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Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer's Disease

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Abstract

Exercise and cardiorespiratory (CR) fitness may moderate age-related regional brain changes in nondemented older adults (ND). The relationship of fitness to Alzheimer's disease (AD) related brain change is understudied, particularly in the hippocampus which is disproportionately affected in early AD. The role of apolipoprotein E4 (apoE4) genotype in modulating this relationship is also unknown. Nondemented (n=56) and early-stage AD subjects (n=61) over age 65 had MRI and CR fitness assessments. Voxel-based morphometry (VBM) techniques were utilized to identify AD-related atrophy. We analyzed the relationship of CR fitness with white and gray matter within groups, assessed fitness-related brain volume change in areas most affected by AD-related atrophy, and then analyzed differential fitness-brain relationships between apoE4 carriers. Atrophy was present in the medial temporal, temporal, and parietal cortices in subjects with mild AD. There was a significant positive correlation of CR fitness with parietal and medial temporal volume in AD subjects. ND subjects did not have a significant relationship between brain volume and CR fitness in the global or SVC analyses. There was not a significant interaction for fitness × apoE4 genotype in either group. In early-stage AD, cardiorespiratory fitness is associated with regional brain volumes in the medial temporal and parietal cortices suggesting that maintaining cardiorespiratory fitness may modify AD-related brain atrophy.

Keywords

Alzheimer Disease; Cardiorespiratory Fitness; Physical Activity; Hippocampus; Voxel-Based-Morphometry; APOE; Dementia; Aging

Introduction

Accumulating evidence suggests exercise might reduce the deleterious effects of biological and cognitive aging in humans [1,2]. Aerobic exercise in elderly individuals has been shown to enhance efficiency of attentional processes [3], executive-control processes [4], cognition [2], and possibly moderate age-related brain atrophy [1,5]. Healthy elderly with higher fitness levels have less cognitive decline[6,7] and reduced risk for dementia [8,9] than those with lower fitness levels.

A recent randomized trial in subjects at risk for AD demonstrated modest improvement in cognition after 6 months of exercise [10]. Morever, brain imaging studies have demonstrated better attention and performance in elderly individuals that were exercising verses those that were not [1]. Improving fitness can also lead to both morphological and functional changes in the brains of older animals (reviewed in [11]), perhaps by activating neurotrophic factors, enhancing vascularization, or altering expression in a variety of gene transcripts [12]. Moreover, exercise appears to stimulate cellular proliferation and dendritic complexity in the dentate gyrus of adult animals [13, 14]. Finally, recent imaging studies in aging humans have also revealed reduced atrophy in the temporal and parietal cortices [5], as well as increased cerebral blood volume in the hippocampal dentate gyrus associated with exercise [14].

Cardiorespiratory (CR) fitness might be of therapeutic benefit to individuals with Alzheimer's disease (AD) [15]. Exercise in a mouse model of AD inhibited the normal progression of AD-like neuropathology, suggesting that exercise may have disease-modifying effects [16]. Exercise training appears to positively affect physical function, cognitive function, and behavioral indices of mood and well-being in individuals with dementia [17]. Few studies have looked at the effect of CR fitness on brain volume using imaging, and these have been restricted to cognitively normal older adults [1, 5]. We previously assessed the relationship of CR fitness to whole brain volume in AD subjects and found that CR fitness, as defined by peak oxygen consumption (VO_2^{peak}), the standard measures of fitness, was positively associated with whole brain and whole white matter volumes in subjects with early AD [18].

In the present study, we utilized novel voxel-based morphometry (VBM) techniques to more closely examine the relationship between CR fitness and regional brain volume in a sample of early AD and nondemented controls previously studied at the whole brain level. We were particularly interested in the relationship between CR fitness and medial temporal lobe structures, such as the hippocampus, which are affected early in the AD process and have demonstrated exercise-related changes in function and structure in animal studies [13, 14, 19]. Previous studies have examined the relationship between risk for AD, APOE, and positive effects of exercise, with mixed results [8, 9]. Thus we will examine if the relationship between CR fitness and brain volume is influenced by the presence of the Apolipoprotein E E4 allele (apoE4), a risk factor for AD [20] that is associated with structural brain changes [21].

Materials and Methods

Sample and Recruitment

Nondemented (Clinical Dementia Rating (CDR) 0, n=67) and early-stage AD subjects (CDR 0.5 and 1 combined, n=71) aged 65 and over were enrolled in the University of Kansas Brain Aging Project. Participants were recruited from a referral-based memory clinic and by media appeals. Study exclusions have been described previously [18] but included neurological disease other than AD, recent history of cardiovascular disease, history of significant mental illness, diabetes mellitus, or other systemic illness that might impair completion of the study.

Clinical Assessment

The clinical assessment included a semi-structured interview with the participant and with a collateral source knowledgeable about the participant. Diagnostic criteria for AD require the gradual onset and progression of impairment in memory and in at least one other cognitive and functional domain [22]. The presence or absence of dementia, and its severity if present, was determined using the CDR [23]. These methods have a diagnostic accuracy for AD of 93% [24], are sensitive to detecting the earliest stages of AD by focusing on intraindividual change rather than comparison with group norms [25] and are accurate in identifying the subset of individuals meeting criteria for MCI who have early stage AD [26]. Only nondemented (CDR 0) and early

stage AD (CDR 0.5 and 1.0) were enrolled. Details on the physical and neurological examinations, neuropsychiatric evaluations and functional activity levels of this group have been discussed previously [18, 27].

Physical Activity Assessment—The participant's level of habitual physical activity was estimated using the Physical Activity Scale in the Elderly (PASE), as described previously [28]. The PASE is a reliable and valid measure of physical activity and physical function developed specifically for older individuals [29]. The PASE assesses an individual's level of physical activity within the last seven days as an estimate of habitual physical activity. We modified the PASE by administering it to the subject's study partner for both nondemented and AD subjects.

