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Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans

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Background. The human brain gradually loses tissue from the third decade of life onward, with concomitant declines in cognitive performance. Given the projected rapid growth in aged populations, and the staggering costs associated with geriatric care, identifying mechanisms that may reduce or reverse cerebral deterioration is rapidly emerging as an important public health goal. Previous research has demonstrated that aerobic fitness training improves cognitive function in older adults and can improve brain health in aging laboratory animals, suggesting that aerobic fitness may provide a mechanism to improve cerebral health in aging humans. We examined the relationship between aerobic fitness and in vivo brain tissue density in an older adult population, using voxel-based morphometric techniques.

Methods. We acquired high-resolution magnetic resonance imaging scans from 55 older adults. These images were segmented into gray and white matter maps, registered into stereotaxic space, and examined for systematic variation in tissue density as a function of age, aerobic fitness, and a number of other health markers.

Results. Consistent with previous studies of aging and brain volume, we found robust declines in tissue densities as a function of age in the frontal, parietal, and temporal cortices. More importantly, we found that losses in these areas were substantially reduced as a function of cardiovascular fitness, even when we statistically controlled for other moderator variables.

Conclusions. These findings extend the scope of beneficial effects of aerobic exercise beyond cardiovascular health, and they suggest a strong solid biological basis for the benefits of exercise on the brain health of older adults.

IN the course of normal aging, the human brain begins to lose tissue early in the third decade of life. Average losses are estimated at roughly 15% of the cerebral cortex and 25% of the cerebral white matter between ages 30 and 90 (1), with disproportionately high losses in the frontal, parietal, and temporal cortices (2). This pattern is closely matched by declines in cognitive performance throughout this period (3).

Given the projected rapid growth in the aged population in developed countries (4), and the staggering costs associated with cognitive deterioration (4,5), identifying effective mechanisms to ward off structural and functional declines of the central nervous system (CNS) is rapidly emerging as an imperative public health goal. Several rigorous longitudinal studies (6,7) and a recent meta-analysis (8) have demonstrated that improvements in cardiovascular fitness can exert positive effects on human cognitive abilities. In this article, we report the first known evidence linking higher levels of aerobic fitness to the sparing of brain tissue in aging humans.

Recent examinations of the link between cardiovascular exercise and CNS health that used animal models have shown positive effects of aerobic fitness on a wide range of brain health markers. These effects are exerted by a chain of cellular and molecular cascades, including increased levels of brain-derived neurotrophic factor, serotonin, capillary density (9), and neurogenesis (10). These changes result in a well-preserved brain that is more plastic and adaptive to change.

Given the robust moderating effects of exercise on executive functions, some have speculated that the frontal, prefrontal, and temporal cortices that support these functions should show selective sparing of age-related deterioration with increased cardiovascular fitness (6,7,11), presumably through the same mechanisms implicated in animal models (9,10). However, to date, the effects of aerobic fitness on the human brain have not been systematically examined.

Methods

Participants

Our target participant pool was right-handed, high functioning, community-dwelling older adults who were at least 55 years of age, and who were recruited from newspaper ads, public flyers, and campuswide e-mailings. Participants were excluded from the study if they were younger than 55 years of age, scored below 20 on the Mini-Mental State Examination (MMSE) (12), or had a known history of stroke or other organic brain dysfunction. Additionally, for safety concerns related to a magnetic resonance imaging (MRI) setting, participants were excluded if they had metallic implants or pacemakers, or if they reported claustrophobia prior to, or during, the assessment. Participants also were required to gain written approval from their physicians for participation in a cardiovascular stress test before entering the study. The Institutional Review Board of the University of Illinois approved this research project, and all relevant ethical standards of human

Table 1. Participant Characteristics

Characteristic	Percent	Mean	Range	*SD*
Age	—	66.5	55–79	5.3
Est. $\dot{V}O_2$	—	31.1	11.2–49.9	8.5
Education (y)	—	16.1	10.0–22.0	2.9
MMSE	—	28.6	24–30	1.9
Caffeine consum. (mg/d)	—	196	0–610	157
Hypertensive	24	—	—	—
HRT females	52	—	—	—
Smoke tobacco	9	—	—	—
Alcohol consum. (per wk)	—	1.5	0–6.6	2.1
<1/wk	64			
1–4/wk	16			
>4/wk	20			

Notes: MMSE = Mini-Mental State Examination; HRT = hormone replacement therapy; $\dot{V}O_2$ = oxygen consumption per unit time.

subject treatment were met or exceeded. All participants provided written informed consent before participation.

