation in an exercise training protocol.

The blue regions in Figure 1 show areas of gray matter in which older adults who participated in the 6-month aerobic exercise program showed a significant increase in regional brain volume, compared to older adult controls. As might be expected from the human behavioral research on aerobic training effects on cognition (3,4), the largest changes in volume were present in the frontal lobes of the brain, and included regions of cortex that are implicated in a broad array of higher order attentional control and memory processes (20–22). The largest region subsumed portions of the dorsal anterior cingulate cortex, supplementary motor area, and middle frontal gyrus bilaterally within the medial walls of the brain (ACC/SMA). The second region subsumed a moderately large portion of the dorsolateral region of the right inferior frontal gyrus, but also part of the posterior aspect of the middle frontal gyrus (rIFG), and a third region included the dorsal aspect of the left superior temporal lobe (lSTL). The yellow region in Figure 1 shows the area in which aerobically exercising participants showed a significant increase in white matter volume after the 6-month intervention, compared to control participants. This region was in the anterior white matter tracts (AWM), subtending roughly the anterior third of the corpus callosum. These white matter tracts allow the left and right hemispheres of the brain to communicate, and deterioration in these regions has been implicated in age-related cognitive decline (23,24). See Table 2 for peak locations, *z* scores, and cluster sizes.

Considering the detrimental impact of age-related brain volume loss on a broad spectrum of outcomes, it would be interesting to investigate the potential for fitness to reduce the risk of brain tissue loss during the intervention. To address this issue, we computed a binary outcome measure of volume change, in which volume loss was coded as a negative outcome. From this we computed, within each cluster reported in Table 2, the relative reduction in risk for brain volume loss associated with participation in the aerobic fitness training protocol. Older adults who participated in the aerobic fitness training protocol showed average reductions in risk, relative to participants in the stretching and toning control group, for brain volume loss of 42.1%, 33.7%, 27.2%, and 27.3%, in the anterior cingulate cortex (ACC/SMA), right superior temporal gyrus (rtSTG), right middle frontal gyrus (rtMFG), and anterior white matter (AWM) clusters, respectively. We should note that our sample is somewhat smaller than the recommended minimum for risk-reduction estimates, and as such, the risk reduction estimates should be viewed with some caution.

Discussion

In this study, we randomly assigned older adult participants to either an aerobic exercise group or a nonaerobic exercise control group for 6 months and then examined whether participation in an aerobic exercise regimen would alter brain volume in an aged cohort. In short, we found that participation in an aerobic exercise program increased volume in both gray and white matter primarily located in prefrontal and temporal cortices—those same regions that are often reported to show substantial age-related deterioration. The current findings are the first, to our knowledge, to confirm benefits of exercise training on brain volume in aging humans. These findings both compliment and extend extant human and nonhuman research on the benefits of exercise on cognition and brain structure such as neuron proliferation and survival, growth of capillary beds, and increased dendritic spines (5–13,25). These findings also highlight the potential importance of aerobic exercise in not only staving off neural decline in aging humans, but also suggest promise as an effective mechanism to roll back some of the normal age-related losses in brain structure (1,23).

These results also directly bear on issues of public policy and clinical recommendations in that they suggest a rather simple and inexpensive mechanism to ward off the effects of senescence on human brain tissue. Most importantly, the regions of cortex and white matter that show the greatest sparing with aerobic fitness play central roles in successful everyday functioning, and declines in these regions are associated with a broad array of clinical syndromes. For example, the prefrontal cortex has been associated with critical cognitive processes ranging from inhibitory functioning (22) to measures of general intelligence (26). Losses in this area have been associated with devastating clinical syndromes such as schizophrenia. The temporal lobes are associated with effective long-term memory function, and losses in these areas of cortex have been associated with Alzheimer's dementia in aging populations. Importantly, these are the same locations that we report brain volume increases with exercise.

These findings, as provocative as they are promising, must be viewed with some caution. For example, the older adults in our sample were all very healthy and cognitively intact. It is not clear whether similar benefits will accrue in pathologically aging individuals. Furthermore, a detailed neuropsychological battery was not collected on these participants at each time point; therefore, we do not have the data to assess how these volumetric changes relate to changes in cognitive scores [but see Erickson and colleagues (27) for a cross-sectional examination of the relationship of fitness-related brain volume differences and cognition]. Our relatively small sample size is also a limiting factor. Our exclusionary criteria limit the interpretation of our results to a select group of individuals. Additionally, data from nonhuman models suggest that the changes in brain volume seen in our study are likely due to changes in synaptic interconnections, axonal integrity, and capillary bed growth, but very little is known about the relationship between the voxel-based morphometry methodology used in this study, and the underlying cellular changes that might occur.

Conclusion

We report the novel and intriguing finding that only 6 months of regular aerobic exercise not only spares brain volume but also increases brain volume in an aged cohort. These effects cannot be driven by methodological limitations because neither of the control groups (the older nonaerobic exercise participants or the younger control group) showed significant changes in brain volume over 6 months. Our results suggest that brain volume loss is not an inevitable effect of advancing age and that relatively minor interventions can go a long way in offsetting and minimizing brain volume loss. Future studies should replicate these effects using a larger sample size and a more extensive neuropsychological battery to examine the relationship between brain volume changes and cognitive changes.

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