Cardiorespiratory Fitness

Peak oxygen consumption (VO_2^{peak}), the standard measure of CR fitness [30], reflects physical activity in addition to other factors, such as age and heredity [31]. VO_2^{peak} was assessed during a graded treadmill test limited by subject report of fatigue [32], as previously described [18]. Expired air was measured for oxygen and carbon dioxide at 15-second intervals using a Parvomedics system. American College of Sports Medicine (ACSM) guidelines [30] were used to determine safety. Blood pressure and the participant's self-assessment of exertion using the 15-point Borg Rating of Perceived Exertion scale [33] were acquired during the last 30 seconds of each 2-minute stage. Participant effort during the treadmill test was assessed with measures of the respiratory exchange ratio (RER). Heart rates were recorded every 15 seconds, with mean heart rate for each subject group listed in Table 1. VO_2^{peak} was considered the highest observed value during the test and was normalized by total lean mass as determined by dual energy x-ray absorptiometry (DEXA, [Lunar Prodigy, GE Healthcare, Madison WI]). Test-retest reliability of treadmill testing to determine peak oxygen consumption has been demonstrated in individuals with brain injury or cognitive impairments, including traumatic brain injury [34], stroke [35], and mental retardation [28, 36, 37].

Imaging and Voxel-Based Morphometry

Structural MRI data was acquired using a Siemens 3.0 Tesla Allegra MRI Scanner. High-resolution T1 weighted anatomical images were acquired (magnetization-prepared rapid gradient echo [MPRAGE]; $1 \times 1 \times 1$ mm^3 voxels, repetition time [TR]=2,500, echo time [TE] =4.38ms, inversion time [TI]=1,100ms, field of view 256×256 with 18% oversample, flip angle=8 degrees) and processed for voxel-based analysis. Every scan was checked for image artifacts and gross anatomical abnormalities. Eleven nondemented and 10 demented subjects were excluded for movement artifact or inhomogeneity that distorted brain matter. Data analysis for 56 ND and 61 AD subjects was performed using the VBM5 toolbox (http://dbm.neuro.uni-jena.de), an extension of the SPM5 algorithms (Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB 7.1 (The MathWorks, Natick, MA, USA) on Linux. Apolipoprotein E genotyping results were obtained using restriction enzyme isotyping, and available for 98 of these subjects with imaging data.

The VBM5 toolbox extends and enhances the unified segmentation approach implemented in SPM5 [38] by using a generative model that integrates tissue classification, image registration and MRI inhomogeneity bias correction. This model avoids the "circularity problem" of the optimized VBM procedure in SPM2,[39] as the initial image registration does not require a tissue segmentation. We used the Hidden Markov Field (HMRF) model on the estimated tissue maps ($3 \times 3 \times 3$). Based on recommendations [38] for aging and diseased populations, estimated tissue probability maps were written without making use of the ICBM tissue priors to avoid a segmentation bias, as these priors are derived from young healthy controls. This approach is a specific feature of the VBM5 toolbox and has been described in detail elsewhere[40]. The

approach is designed to more accurately classify tissues in brains with excess atrophy or abnormal morphology [41, 42] and has been shown to be useful when handling MR imaging data from infants and in cases where the age of the study population is different than the pre-derived priors in SPM5 [41, 43]. Images were then modulated and saved using affine registration plus non-linear spatial normalization ([Wilke, Holland et al. 2008]), resulting in final tissue maps of gray matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) which we smoothed with a 10 mm FWHM Gaussian kernel before statistical analysis. Additionally, total GM, WM, CSF and whole brain volumes (GM plus WM) were computed in cm^3 using the normalized tissue maps of each study participant.

Statistical Analyses, Demographics—SPSS 16.0 was used for all statistical analysis outside of imaging space. Continuous variables were summarized by means and standard deviations, while categorical variables were summarized by frequency and percent. Continuous demographic and imaging variables were compared in early AD and nondemented groups using ANOVA. Chi-square was used to compare categorical variables between groups.

Imaging Statistics

To analyze brain images in SPM5, we used a full-factorial model (regression and a 2-sample t-test) with independence between subject groups, unequal variance, no grand mean scaling, and centered covariates on the overall mean. We used absolute threshold masking set at 0.10 to restrict each analysis to one tissue type. This model removes the confounding effects due to different brain size between patient and control groups.

First, GM and WM maps of ND and AD subjects were compared to identify areas of AD-related atrophy ($p<.05$, family-wise error (FWE) corrected) using a 2-sample t-test. Next, the relationship of CR fitness to brain volume was assessed globally within each group using multiple regression, with VO_2^{peak} as the variable of interest, and age and gender as confounding variables. The relationship between CR fitness and GM and WM was considered significant at $p<0.05$ corrected for multiple comparisons (FWE). We then examined the relationship of CR fitness with hippocampal and parahippocampal volumes. The small volume corrections (SVC's), the bilateral hippocampus and bilateral parahippocampus, were derived from the Wake Forest University Pickatlas (http://www.fmri.wfubmc.edu) [44]. These medial temporal regions of interest (ROI's) were pre-selected as they are affected early in AD [45] and hippocampal volume loss is considered a valid biomarker of AD neuropathology [46]. Additionally, exercise studies in animals suggest that fitness is related to brain volume in the medial temporal lobe [47]. In addition we ran a second SVC regression analysis assessing VO_2^{peak} in relation to GM and WM controlling for additional confounding variables (physical activity and effort on the treadmill test as measured by RER) in the AD subjects. To correct for multiple comparisons in SVC analyses, results were considered significant at $p<0.05$ FWE.

