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Cerebrovascular Disease and Neurodegeneration in Alzheimer's Disease with and without a Strong Family History: A Pilot Magnetic Resonance Imaging Study in Dominican Republic

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Abstract

The incidence and prevalence of Alzheimer's disease (AD) dementia are higher among Caribbean Hispanics than among non-Hispanic Whites. The causes of this health disparity remain elusive, partially because of the relative limited capacity for biomedical research in the developing countries that comprise Caribbean Latin America. To begin to address this issue, we were awarded a Development Research Award from the US NIH and Fogarty International Center in order to establish the local capacity to integrate magnetic resonance imaging (MRI) into studies of cognitive aging and dementia in Dominican Republic, establish collaborations with Dominican investigators, and conduct a pilot study on the role of cerebrovascular markers in the clinical expression of AD. Ninety older adult participants with and without AD dementia and with and

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without a strong family history of AD dementia received MRI scans and clinical evaluation. We quantified markers of cerebrovascular disease (white matter hyperintensities [WMH], presence of infarct, and presence of microbleed) and neurodegeneration (entorhinal cortex volume) and compared them across groups. Patients with AD dementia had smaller entorhinal cortex and greater WMH volumes compared with controls, regardless of family history status. This study provides evidence for the capacity to conduct MRI studies of cognitive aging and dementia in Dominican Republic. The results are consistent with the hypothesis that small vessel cerebrovascular disease represents a core feature of AD dementia, as affected participants had elevated WMH volumes irrespective of family history status.

Keywords

Alzheimer's disease; cerebrovascular disease; developing countries; neurodegeneration

INTRODUCTION

Ongoing research in our center in Northern Manhattan consistently shows that the prevalence and incidence of clinical Alzheimer's disease (AD) is greater among Caribbean Hispanics than among non-Hispanic Whites [1, 2]. Despite the consistency of this observation, the causes for this health disparity remain elusive. Older Caribbean Hispanics tend to have elevated markers of small vessel cerebrovascular disease relative to non-Hispanic Whites [3], and there is an emerging consensus that cerebrovascular factors play a critical role in the clinical expression of AD [4] or perhaps its pathogenesis [5]. These issues are difficult to study for two primary reasons. First, there is under-representation of Caribbean Hispanics in large-scale research studies and the limited access to cutting-edge biomedical methodology in the developing countries that comprise Caribbean Latin America. Second, cerebrovascular disease and AD pathology co-occur more frequently than not among individuals diagnosed clinically with AD [4], so it is difficult to disambiguate the extent to which cerebrovascular disease represents a comorbidity or whether it is a primary feature of AD.

To begin to address these questions, we were awarded a Development Research Grant Award from the US National Institutes of Health and the Fogarty International Center in response to PAR-11–031 ("Brain disorders in the developing world: Research across the lifespan") in order to establish the local capacity to integrate research-grade magnetic resonance imaging (MRI) studies into studies of cognitive aging and dementia in Dominican Republic, to establish collaborative relationships with Dominican investigators interested in translational cognitive aging research, and to carry out a pilot study to support a prospective study that examines the extent to which markers of cerebrovascular disease contribute to the expression of AD dementia.

The purpose of the current study was to first to establish the capability and test the feasibility of conducting an MRI study focused on AD dementia in Dominican Republic and second, to examine differences in markers of cerebrovascular disease and neurodegeneration in affected (i.e., with a clinical diagnosis of AD) and unaffected (i.e., without a clinical diagnosis of

AD) older adults with and without significant family history of AD. The pilot study was designed in the context of ongoing debate in the extant literature about the role of vascular factors and cerebrovascular disease in the clinical manifestation and pathogenesis of AD. Vascular risk factors have long been known to increase the risk of AD dementia, and it is well-established that cerebrovascular disease at least plays an additive role in the expression of clinical symptoms of AD, either by lowering clinical diagnostic thresholds or by contributing directly to the severity of symptoms in manifest disease [6, 7]. However, it is yet to be established whether cerebrovascular disease should be considered a primary pathological feature of AD and whether it is mechanistically related to the disease. Our previous work demonstrated that markers of cerebrovascular disease, including white matter hyperintensities (WMH) in particular, are elevated among individuals with and at risk for AD dementia [3, 8–12], including in those with autosomal dominant forms of AD [13,14]. In the current study, we leveraged the unique structure of a family-based study to examine the potential role of cerebrovascular disease in AD dementia. We hypothesized that if cerebrovascular disease represents a primary feature of AD dementia, cerebrovascular markers would be elevated in affected individuals irrespective of their familial status, while —if cerebrovascular markers are not a core feature of AD dementia—they would be lower among affected individuals with strong family histories due to the supposedly “genetically purer” form of the disease. Similarly, we expected that both AD dementia patients with and without a family history of disease would manifest similar degrees of neurodegeneration relative to controls; however, if affected individuals without a strong family history had a greater degree of cerebrovascular disease than those with a strong family history, we would expect them to manifest less neurodegeneration for any given level of dementia.

