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Physical activity, body mass index, and brain atrophy in Alzheimer's disease

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ABSTRACT

The purpose of this study was to use a novel imaging biomarker to assess associations between physical activity (PA), body mass index (BMI), and brain structure in normal aging, mild cognitive impairment, and Alzheimer's dementia. We studied 963 participants (mean age: 74.1 ± 4.4 years) from the multisite Cardiovascular Health Study including healthy controls (n = 724), Alzheimer's dementia patients (n = 104), and people with mild cognitive impairment (n = 135). Volumetric brain images were processed using tensor-based morphometry to analyze regional brain volumes. We regressed the local brain tissue volume on reported PA and computed BMI, and performed conjunction analyses using both variables. Covariates included age, sex, and study site. PA was independently associated with greater whole brain and regional brain volumes and reduced ventricular dilation. People with higher BMI had lower whole brain and regional brain volumes. A PA-BMI conjunction analysis showed brain preservation with PA and volume loss with increased BMI in overlapping brain regions. In one of the largest voxel-based cross-sectional studies to date, PA and lower BMI may be beneficial to the brain across the spectrum of aging and neurodegeneration.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and the number of persons predicted to have the disease in the United States alone will increase to 13.5 million from 2.2 million by the year 2050 (Sperling et al., 2011). Currently, about 34 million people worldwide have the disease, and lifestyle factors that are modifiable in principle, such as physical inactivity and obesity, are associated with a heightened risk for AD. If these associations were related to the risk of expressing clinical dementia, then increasing physical activity and decreasing the prevalence of obesity may reduce the number of AD cases by an estimated 50% (Barnes and Yaffe, 2011). These estimates are the foundation for developing prevention strategies, which are becoming particularly important given the relatively poor efficacy of current drug treatments for AD.

Lack of physical activity (PA) may be the most important modifiable risk factor for AD in the United States and the third most important worldwide (after low education and smoking) (Barnes

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and Yaffe, 2011). Midlife obesity also contributes to a substantial proportion of cases worldwide and in the United States (Barnes and Yaffe, 2011). Thus, the risk of AD might be reduced by systematically increasing PA (Chang et al., 2010; Lautenschlager et al., 2008; Rolland et al., 2008; van Gelder et al., 2004) and reducing obesity. We have previously shown that self-reported PA in healthy elderly people is associated with larger regional brain volumes and reduced risk for future conversion to AD or its prodrome, mild cognitive impairment (MCI) (Erickson et al., 2010; Petersen et al., 1999). Higher body mass index (BMI) in midlife is associated with structural brain changes, cognitive decline, and an increased risk of AD in late life (Cronk et al., 2010). This suggests that differences in brain structure are a useful intermediary in understanding the association between risk modifiers such as PA and BMI, and the clinical manifestations of neurodegeneration, in this case AD and MCI.

Here, we set out to assess the associations between self-reported PA, computed BMI, and regional brain volumes in a large cohort including people with MCI and AD. We were especially interested in understanding whether potential effects of these variables were more easily detected in some parts of the brain relative to others, or if it was simply a pervasive association across the entire brain. To answer this, we used tensor-based morphometry (TBM), which creates detailed 3D maps pinpointing brain regions with the strongest statistical associations with PA and/or BMI, throughout the gray matter, white matter, and cerebrospinal fluid. Finally, we examined how BMI influenced the association of PA with brain structure, as BMI is negatively associated with both PA and brain structure in aging, MCI, and AD (Ho et al., 2010a; Raji et al., 2010a). We also examined whether PA explained associations between BMI and brain structure, and whether there were any common areas associated with both PA and BMI.

2. Methods

2.1. Participants

The Cardiovascular Health Study (CHS) is a multisite, population-based longitudinal study of coronary heart disease and stroke in individuals aged 65 years and older (Fried et al., 1991). CHS recruitment was based on the Medicare eligibility lists in: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. In a first wave, 5201 participants were recruited from 1989 to 1990. In a second assessment, 687 African-Americans were recruited from 1992 to 1993 leading to a cohort of 5888 participants. The institutional review board at each site approved the study methods, and all participants gave written informed consent.

2.2. The CHS Memory Study

In 1991 and 1992, 3608 of the CHS enrollees participated in the CHS Memory Study (CHS-MS) and underwent a low-resolution magnetic resonance imaging (MRI) scan of the brain. In 1998 and 1999, a follow up high-resolution MRI scan and neurobehavioral evaluations were completed for all available, living participants ($n = 2101$) (Kuller et al., 2003). Because of the late inclusion of the high-resolution spoiled-gradient echo (SPGR) sequence into the scanning protocol, not all participants had high-resolution anatomic imaging. Thus, the present study includes only the data from the 963 CHS-CS participants who had an SPGR scan and whose MRI data met quality control standards. Prior CHS quality control measures included visual review of scans by a neuroradiologist, to ensure that no large space occupying lesions existed that could potentially hinder analysis (Bryan et al., 1997; Raji et al., 2009). We also performed our own visual assessment to ensure against any cropping of brain tissue from the scan field of view or corruption of MR images in the TBM processing stream.