Finally, we analyzed a group $\times$ ApoE4 interaction for differential fitness-brain relationships (GM and WM) in ApoE4 carriers verses noncarriers in both subject groups. Given few homozygous ApoE4 carriers (n=7), we combined E4 homozygotes and heterozygotes (n=36) into a single group for the AD analysis with noncarriers (n=18). In the ND group there were also too few homozygous ApoE4 carriers (n=3), so we combined them with the 34 heterozygotes (n=15) to compare with the noncarriers (n=29). ApoE4 group was then multiplied by CR fitness (VO_2^{peak}) to create an interaction factor for the multiple regressions, done within diagnosis groups. All analyses were covaried for age, gender, and education. Voxels are reported with reference to the Montreal Neurological Institute (MNI) standard space within SPM5 after conversion to the standard space of Talaraich and Tournoux using custom software [48].

Results

Sample Characteristics (Table 1)

The mean age of the cohort (n=117) was 73.8 years (SD=6.3), with no significant difference between ND (n=56) and early-stage AD (n=61) participants. AD subjects had lower CR fitness (VO_2^{peak}), education, MMSE performance, and GM and WM volumes (p<.001, Table 1). AD subjects had significantly lower RER, mean heart rate, and exercise duration than the ND group; however there were no differences in ratings of perceived exertion between groups. ApoE4 allele was not related to age, gender, education, MMSE, whole brain volume, GM, WM, and CR fitness.

The role of dementia severity on treadmill testing was examined by assessing the correlation between dementia severity (CDR box score) and measures of effort and VO_2^{peak} in the early AD group. Dementia severity was not related to VO_2^{peak} (r=-0.32, p=0.81), RER (r=-0.002, p=0.98), peak heart rate (r=0.12, p=0.37), exercise duration (r=-0.09, p=0.50), or rating of perceived exertion (r=-0.84, p=0.52), nor was VO_2^{peak} correlated with MMSE in AD subjects when controlling for age and sex (r=.027, p=.842).

Group comparison

First, we used VBM to identify areas of AD related atrophy by comparing GM and WM maps in early AD vs. ND. As expected, we found significantly smaller regional volumes in AD subjects (p<0.05, family-wise error (FWE) corrected) in both GM and WM in medial temporal (hippocampus, parahippocampal gyrus), temporal, and frontal cortices (Table 2, Figure 1). The largest and most significant cluster (k) of GM atrophy was in the left limbic regions, including the hippocampus, insula, left superior temporal and middle temporal cortices (peak at 42, -4, 13, p<0.001 FWE, all coordinates given as x, y, z in Talairach space). GM was lower in AD compared to ND in the bilateral cingulate, bilateral middle frontal gyrus, left inferior temporal gyrus, bilaterally fusiform gyrus, and right supramarginal gyrus. The most significant cluster (k) of WM atrophy was in the left parahippocampal gyrus (peak at -28, -22, -22, p<.001 FWE), followed by decreases in the bilateral parahippocampal/hippocampal cortices, the right superior temporal gyrus, and right posterior cingulate cortex. There were no regions where GM or WM volume was lower in ND compared to AD.

Fitness and Brain Volume

Next, we assessed the relationship of CR fitness with regional brain volumes on a global level (across the entire brain) followed by SVC analyses confined to the hippocampal and parahippocampal regions.

Nondemented Participants—In nondemented participants, CR fitness was not significantly (FWE p<0.05) correlated with gray and white matter regional volumes. There was a trend for a positive relationship of CR fitness and GM in the right inferior frontal gyrus, and WM in the bilateral occipital cortex, lentiform nucleus, and lingual gyrus (p<.001 uncorrected, Table 3, Figure 2). The SVC analysis did not reveal a significant relationship of CR fitness with the hippocampus or parahippocampus in nondemented older adults.

Early Alzheimer's Disease—At a global level, CR fitness was positively associated with WM in the bilateral inferior parietal cortex (left at -59, -16, 27, p<0.05 FWE corrected; right at 58, -9, 19, p<0.05 FWE corrected) with positive trends (p<.001 uncorrected) in the frontal, temporal, parietal, and occipital cortices (Table 3, Figure 2). Trends (p<.001) existed in global analyses between CR fitness and GM in the cerebellum, right superior parietal gyrus, inferior and superior frontal cortices, and the temporal and medial temporal cortex (parahippocampal gyrus and uncus). The hypothesis-driven SVC isolating the medial temporal cortex

demonstrated a significant positive relationship between CR fitness and WM in the hippocampal region and a significant positive relationship between CR fitness and volume in the parahippocampal gyrus (Table 4, p<0.05 FWE corrected, plotted and detailed in Figure 3). The significant cluster for each result was extracted using the VOI function in SPM5 and the mean volume per cluster for each individual was used to plot the results for visualization purposes in Figure 3. As a secondary analysis, we performed a SVC analysis controlling for RER and PASE and found similar results in AD subjects, demonstrating a significant relationship of fitness with GM and WM in the medial temporal cortex (p=.034 FWE corrected), identical to the results detailed above.

Influence of apoE4 on CR fitness – Brain Volume Relationship—Next we examined the role of apoE4 genotype in modifying the relationship between CR fitness and brain volume in ND and AD participants. There were no regions where significant interactions of apoE4 genotype and CR fitness existed in GM and WM in AD or ND at an FWE corrected level p<0.05.

Discussion

Building on our previous work suggesting a relationship between CR fitness and whole brain volume in the earliest clinical stages of AD [18], we used novel methods and identified regionally-specific correlations between increased CR fitness and more regional brain volume in the parietal and medial temporal cortex of individuals with early-stage AD. There was no significant association between CR fitness and regional brain volumes in ND participants. The medial temporal cortex is known to be affected early in the AD course [49], consistent with our findings of lower medial temporal volume in early AD subjects compared to ND (Figure 1). This data suggests that CR fitness, or the maintenance of CR fitness in the early stages of AD, might be associated with a reduction in AD-specific brain atrophy. This relationship between brain volume and CR fitness does not appear to be modified by genetic risk for AD (APOE E4).