METHODS

Overall study procedures and barriers

This project interfaced with a study titled “Estudio Familiar de Influencia Genetica de Alzheimer” (EFIGA; Family Study of the Genetic Influence of Alzheimer’s Disease), an ongoing National Institutes of Health-supported genetic epidemiological study (AG015473, PI: Richard Mayeux) that has recruited older clinical AD affected and unaffected adults from families with and without genetic enrichment for AD, as defined by having at least two siblings with suspected AD dementia and no first-degree relatives with suspected AD dementia, respectively. The research team at Columbia University travelled to Dominican Republic several times first to establish a partnership with Centro de Radiología Especializada (CRESA; Center for Specialized Radiology) in Santiago and next to establish a research-grade MRI protocol, file transfer protocol, and recruitment and enrollment procedures. Following attainment of Institutional Review Board approval at Columbia University and in the Dominican Republic, stratified participant recruitment from the parent EFIGA study included quasi-random sampling from four discrete groups: healthy controls with no known family history of AD dementia, healthy controls with significant family history of AD dementia (operationally defined as having at least 2 siblings with AD dementia), individuals with AD dementia with no family history (operationally defined as having no first degree family member with AD dementia), and individuals with AD

dementia with significant family history for the pilot study, who received structural MRI scans at the time of their planned clinical follow-up assessment in the parent study.

There were several barriers that emerged during the planning and implementation phases of this work. Identification of an MRI facility that was willing to collaborate on a research project required contact with established collaborators who referred us to a private clinical imaging facility, Centro de Radiologia Especializada (CRESA). This study was the first systematic research project that had been implemented at CRESA and we needed to establish 1) a research fee and payment structure, 2) a highly standardized protocol for the acquisition of research-grade MRI scans, 3) a reliable data transfer protocol, 4) procedures to identify incidental findings, and 5) incentives for prospective subjects to participate in the research. Each of these barriers is discussed here. We very much viewed the partnership with CRESA as a scientific collaboration and the MRI scan research rate was established to reflect the goal of collecting data rather than of generating clinical revenue. To not interfere with clinical services at the imaging center, research MRI scans tended to be scheduled in blocks outside of high-traffic clinical hours. To establish a research protocol, an expert in MR sequences from Columbia University travelled to CRESA to set up the individual MRI sequences. Over a two-day period, we piloted the protocol on local volunteers, assessing the images for resolution, inhomogeneity, contrast, and signal-to-noise, adjusting the sequences as necessary. Once the protocol was established, it was saved on the MRI console and implemented for every research participant. The secure file transfer protocol for data transfer to Columbia University was unreliable over the Internet; to overcome this issue, entirely de-identified scan data were stored on an encrypted hard-drive and shipped via courier after every 10 participants. Data were backed up on local servers until they were successfully received at Columbia University, where they were transferred to local servers with regular back-up. Each acquired MRI scan was reviewed by a local radiologist for incidental findings following a protocol established at Columbia University. Severity ratings were assigned to each read as follows: Level 1 indicated no clinically significant abnormalities noted; Level 2 indicated minor, although not unexpected, findings were noted that did not require clinical follow-up; Level 3 indicated potentially clinically relevant incidental findings that required clinical follow-up; and Level 4 indicated emergent findings that required immediate clinical attention. The local radiologist completed the safety review on the same day of the MRI scan. Within one week, a standardized letter was sent to the participant that explained the nature of the clinical findings, if any. Also, within one week, the study physician called and spoke with each participant (or their delegate) to explain the outcome of the safety review. Only one finding required clinical follow-up (Level 3); in that case the study physician, with the explicit permission of the participant, contacted the participant’s primary care physician to describe the finding and faxed him the radiological report. Finally, participants were compensated for their time and effort, and transportation was reimbursed or arranged.