Participant demographics are shown in Table 1. A separate column identifies sites that were independently correlated with study variables, based on analysis of variance (ANOVA). Hagerstown and Pittsburgh were the sites most frequently correlated with the variables characterized in this study based on the ANOVA weighting the correlation of these sites against the 2 other study locations ($p < 0.05$). Of the 963 participants included, APOE4 genotype was available in 894 and 221 (24.7%) were APOE4 positive. Full methods for obtaining the APOE4 genotypes in our study are described elsewhere (Kuller et al., 1998).

Neurobehavioral evaluations were assessed to determine the presence of any disorder that could affect cognition. Participants were classified as having normal cognition, MCI, or AD (Lopez et al., 2003b). The diagnosis of dementia was based on deficits in performance in 2 or more cognitive domains that were sufficiently severe to affect activities of daily living and their history of normal intellectual function before the onset of cognitive abnormalities; a memory deficit was not required for the diagnosis of dementia (Lopez et al., 2012). The Adjudication Committee consisted of experts in dementia who had access to the historical CHS cognitive test scores, primarily the Modified Mini Mental Status Examination (3MSE) (and subscales), Benton Visual Retention Test, and the DSST, as well as the CES-D scores. The committee also reviewed data from vision and hearing tests, history of alcohol intake, activities of daily living questionnaire, IQ-CODE, Dementia Questionnaire, vital status, date of death where relevant, history of hospitalizations, medications to treat dementia, findings from MRI scans, results of neuropsychological assessments, and hospital records (Lopez et al., 2003a).

Table 1
Characteristics of CHS Memory Study participants with MRI in 1998 and 1999 by CHS site

	Winston- Salem	Sacramento	Hagerstown	Pittsburgh	Total sample	Study site as a main effect (t, *p*-value)
Number of MRI scans analyzed	18	315	192	438	963	
Age[a]	75.6 (4.4)	74.8 (4.4)	73.5 (4.1)	73.8 (4.3)	74.1 (4.3)	Hagerstown (−2.3, 0.02)
Sex, male, % (n)	61 (11)	41 (130)	44 (84)	40 (176)	42 (401)	No study site was predictive
Race, white, % (n)	100 (18)	92 (289)	99 (190)	80 (348)	88 (845)	Hagerstown (−2.7, 0.008); Pittsburgh, (4.6, 0.001)
Years of education[a]	13 (2.1)	13.4 (2.4)	11.6 (3.1)	13.8 (2.7)	13.2 (2.8)	Pittsburgh (2.4, 0.02)
BMI[a]	23.9 (3.4)	26.4 (4.3)	27 (4.5)	26.6 (4.2)	26.6 (4.3)	Hagerstown (-2.3, 0.02)
Blocks walked[a]	97.3 (87.4)	34.5 (56.1)	33.1 (50.8)	35.3 (45.2)	35.6 (51.4)	Hagerstown (4.7, 0.001)
Time taken to walk 15 feet[a]	4.8 (0.9)	6 (3.3)	5.6 (4.6)	5.6 (2.2)	5.7 (3.2)	No study site was predictive
Number of infarcts[a]	0.39 (0.7)	0.59 (1.0)	0.53 (0.99)	0.48 (0.89)	0.52 (0.96)	No study site was predictive
Sulcal grade (0–9, worst)[a]	4.11 (1.3)	3.9 (1.4)	3.89 (1.7)	4 (1.6)	3.96 (1.6)	Pittsburgh (4.2, <0.001); Hagerstown (−2.3, 0.02)
Ventricular grade (0–9, worst)[a]	3.72 (0.83)	3.86 (1.4)	3.48 (1.2)	3.71 (1.4)	3.72 (1.4)	Hagerstown (−2.7, 0.007)
White matter grade (0–9, worst)[a]	3 (1.9)	2.88 (1.7)	2.34 (1.5)	2.45 (1.6)	2.58 (1.6)	Hagerstown (−3.7, <0.001); Pittsburgh (−3.6,<0.001)
Infarcts, % (n)	28 (5)	34 (107)	30 (58)	30 (130)	31 (300)	No site was predictive

Key: BMI, body mass index; CHS, Cardiovascular Health Study; MRI, magnetic resonance imaging; SD, standard deviation.
[a] Mean (SD).