Accumulating data primarily generated from animal studies support the biological plausibility that CR fitness could provide disease-modifying benefits in AD. Exercise is associated with increased levels of brain-derived neurotrophic factor [50], enhanced neuronal survival and resistance to brain insults [51], increased vascularization [2], and upregulated neurogenesis in the hippocampus [52]. Adult neurogenic zones have been identified in the hippocampus and lateral ventricle walls [53] and physical activity has been correlated with increased neuronal proliferation in the hippocampus and surrounding limbic brain tissue [13, 14, 19]. In fact, a recent study in mice suggests that exercise may differentially target the dentate gyrus within the hippocampus and result in local increases in cerebral blood volume, a putative *in vivo* correlate of adult neurogenesis [14]. It has even been suggested that therapeutic stimulation of neurogenesis might contribute to functional 'repair' of diseased brain in adults [54]. Our findings, while preliminary, suggest that the relationship between CR fitness and medial temporal lobe brain volume are consistent with a fitness-related increased capacity for neuronal proliferation in early AD.

In early AD, CR fitness was positively associated with WM volume in the bilateral inferior parietal cortex (Brodmann's Areas (BA) 3 and 42). This is particularly interesting as BA 3 and 43 are involved in executive processing which may be preferentially enhanced with increased CR fitness through exercise [4]. Additionally, strong connections exist between these regions and the hippocampus; the body of the hippocampus and posterior parahippocampal cortex connect with the lateral parietal cortex.[55] Our data suggest that CR fitness may be associated with less structural atrophy in early AD within this disease-affected region[56, 57] and pathway [58]. It is also possible that CR fitness is affecting the vascular burden of the white matter, and

that this, in turn, is affecting the VBM results in the white mattet. Still, individuals with a history of clinical stroke, diabetes, and cardiovascular disease were excluded, thus minimizing the role of vascular-related burden on brain change.

Our SVC analysis restricted to the medial temporal lobes demonstrated a relationship between CR fitness and white and gray matter volume. While the hippocampus is largely a gray matter structure, there are four endofolial fiber pathways within the hippocampus [59], and the identified white matter cluster appears to localize to the border of the fimbria and CA3. Despite our usage of the more accurate unified segmentation procedure, it is possible that there is a partial volume effect of gray and white matter segmentation. The stringent correction for multiple comparisons calculated across approximately 6,500 voxels minimizes the possibility that this represents a false-positive. Additionally, there were some assymetries in our findings. Fitness was correlated to parahippocampal gyrus volume on the right, and hippocampal gyrus volume on the left. While we are unable to fully explain these findings, assymetrical patterns in AD atrophy have been reported [60, 61]. In addition there were more hippocampal gray and white matter volume decreases in the AD group on the left side, arguing that asymmetries in the CR fitness relationship to brain might reflect the disease-specific changes in this particular subject group.

Our data does not suggest that ApoE4 genotype influences the relationship of CR fitness on atrophy. We hypothesized the presence of an E4 allele might interact with the relationship of fitness on brain volume, based on data showing that the presence of the apoE4 allele has been associated with increased atrophy [62]. Prior studies have reported that ApoE4 carriers did not attain the same benefit as noncarriers from physical activity in terms of blood pressure and lipid patterns [63, 64]. In addition a previous longitudinal study suggested that the the presence of the ApoE4 allele moderated the benefits of exercise on dementia risk. [8]. We found no evidence to suggest the relationship between CR fitness and brain volume was modulated by apoE4 genotype. In line with our results, a longitudinal study measuring the positive effect of self-reported physical activity did not find a mediating effect of ApoE4 genotype on dementia risk [9]. Our subject group contained a very low number of E4 homozygotes (n=7 in AD, n=3 in ND). The gene-fitness interaction might have had more power if there was a stronger genetic load of the risk allele in the two analyses. It is also possible that there are other genetic mechanisms mediating the relationship between fitness and brain atrophy, and understanding these will be beneficial to characterizing efficacy of fitness and exercise as a therapeutic option for AD.

Our data can be interpreted as validation of the most recent VBM analytic techniques by replicating previous findings of AD-related atrophy[65, 66] in both gray and white matter in medial temporal (hippocampus, parahippocampal gyrus), temporal (superior temporal and middle temporal gyrus), and parietal cortices ($p<0.05$, FWE). Atrophy in these regions has been shown to be specific to AD as opposed to aging-related changes [65, 67]. Comparisons of AD and ND regional brain volume are not novel. However, it was necessary to clarify if this group of very early AD subjects did in fact have significant regional brain atrophy (especially atrophy in the medial temporal cortex) before we could interpret any effect of fitness on "disease-related" brain volume decrease.

The study design is cross-sectional and therefore limits our ability to infer a causal relationship between CR fitness and brain atrophy. Thus, it is possible that AD-related processes may be driving reductions in CR fitness. Our data, however, suggests that individuals with AD performed well on the treadmill tests, and dementia severity (CDR box score) was not associated with cardiorespiratory fitness ($VO_2{}^{peak}$) or physiologic measures of effort (RER and peak heart rate). Additionally, secondary analyses controlling for participant effort (RER) and physical activity level (PASE), which were both lower in the AD group, did not alter the results of the SVC analysis.