Participants

Participants in the current study came from the ongoing EFIGA study (AG015473, PI: Richard Mayeux [15, 16]), which recruits and enrolls two groups of participants, including families in which multiple persons are affected with AD dementia and a case-control sample that includes unrelated individuals with and without AD dementia. The participants recruited

therefore comprise four discrete groups: normal controls with (NC+) and without (NC–) a family history of AD dementia and affected individuals with (AD+) and without (AD–) a family history of AD dementia. Here, we refer to controls as participants without a diagnosis of dementia. EFIGA participants were recruited through multiple sources, including local clinics in Dominican Republic, advertisement through local media, and word-of-mouth. For the EFIGA familial cases, which required that at least two siblings are affected with AD dementia, the diagnostic and recruitment strategy involved identification of the affected proband and then a structured family interview (with the proband and an informant) to determine whether siblings were also affected. Unaffected and affected siblings were then invited to participate in the study, and diagnosis of affected siblings was confirmed via the same diagnostic procedures applied to probands. For the case-control participants, recruitment strategies were similar but required that participants were unrelated and did not have a significant family history of dementia (i.e., no first degree family member affected with AD dementia). Participants were evaluated with comprehensive medical, neurological, and neuropsychological assessments at each visit. A consensus panel comprising attending physicians and neuropsychologists with expertise in cognitive aging and dementia assigned diagnoses according to standardized criteria [17].

For the MRI substudy, participants were recruited in a semi-random, stratified fashion. Our goal was to include approximately equal numbers of participants with and without dementia. During regularly-scheduled EFIGA visits, eligible participants were approached consecutively about participation in the MRI substudy, such that each cell was filled at approximately the same rate. For affected and unaffected individuals with a family history, only one member of each family was approached about participating. Table 1 displays demographic features for the four groups. A total of 90 participants completed the MRI substudy (Table 1). We approached approximately 115 potential participants in order to reach our target N of 90. Primary reasons for refusal included an unwillingness to travel to the MRI center for the scan, family refusal to consent on behalf of their impaired family member, and claustrophobia. This refusal rate is comparable to our experience conducting similar studies in New York. An additional two participants were considered but not approached after a research chart review revealed that they had contraindications for MRI scanning (history of hip replacement surgery and pacemaker). Similar to what we have done in previous studies (e.g., [3]), we created a vascular risk factor summary score based on variables ascertained by participant self-report [18]: hypertension, heart disease, type 2 diabetes, and smoking history. The heart disease variable included history of myocardial infarction, congestive heart failure, or any other heart disease history. The sum of these four dichotomous variables yielded a vascular risk summary score that could range from 0 to 4. The highest number of years of formal education was also ascertained by self-report.

Magnetic resonance imaging

MRI was conducted in a single session at a single site within one month of the participant's most recent EFIGA study follow-up visit. Participants were scanned on a GE Signa Excite 1.5 Tesla system at CRESA in Santiago, Dominican Republic. The MRI protocol included a high-resolution T1-weighted spoil gradient echo (SPGR) image (TE=1.7, TR = 8, flip angle = 20, 1mm isotropic), a T2-weighted fluid attenuated inversion recovery (FLAIR) image

(TE=120, TR=8000, 3 mm slice thickness), and a gradient echo image (TE=15, TR = 650, 3 mm slice thickness) acquired in the axial orientation.

MRI data were transferred electronically to Columbia University for morphometric analysis. Freesurfer (v.5.3) was used to quantitate regional volumetry and cortical thickness. For the purposes of this study, we focused on entorhinal cortex volume as a marker of AD-related neurodegeneration because it is among the earliest regions affected [19, 20]. T2-weighted FLAIR images were analyzed for regional WMH volume as previously described [10]. Briefly, FLAIR images were skull-stripped and a study-specific intensity threshold was applied to label voxels that fell above a pre-specified threshold (1.7 standard deviation units above the image mean intensity value) that was defined by the mean and standard deviation of the image intensity value. Labeled images were inspected visually and corrected for mislabeled voxels. Total WMH volume was derived by summing the number of voxels and multiplying the sum by voxel dimensions. A lobar atlas was co-registered to each labeled FLAIR image and frontal, temporal, parietal, and occipital WMH volumes were derived by considering the intersection between the labeled voxels and the respective atlas-defined lobe. Radiological lacunar infarcts were assessed visually by a trained rater. Briefly, hypointense lesions on T2-weighted FLAIR images with a complete surrounding hyperintense ring were coded as infarcts [21]. Finally, we evaluated gradient echo images for presence of cerebral microbleeds in deep regions and in lobar regions, following established protocols [22–25]. Microbleeds in each region were coded as “present” or “absent.”