Measures

Our primary outcome measures were based on standardized gray and white matter density maps, rendered from high-resolution Magnetic Resonance (MR) images, explained in more detail later, and estimates of maximal oxygen uptake ($\dot{V}O_2$max). In an initial session, high-resolution (0.98 × 0.98 × 1.30 mm) brain images were acquired by using a three-dimensional (3-D) spoiled gradient sequence on a 1.5 T MR scanner (General Electric, Milwaukee, WI). In a second session, the cardiovascular fitness of the participants was assessed by using the Rockport 1-mile walk protocol (13).

We used a voxel-based morphometric (VBM) technique (14) to assess the impact of cardiovascular fitness on age-related differences in brain tissue density. The VBM technique provides a means to estimate tissue atrophy in a point-by-point fashion throughout the brain with reasonably high spatial resolution. This allows regionally specific conclusions about the variables of interest on changes in brain matter, and it represents a significant advantage over measures of global atrophy in estimating brain health.

Prior to analysis, the MR images were subjected to several requisite preprocessing stages. All nonbrain tissue was first stripped from the image of the participant's head (15). The remaining 3-D brain images were then segmented into three separate 3-D maps representing the density of the cerebrospinal fluid, gray matter, and white matter, at each point in the MR image for each participant, using a well-established automated segmentation algorithm (16) that requires minimal user intervention. The gray and white matter maps were then registered into a common stereotaxic coordinate system by using an optimized affine registration algorithm (17). The images were examined by experts who were blind to the fitness status of the participants at each step of segmentation and registration to ensure proper calibration. The final gray and white matter images were spatially smoothed with a 12-mm full-width at half-maximum Gaussian kernel to satisfy the requirements of the random field theory upon which the final analyses would be based (18), and then they were forwarded to the analysis stage.

Analysis

To assess the effects of age and fitness on regional deterioration of the brain, we examined the preprocessed MR images for systematic variation associated with the participant's age and estimated $\dot{V}O_2$ score, using a statistical parametric mapping (19) (SPM) technique. We performed conceptually identical analyses separately for the gray and white matter maps. Simply stated, each point in the density map for each participant was entered into a multiple regression with the participant's age (age) and estimated $\dot{V}O_2$ score (fitness) as independent variables, and the estimated tissue density at that point in the map as the dependent variable. This analysis yielded three parametric maps—one representing the change in tissue density at each point in the brain associated with age alone (main effect of age), one representing changes caused by fitness level alone (main effect of fitness), and one representing the degree to which fitness moderated the change in tissue density associated with age (the Age × Fitness interaction). To compensate for the large number of comparisons, we corrected the statistical estimates by using a conjunction between size of the statistical effect ($Z > 3.25$) and the number of contiguous points in the map exceeding that threshold ($n > 12$), and a minimum clusterwise threshold of $p < .01$ (20).

Results

Sixty-eight individuals expressed interest in the study. A total of 55 were deemed eligible for participation and completed both phases of the study. Reasons for exclusion were as follows: too young (3 people), pacemaker (1 person), impaired score on MMSE (1 person), claustrophobia (8 people).

Descriptive information on the participants is presented in Table 1. Participant ages ranged from 55 to 79 years, with a mean of 66.5 years. The sample was 55.6% female, and tended to be well educated, with an average of 16.1 years of education. The estimated $\dot{V}O_2$ scores ranged from 11.21 to 49.90. A subset of 25 participants were also subjected to a treadmill stress test to examine the concordance between the Rockport protocol and the gold standard estimate of $\dot{V}O_2$. The Rockport and treadmill tests showed very high concordance ($r = .86$; $p < .01$), confirming the validity of the Rockport protocol in our sample.