A previous cross-sectional VBM study found evidence that fitness may moderate age-associated atrophy in nondemented older adults. Their analysis, however, assessed the age $\times$ $VO_2{}^{peak}$ interaction effect on brain volume while a direct assessment of $VO_2{}^{peak}$ and brain volume, similar to our analysis of interest, did not reveal significant regional relationships with fitness ([Colcombe 2003]). In addition, another study found an interactive effect of hormonal treatment and $VO_2{}^{peak}$ on brain volume in women while a direct relationship between brain volume and fitness was not evident [68]. Our stringent approach of maintaining a rigorous level of statistical significance may have reduced the power to detect fitness-brain associations in nondemented subjects. Additionally, these cross-sectional studies may lack the power to detect direct relationships in nondemented individuals, perhaps related to reduced variability in regional brain atrophy compared to the AD participants. Larger studies with longitudinal outcome measures may provide increased power to detect fitness relationships with brain volume. For instance, a randomized controlled trial of 6 months of exercise in nondemented elderly subjects demonstrated increased brain volume in several regions in those exercising vs. controls [69]. Longitudinal studies and randomized controlled trials will be necessary to further define the role of exercise and fitness in promoting brain health.

There are limitations to VBM, including sensitivity to methodological variation in normalization, smoothing kernel, and template. We chose a smoothing kernel of 10mm based on *a priori* hypotheses about the likely scale of interest. In addition, the use of SVC reduces false negatives that can result from smoothing kernels over 8mm. In this study we used current VBM methods, including unified segmentation without the use of priors to decrease the deleterious effects of template usage in this aging and diseased sample [38]. In addition, we compared the global volumes from this new method compared to another version of segmentation (FSL) and found them to be comparable to a previous study in our sample [18]. This is one of the first studies in the AD literature to use these newer steps, and first to look at the relationship of CR fitness and medial temporal volume using novel VBM techniques in AD subjects. Finally, further longitudinal and interventional (i.e., exercise trials) are necessary to more precisely define these relationships, in particular the role of exercise in modifying AD-related changes.

Conclusions

This is the first imaging study to characterize the relationship of cardiorespiratory fitness to regional brain volume changes in early Alzheimer's disease. Our data suggest that cardiorespiratory fitness might have a disease-modifying effect in the earliest stages of AD, where increased CR fitness is associated with increased regional brain volumes, particularly in the medial temporal lobes. There is no evidence to suggest this relationship is modified by the presence of the apoE4 risk allele. Longitudinal and interventional studies are necessary to assess the role of exercise to enhance cardiorespiratory fitness as a therapy for attenuating AD-related atrophy.