Statistical analysis

Relevant demographic and clinical data, including age, education, sex distribution, CDR score, and vascular risk factors, were compared across the four groups with general linear models for continuous variables, Chi-squared tests for proportional data, and Kruskal-Wallis or Mann-Whitney U tests for rank ordered data. Similarly, we compared these same variables between those included in the MRI sub-study and those who did not. For the latter group, we used the last available data from any participant who had been in the history of the studies up until the end of the time of the MRI substudy (n = 4173, not including MRI substudy participants, which included NC+ n = 1209, NC– n = 566, AD+ n = 1486, AD– n = 778, no available diagnostic information n =134). Each neuroimaging marker—entorhinal cortex volume, total and regional WMH volume, presence of radiological infarct, and presence of microbleed—was compared across the four Diagnostic Groups, NC+, NC–, AD +, AD–. For entorhinal cortex volume and total WMH volume, we used a general linear model, controlling for age and total intracranial volume, followed by pairwise *post hoc* tests to examine differences across groups. For these analyses we also embedded a planned statistical contrast (0 0 –1 –1) in which we compared volumes between controls and those diagnosed with AD dementia in order to test the hypothesis that individuals with AD dementia had smaller entorhinal cortex volumes and greater WMH volumes than those without. For regional WMH, we re-ran the same analysis with brain region (frontal, temporal, parietal, occipital) as an additional within-subjects factor. An additional logistic regression analysis was run in which total WMH volume, age, and intracranial volume were entered as predictors and diagnosis of dementia was the outcome. The proportion of individuals with one or more radiological infarct and one or more cerebral microbleed was

compared across groups with Chi-squared analyses. We also considered presence of lobar versus deep microbleeds separately.

RESULTS

The two control groups (with and without family history) were younger than the two AD groups, but sex distribution was similar across the four groups. The four groups did not differ in terms of vascular risk factors but patients with AD dementia had lower levels of education than those without (see Table 1). Patients with AD dementia had moderate levels of dementia, as indicated by a Clinical Dementia Rating (CDR; [26]) median score of 2; participants in the control group had CDR scores of 0 ($n = 49$) or 0.5 ($n = 2$) and all participants in the patient groups had CDR scores of 1 ($n = 9$), 2($n = 25$) or 3 ($n =5$). Compared with participants not enrolled the MRI substudy, those enrolled in the study were younger (72.40 ± 8.14 versus 81.50 ± 12.31$t =6.76$, $p < 0.001$,95% confidence interval [CI]: 6.27–11.40), had similar sex distribution ($\chi^2 = 1.75$, $p = 0.19$), had less overall impairment (median CDR score 0 versus 1, U= 148165.50, $p = 0.002$), and similar levels of vascular risk (median vascular risk score 1 versus 1,U= 166188.00, $p = 0.049$).

For entorhinal cortex volume, patients diagnosed with AD dementia had smaller volumes than controls (planned contrast F(1,79) = 8.60, $p = 0.004$), although the main effect of Diagnostic Group (F(1,79) = 0.62, $p = 0.60$) and the pairwise comparisons were not statistically significant ($p > 0.05$). These findings suggest that AD dementia patients consistently have smaller entorhinal cortex volumes than controls but that there is no differential effect of family history (see Fig. 1).