As depicted in Figure 1, we observed substantial deterioration in gray and white tissue densities as a function of age ($Z = 3.25$–6.30). In accord with the previously reported volumetric findings (2), age-related declines in gray matter density were observed in the prefrontal, superior parietal, and middle/inferior temporal cortices. No statistically reliable differences were noted in the motor and occipital regions. In addition, consistent with the volumetric (2) and recent diffusion tensor imaging studies (21), the anterior white matter tracts evidenced greater

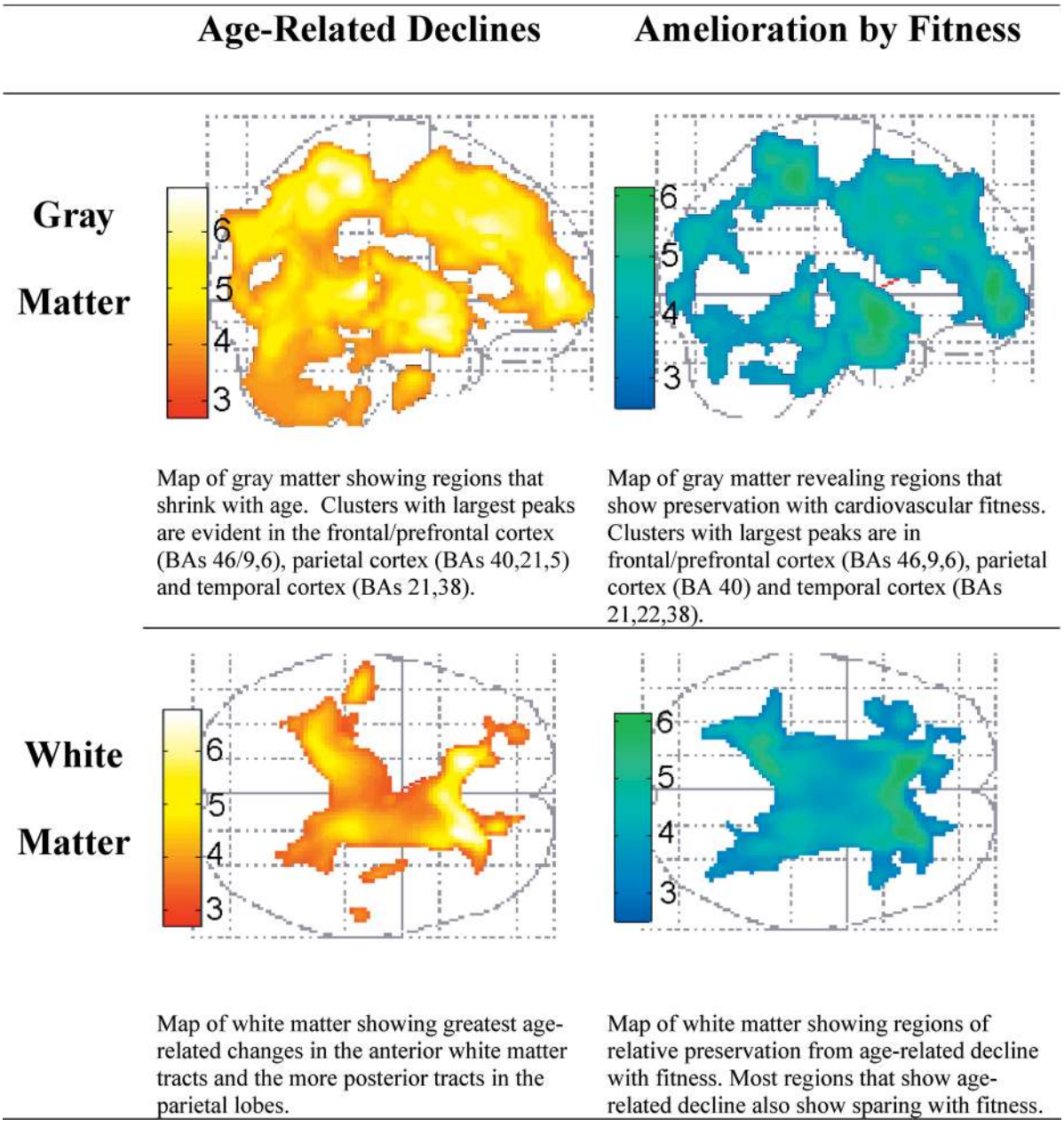

Figure 1. Statistical maps derived from multiple regressions of age and cardiovascular fitness on gray (top row) and white matter (bottom row) density. Images are rendered for display purposes as glass brains, thresholded at a minimum Z of 3.25, $p < .002$, collapsing across the sagittal (top row) and axial (bottom row) planes. The brighter colors represent greater tissue density changes with age (left side) and greater sparing of tissue density with increasing fitness (right side). The entire cluster report is available at http://www.psych.uiuc.edu/~scolcomb/volumeclusters.html.

age-related decline in tissue density than posterior and temporal regions.

Notably, the regions that are the most gravely affected by aging also show the greatest advantage of aerobic fitness ($Z = 3.25$–6.10). As shown in Figure 1, the sparing effects of cardiovascular fitness on gray matter are the greatest in the prefrontal, superior parietal, and temporal cortices. In the white matter, the largest beneficial effects of fitness are observed in the anterior tracts and in transverse tracts running between the frontal and the posterior parietal lobes.

It is also noteworthy that in the maps representing the main effect of fitness, no regions survived the corrected statistical threshold. This suggests that fitness itself has little effect on brain tissue density. Moreover, it confirms that neither fitness status nor some other third variable associated with fitness biased the results in any direct fashion. Fitness played its only detectable role in moderating the age-related decline in tissue density.

In addition to measures of cardiovascular fitness, we collected data on other potential moderator variables,