Acknowledgments

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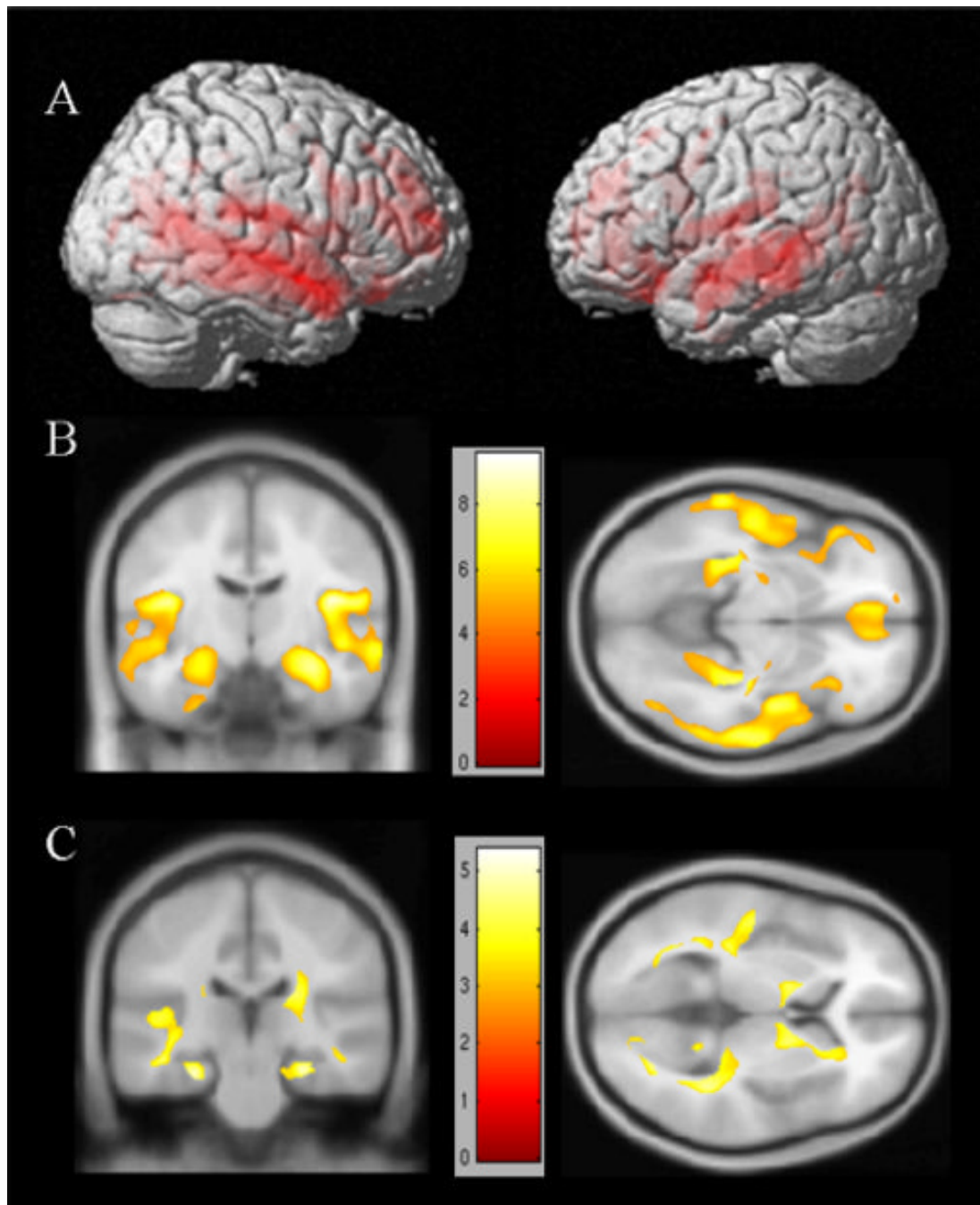
Figure 1.
Statistical maps of the entire brain (A) showing areas where gray matter (A, B) and white matter volume (C) are reduced in patients with Alzheimer's disease compared to nondemented older adults. All shown at a threshold of p<.05 FWE corrected, cluster size (k) > 20. Z scores noted on color charts for gray matter (B) and white matter (C) maps, overlaid on the MNI T1 brain consisting of 154 subjects.
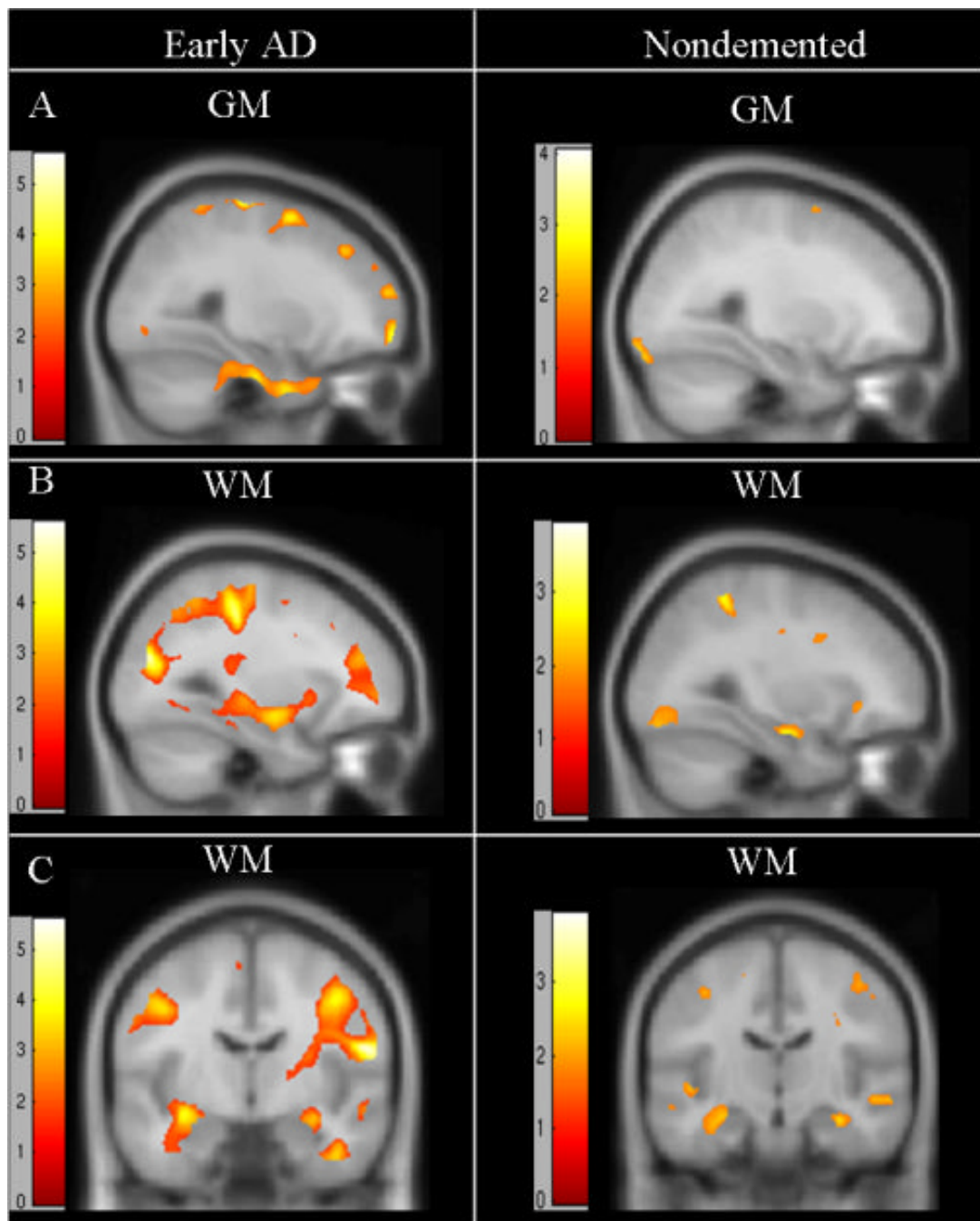
Figure 2.
Statistical maps of regions where cardiorespiratory fitness (VO_2^{peak}) is positively correlated with brain volume in global analyses of the entire brain (p<.001 uncorrected, Z>2.5). Images represent regions where fitness is associated with gray matter (GM) and white matter (WM) volumes in early AD (left column) and nondemented (right column) subjects. Sagittal views are presented in rows A and B and coronal views in row C. Z scores noted on color charts for each analysis, overlaid on the MNI T1 brain consisting of 154 subjects. Significant regions for each analysis are detailed in Table 3.
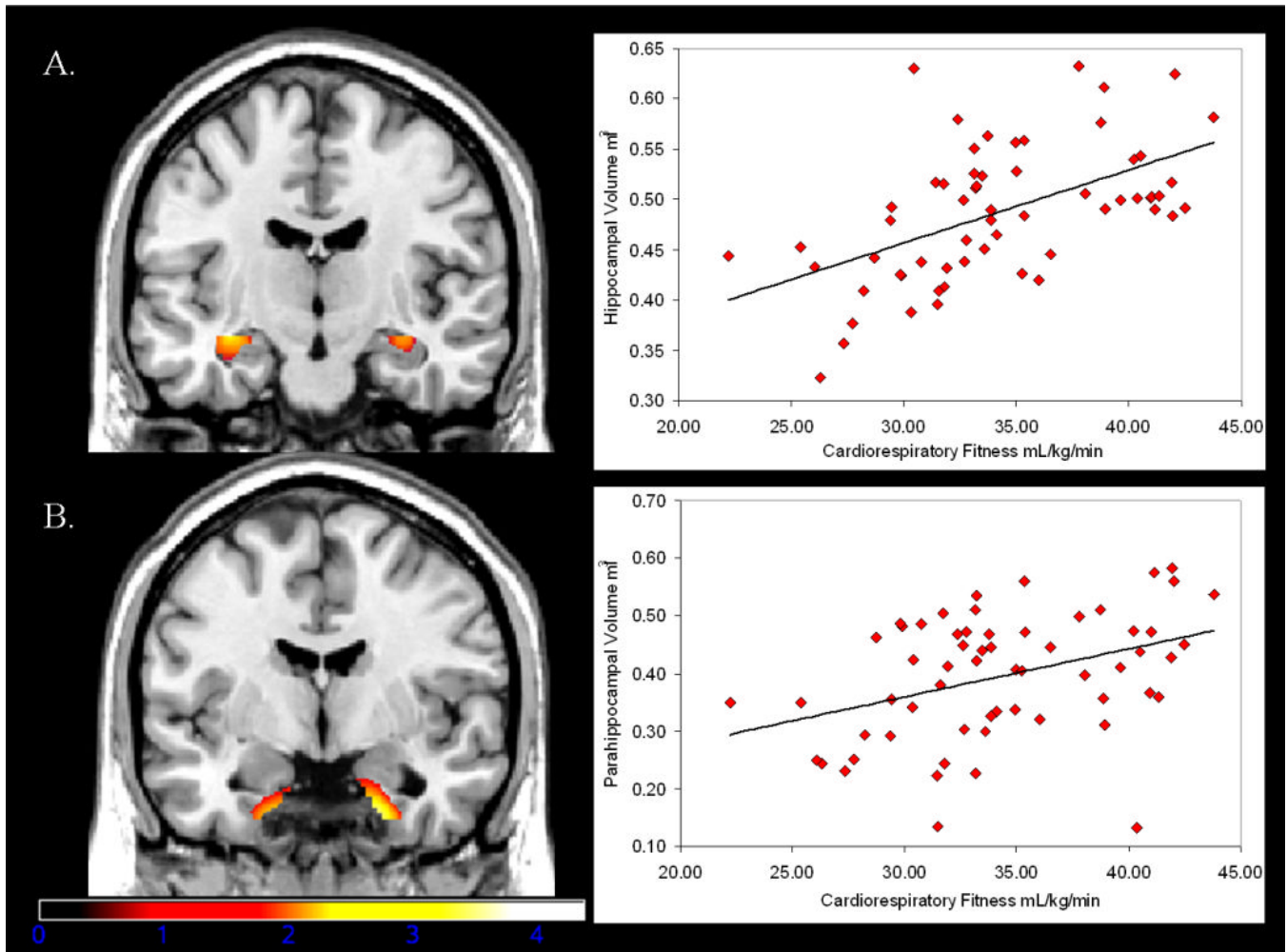
Figure 3.
Statistical maps and distribution plot from the small volume corrected (SVC) analysis of early AD subjects (p <.05 FWE Corrected). A) Image represents regions where cardiorespiratory fitness is positively associated with hippocampal white matter (WM) volume accompanied by a scatterplot demonstrating the relationship extracted from the left hippocampal cluster at peak (-32, -9, -13). B) Image represents regions where fitness is related to parahippocampal gray matter (GM) volume with scatterplot representing the relationship extracted from the parahippocampal cluster at peak (23, 1, -36). Peak coordinates are significant at p<.05 FWE corrected, and detailed in Table 3. Z scores are noted on the color chart for each analysis, overlaid on the MNI T1 brain consisting of 154 subjects.