For total WMH volume, both the planned contrast (F(1,79) = 4.85, $p = 0.031$) and main effect of Diagnostic Group (F(1,79) = 5.49, $p = 0.002$) indicated differences across the four groups. The overall logistic regression model was highly significant ($\chi^2 = 31.17$, $p<0.001$), correctly classifying 78% of participants, and total WMH was strongly associated with increased odds of dementia ($\beta = 0.215$, SE = 0.07, $p = 0.001$). Pairwise comparisons showed that the two control groups had similar WMH volumes ($p = 0.86$) as had the two AD groups ($p = 0.525$). NC– had lower WMH volume than AD– ($p <0.001$) and AD+ ($p = 0.019$); similarly, NC+had lower WMH volume than AD– (p = 0.005) and AD+ ($p = 0.049$) groups (see Fig. 2). For regional WMH, a main effect of Diagnostic Group (F(3,79) = 6.12, $p =$ 0.001) and a Diagnostic Group by Region interaction (F(9,237) = 5.266, $p <0.001$) indicated that participants diagnosed with AD dementia had greater WMH volumes than controls, particularly in frontal and parietal lobes (see Fig. 3). The two control groups were similar across lobes as were the two AD groups.

The overall proportion of individuals with radiological infarcts was 22%; this proportion did not differ across diagnostic groups ($\chi^2 = 5.43$,$p = 0.142$). Similarly the proportion of individuals with cerebral microbleeds was 12%, which did not differ across diagnostic groups ($\chi^2 = 2.23$, $p = 0.527$).

DISCUSSION

We successfully completed a pilot study in Dominican Republic that showed the feasibility of collecting research-grade MRI scans for studies of cognitive aging and dementia, which included establishment of a standardized protocol on a local scanner, successful data transfer protocols, and the ability to integrate neuroimaging data with demographic and clinical data. The results of the pilot study indicated that WMH, as an operationalized marker of small vessel cerebrovascular disease, are elevated similarly among individuals with and without a strong family history of AD dementia compared with normal controls with and without a strong family of AD dementia. The same pattern of results was observed for entorhinal cortex volume, the operational definition of AD-related neurodegeneration. That is, there was reduced volume in patients with AD dementia, irrespective of their familial history status, compared with both sets of controls, who did not differ from each other.

Results of this pilot study are consistent with the hypothesis that WMH, as one marker of cerebrovascular disease, represents a core feature of AD dementia, and not simply a comorbidity reflecting mixed disease pathology. That is, like autosomal dominant forms of AD [27], individuals with strong family histories of AD dementia, indexed here by the documentation of at least 2 siblings with a history of AD dementia, could be considered to have a more heritable and therefore “purer” form of the disease compared with those with late onset sporadic AD, whose clinical presentation might be “contaminated” by multiple morbidities. That the two AD groups evidenced similar levels of impairment and similar degrees of entorhinal cortex atrophy and regional WMH increases suggests that both biological markers are operating equivalently in AD, irrespective of genetic loading. By “core feature” we mean that the clinical manifestation of AD may be the result of a combined, weighted influence of cerebrovascular and neurodegenerative factors that can be estimated on standard structural MRI scans (e.g., [28]); that WMH levels were similar in affected patients with and without a strong family history provides additional evidence for this idea. These data are, of course, preliminary and need to be replicated in larger samples that would provide greater statistical power to detect subtle differences between groups; it is also important to note that we did not observe similar effects with the other markers of cerebrovascular disease and that WMH may represent additional non-vascular pathology to some extent. However, they are consistent with our recent report of increased WMH burden among individuals who carry fully penetrant, autosomal dominant genes for AD up to 20 years prior to the estimated time of symptom onset [13]. With respect to the regional distribution of WMH, in that report and in work with late onset AD dementia [9, 10], we have observed a selective elevation in posterior WMH. However, in an exclusively African American sample [29], we found both frontal and parietal WMH increases associated with AD dementia, as observed here.

Existing large cohort neuroimaging studies of cognitive aging and dementia have typically comprised predominantly white participants from developed countries. There are many reasons to pursue research that incorporates more diverse participants into these efforts. Racial and ethnic disparities in AD dementia incidence and prevalence are well-documented but the factors that account for these disparities are poorly understood. The relationship between neuroimaging-derived biological markers and clinical outcomes may differ between

cultural groups (e.g., [30]) and, similarly, genetic profiles may differ across groups and be associated differentially with biological aspects of the disease. Mediators and moderators of these associations may vary across cultural groups and it is unknown the degree to which results derived in primarily white, educated cohorts from developed countries can generalize to other populations. Our efforts here indicate that research-grade neuroimaging studies can be initiated in developing countries like Dominican Republic, particularly when strong collaborative relationships are formed and funding is available for these types of efforts. We also showed that with strong collaborative relationships with study participants we are able to recruit individuals to participate in neuroimaging studies; our recruitment rates were comparable to what we have observed in similar efforts in New York.