including alcohol and caffeine consumption, hormone replacement therapy, years of education, and hypertension. A confirmatory analysis showed that none of the peaks of activation were negated, even when we statistically controlled for all moderating variables that were reliably correlated with fitness, thereby bolstering the evidence for a more direct link between cardiovascular fitness and neural tissue density.

Conclusions

These results are scientifically important, as they provide the first empirical confirmation of the relationship between cardiovascular fitness and neural degeneration as predicted in the extant behavioral literature on aging and cognition (6–8,11) and in animal models (9,10) in a human population. Thus, the role of cardiovascular fitness as protector and enhancer of cognitive function and CNS integrity in older adults appears to have a solid biological basis.

These results, however, 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 (11) to measures of general intelligence (22). Losses in this area have been associated with devastating clinical syndromes such as schizophrenia (23). 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.

Additionally, several other relatively low-cost approaches to preserve CNS health and function have shown promise. For example, recent research using animal models suggests that increased antioxidant supplementation can help to minimize or reverse markers of aging in older brains (24). And several studies have shown that cognitive training regimens can help to preserve brain function in older humans (25). In this context, it is interesting to consider the potential of multilevel interventions that include cardiovascular, dietary, and cognitive training components. Such multifaceted paradigms that include both neurobiological and cognitive assessments could provide powerful tools to maintain or improve CNS health in older adults, as well as help to elucidate the underlying mechanisms of decline and preservation in the aging brain.

The results reported herein suggest that the potential benefits of aerobic exercise extend beyond cardiovascular health markers and can affect brain health as well. Although the research reported here explicitly targeted relatively high-functioning older adults with no known clinical syndromes, a meta-analysis of cognitive performance of older adults found that increases in aerobic fitness were identical for both clinical and nonclinical populations (8). Future research examining the benefits of aerobic fitness on the functional and structural integrity of the CNS in clinical populations seems both promising and highly desirable.

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