Table 1

Sample Characteristics

All data represent means (SD), unless otherwise noted.

	Nondemented	Early AD	
	(n=56)	(n=60)	P Value
Age, y	73.3 (6.2)	74.3 (6.3)	0.38
% Female (n)	58.9 (33)	61 (37)	0.77
Education (total years of formal)	16.4 (2.2)	15.3 (3.3)	<.05
MMSE	29.4 (.8)	26.2 (3.7)	<.001
Total Intracranial Volume, cm³	1522.5 (134)	1486.2 (145.3)	0.17
Gray matter volume,	501.8 (43.5)	447.9 (52)	<.001
White matter volume, cm³	444.3 (56)	419.3 (53.6)	<.05
Whole Brain Volume, cm³	946.1 (86.5)	867.2 (89.9)	<.001
Cardiorespiratory Fitness (VO_2^{peak})	1.7 (.6)	1.4 (.4)	<.001
Physical Activity Scale in the Elderly (PASE)	122 (59.3)	85.5 (54.5)	<.001
Respiratory Exchange Ratio	1.10 (.11)	1.07 (.08)	<.05
Exercise Duration (seconds)	673.1 (219.6)	549.8 (176.7)	<.05
Maximum Heart Rate (beats per minute)	148.9 (15.5)	139.4 (20.1)	<.001
Rating of Perceived Exertion (6 – 20)	17.1 (1.7)	17.03 (2.3)	.78