There were several reasons why we initiated the study in Dominican Republic specifically, as opposed to other countries in Caribbean Latin America. First, among the cohort we have been studying in New York [3], the vast majority of the Hispanic participants are from Dominican Republic. So, we felt it important to establish the research in the primary country of origin. Second, familial dementia rates are greater in Dominican Republic than in other populations [31], which may be mediated by prevalence of consanguineous marriages and relative geographic insularity, providing the opportunity to incorporate samples of "genetically enriched" populations for AD dementia into studies. Third, a strong collaborative relationship with investigators and a large case-control and family-based cohort have been established already in Dominican Republic, which allowed us to leverage existing resources and experience. Future efforts will seek to design larger-scale neuroimaging studies in this population and integrate the neuroimaging findings with deep genetic and phenotype data.

The study presented here—designed to test feasibility and generate pilot data—is not definitive and does have some limitations. For example, although our statistical models controlled for age, the diagnostic groups did differ significantly in age. We were somewhat surprised that the diagnostic groups differed so dramatically in terms of WMH severity but less so in terms of entorhinal cortex volume, given the severity of dementia in the patient groups. We speculate that in this population cerebrovascular disease might be playing a more important role than neurodegenerative changes for symptom manifestation. Further, given the large educational differences between patients with AD dementia and controls, it is possible that a lesser degree of neurodegeneration was necessary to manifest more severe symptoms of dementia. The MRI scanner we could access had a 1.5 Tesla field strength, which is not considered state-of-the-art, but does reflect the typical available technology in developing countries. We did not observe statistically reliable differences across groups in other markers of cerebrovascular disease, such as microbleeds and frank infarcts, which could reflect a relative lack of statistical power and of sensitivity to detect these lesions given this technology and relatively large slice thicknesses. Nonetheless, the findings do indeed show feasibility and are in line with an emerging literature that highlights the importance of cerebrovascular factors in AD dementia. In this regard, some investigators have proposed that regionally-distributed WMH in the context of AD might reflect Wallerian-like degeneration secondary to tau-mediated cortical neurodegeneration [32, 33], but the vast majority of work on WMH suggest a primarily vascular etiology. Nonetheless, the mechanisms that mediate hyperintense signal on T2-weighted MRI require further study.

In conclusion, this study provides evidence for the capacity to conduct aging- and dementia-related studies that incorporate MRI scanning in Dominican Republic. The preliminary results of the pilot study are consistent with the idea that small vessel cerebrovascular disease plays a significant role in the clinical manifestation of AD, perhaps to a greater extent than neurodegeneration *per se*.

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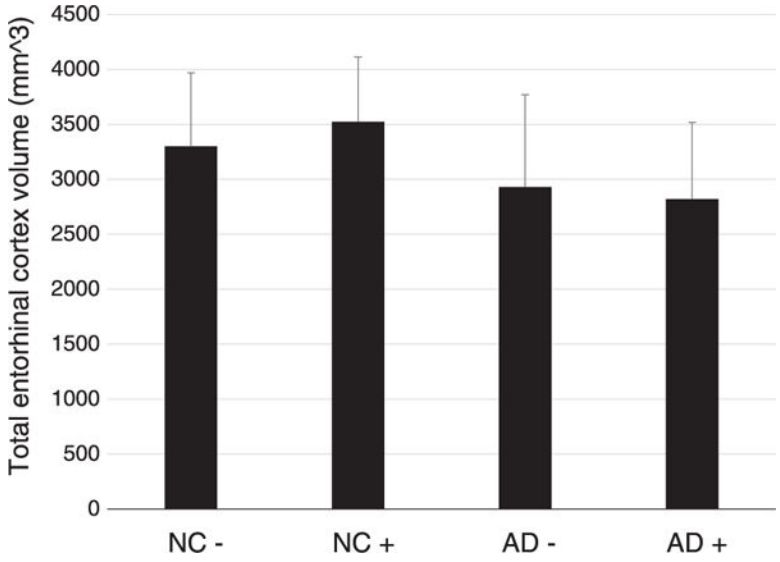

Fig. 1.

Entorhinal cortex volume, adjusted for total cranial volume and age, across the four diagnostic group. Although the main effect of Diagnosis and post hoc comparisons were not statistically significant, a planned polynomial contrast (0 0 –1 –1) indicated that individuals with AD have smaller entorhinal cortex volumes than controls (contrast estimate = –5001.87, $p = 0.004$, 95% CI: –8396.99 to –1606.76). Error bars are standard errors. 95% CI for pairwise differences are as follows: NC– versus NC+ –393.18 to 381.36,$p = 0.976$; NC– versus AD– –117.15 to 523.61, $p = 0.210$; NC– versus AD+ –234.52 to 554.32, $p = 0.422$; NC+ versus AD– –226.40 to 644.69, $p = 0.342$; NC+ versus AD+ –339.32 to 670.95, $p = 0.52$; AD– versus AD+ –442.28 to 355.63, $p = 0.829$.

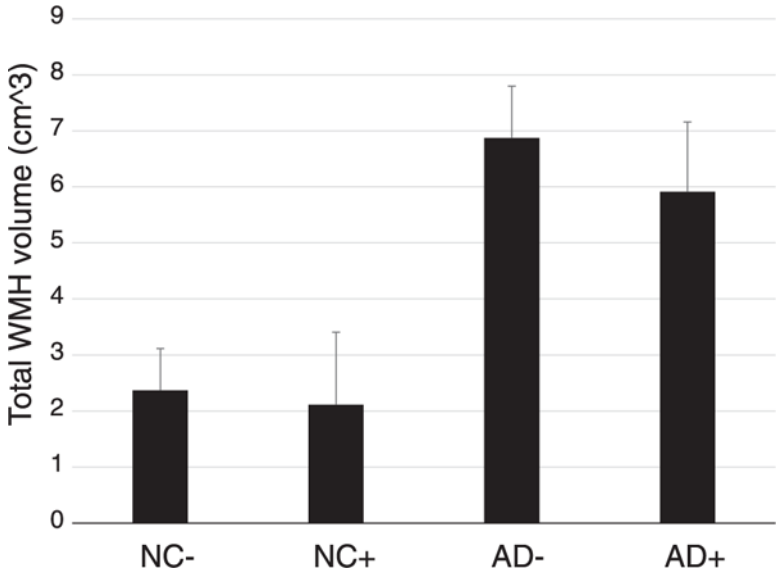

Fig. 2.

White matter hyperintensity volume, adjusted for total cranial volume and age, across the four diagnostic group. Both main effect of Diagnosis and planned polynomial contrasts (0011) indicated reliable differences between each of the two NC groups and each of the two AD groups (contrast estimate = –28.15, $p = 0.031$, 95% CI: –53.59 to –2.71). Error bars are standard errors. 95% CI for pairwise differences are as follows: NC– versus NC+ –2.64 to 3.16, $p = 0.860$; NC– versus AD– –6.90 to –2.10, $p < 0.001$; NC– versus AD+ –6.50 to –0.59, $p = 0.09$; NC+ versus AD– –8.02 to –1.49, $p = 0.005$;NC+versusAD+–7.59 to –0.017, $p = 0.049$;AD– versus AD+ –2.03 to 3.95, $p = 0.525$.