Table 2

Regions of decreased brain volume in AD compared with ND

Type	Region	Peak Coordinate (mm)			k	Z Score	P Value
	Talairach	**x**	**y**	**z**			**FWE**
GM	R Insula (BA 13)	42	-4	13	141815	Inf	<.001
	(Cluster includes L superior temporal, middle temporal, and hippocampus)						
	L Cingulate Gyrus (BA 31)	-3	-40	35	7618	6.77	<.001
	R Posterior Cingulate	14	-59	3	531	5.57	0.001
	L Middle Frontal Gyrus	-29	26	50	390	5.53	0.001
	L Inferior Temporal Gyrus (BA 20)	-31	-5	-43	821	5.25	0.003
	R Middle Frontal Gyrus (BA 6)	29	-6	52	181	5.22	0.003
	R Supramarginal Gyrus (BA 40)	51	-48	37	283	5.14	0.004
	R Middle Frontal Gyrus	42	-34	41	138	5.08	0.006
	L Middle Frontal Gyrus	-29	-7	57	106	5.03	0.008
	L Fusiform Gyrus (BA 37)	-45	-38	-21	37	4.81	0.02
	L Fusiform Gyrus (BA 19)	-42	-77	-20	51	4.75	0.026
	R Fusiform Gyrus	36	-77	-21	105	4.74	0.027
	L Middle Temporal Gyrus (BA 37)	-54	-59	-13	24	4.71	0.03
WM							
	L Parahippocampal Gyrus	-28	-22	-22	71	5.08	0.005
	R Superior Temporal Gyrus	43	3	-17	902	5.06	0.006
	R Posterior Cingulate	20	-54	14	86	4.99	0.008
	L Parahippocampal/Hippocampus	-42	-12	-19	210	4.92	0.01
	R Posterior Cingulate	27	-71	7	23	4.91	0.011
	R Parahippocampal/Hippocampus	28	-23	-20	31	4.77	0.02

uncor=uncorrected p value, k= cluster size, L=Left, R=Right, BA=Brodmann's Area, AD=Alzheimer's Disease, GM=Gray Matter volume, WM=White Matter volume. There were no regions that AD had greater GM or WM than ND.

Table 3

GM and WM Regional Correlations with Cardiorespiratory Fitness, Global Results

Group	Type	Region		Peak Coordinate (mm)			k	Z	P	
		Talairach	x	y	z				FWE	Value uncor
ND	GM	R Inferior Frontal Gyrus	38	37	6	1469	3.76		0.812	<.001
	WM									
		R Inferior Occipital Gyrus	42	-77	-9	4448	3.68		0.771	<.001
		L Middle Occipital Gyrus	-28	-84	-1	5493	3.39		0.996	<.001
		L Lentiform Nucleus Gyrus	-22	14	-3	3489	3.1		0.999	0.001
		L Lingual Gyrus	-7	-78	-2	1549	3.01		1	0.001
AD	GM									
		Cerebellum	0	-69	-14	16346	4		0.404	<.001
		R Superior Parietal Gyrus	-10	-71	58	33822	3.98		0.426	<.001
		R Parahippocampal Gyrus	23	1	-36	5140	3.54		0.896	<.001
		R Inferior Frontal Gyrus	48	49	4	5655	3.42		0.959	<.001
		R Inferior Frontal Gyrus	60	14	22	1335	3.37		0.974	<.001
		R Transverse Temporal (BA 42)	64	-13	13	885	3.26		0.993	0.001
		L Superior Frontal Gyrus	-31	47	28	4004	3.18		0.998	0.001
		R Middle Occipital Gyrus	38	-71	6	2419	3.15		0.998	0.001
		R Superior Frontal Gyrus (BA 8)	-4	21	58	7291	3.03		1	0.001
		L Parahippocampal Gyrus	-19	-17	-31	1802	3.02		1	0.001
	WM									
		L Postcentral Gyrus (BA 3)	-59	-16	27	84440	4.97		*0.01	<.001
		R Postcentral Gyrus (BA 43)	58	-9	19	36123	4.85		*0.018	<.001
		R Middle Occipital Gyrus	48	-58	-11	1772	4.35		0.127	<.001
		R Precentral Gyrus	22	-24	54	38386	4.33		0.136	<.001
		R Middle Frontal Gyrus	36	18	35	2952	4.06		0.325	<.001
		L Cingulate Gyrus	-17	2	49	6801	3.25		0.992	0.001
		R Middle Temporal Gyrus	57	-14	-8	3123	3.06		1	0.001

Regions presented are positively correlated with cardiorespiratory (CR) fitness (VO$_2$peak). No regions negatively correlated with CR fitness. uncor = uncorrected p value, k = cluster size, L = Left, R = Right, BA = Brodmann's Area, AD = Alzheimer's Disease, ND = Nondemented Elderly, GM = Gray Matter volume, WM = White Matter volume.

*
regions in bold reached corrected significance (FWE).

Table 4

GM and WM Limbic Correlations with Cardiorespiratory Fitness

Group	Type	Region	Peak Coordinate (mm)			k	Z	P Value	
		Talairach	x	y	z			FWE	uncor
ND	GM	Hippocampus				N/A			
		Parahippocampal				N/A			
	WM								
		L Hippocampus	31	-11	-20	390	2.54	0.343	0.006
		R Hippocampus	-29	-17	-17	1193	2.26	0.514	0.012
		Parahippocampal				N/A			
AD	GM	Hippocampus				N/A			
		L Parahippocampal Gyrus	-19	-17	-31	1457	3.02	0.118	0.001
		*R Parahippocampal Gyrus	23	1	-36	2424	3.54	*0.032	<.001
	WM								
		*L Hippocampus	-32	-9	-13	2138	3.78	*0.019	<.001
		R Hippocampus	31	-7	-17	915	2.96	0.186	0.002
		L Parahippocampal Gyrus	-25	-43	-9	672	3.15	0.108	0.001
		R Parahippocampal Gyrus				N/A			

Regions presented are positively correlated with cardiorespiratory (CR) fitness (VO2^peak), from small volume correction (SVC) analysis localized to the medial temporal lobe. SVC's were bilateral hippocampus and bilateral parahippocampal gyrus ROIs, listed separately (L and R) for statistics breakdown. N/A = no suprathreshold clusters, SVC = small volume correction, uncor = uncorrected p value, k = cluster size, L = Left, R = Right, BA = Brodmann's Area, AD = Alzheimer's Disease, ND = Nondemented Elderly, GM = Gray Matter volume, WM = White Matter volume.

*
regions in bold reached corrected significance (FWE).