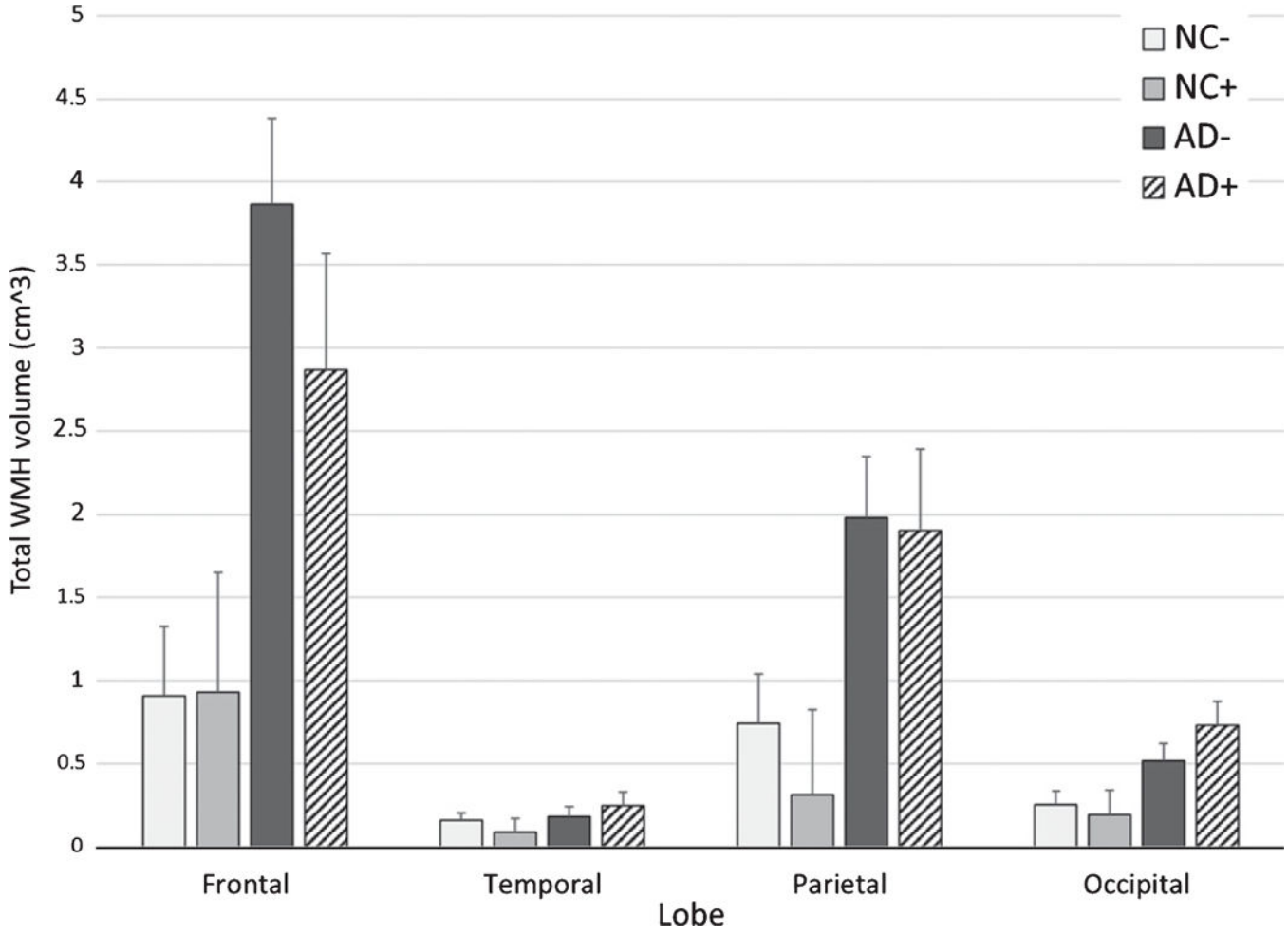

Fig. 3.

Regional WMH volume, adjusted for total cranial volume and age, across the four diagnostic group. Participants diagnosed with AD had greater WMH volumes than controls, particularly in frontal and parietal lobes. Error bars are standard errors.

Table 1

Sample demographics

	NC, negative family history [NC(–)]	NC, positive family history [NC(+)]	AD, negative family history [AD(–)]	AD, positive family history [AD(+)]	Total	Statistic	*Post hoc*
N	36	15	24	15	90		
Age, mean y ± SD	71.36 ±7.43	65.44 ±6.37	74.89 ±6.04	77.86 ±9.21	72.40 ±8.14	F = 8.62, $p < 0.001$	NC(–)>NC(+)<AD(–) = AD(+)
Sex, *n* (%) women	21 (58%)	7 (47%)	15 (63%)	10 (67%)	53 (59%)	χ^2 = 1–43, $p = 0.70$	-
Education, mean y±SD	7.83 ±5.30	7.27 ±5.73	2.29 ±3.11	3.73 ±5.39	5.58 ±5.42	F = 7.411, $p < 0.001$	NC(–) = NC(+)>AD(–) = AD(+)
Vascular risk score, median	1	1	1	1	1	K-W χ^2 =0.522, $p = 0.914$	-
CDR score, median	0	0	2	2	0	K-W χ^2= 80.50, $p < 0.001$	NC(–) = NC(+)<AD(–) = AD(+)

NC, normal control; AD, Alzheimer's disease; K-W, Kruskal Wallis test statistic. The vascular risk score was derived by summing four dichotomous risk variables, including hypertension, heart disease, type 2 diabetes, and smoking history, to yield a value ranging from 0 to 4.