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Association between neuropathology and brain volume in the Framingham Heart Study

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Abstract

Studies of clinical and community cohorts have shown that antemortem imaging measures of hippocampal volume have correlated with postmortem Alzheimer's pathology. Fewer studies have examined the relationship between both Alzheimer's and cerebrovascular pathology, and antemortem brain imaging. The aim of this study was to correlate antemortem brain magnetic resonance imaging (MRI) volumes with postmortem brain pathology (both Alzheimer-related and cerebrovascular) in a community-derived cohort from the Framingham Heart Study (FHS). Participants (n=59) from the FHS were included if they were enrolled in the brain autopsy program and underwent antemortem clinical evaluation, neuropsychological testing and brain MRI. Cortical neurofibrillary tangle pathology correlated with lower total cerebral brain (beta ±SE=−0.04±0.01, p=0.004) and hippocampal volumes (beta±SE=−0.03±0.02, p=0.044) and larger temporal horns (log-transformed, beta±SE=0.05±0.01, p=0.001). Similar findings were seen between total/cortical neuritic plaques and total cerebral brain and temporal horn volume. White matter hyperintensities (also log-transformed) were best predicted by the presence of deep nuclei microinfarcts (beta±SE=0.53±0.21, p=0.016), whereas hippocampal volume was significantly decreased in the presence of hippocampal sclerosis (beta±SE =−1.23±0.30, p<0.001). This study showed that volumetric MRI measures correlated with postmortem Alzheimer-related and cerebrovascular neuropathology in this community-derived cohort, confirming that these MRI measures are important antemortem surrogates for these dementia-related pathologies.

Introduction

Dementia is a heterogeneous disease in which antemortem diagnosis is a challenge. This is particularly pertinent for clinical trials of disease-modifying agents. Antemortem biomarkers such as amyloid neuroimaging and cerebrospinal fluid markers better identify profiles that

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predict postmortem pathology, but at this time, these methodologies are not in wide clinical use. Brain magnetic resonance imaging (MRI), however, is widely used and volumetric markers of structural atrophy and vascular injury are used as biomarkers of antemortem pathology.[1] There are a few studies[2, 3] which compared antemortem MRI to postmortem Alzheimer's disease (AD) pathology, utilizing mixed clinical and community cohorts to show that MRI-derived brain volumes, particularly hippocampal volume, significantly correlate with postmortem neurofibrillary tangle burden. One study in a prospectively-followed, highly select, community-derived cohort[4] showed similar findings. Most of these studies limited their observations to AD pathology. However, community-dwelling subjects with dementia often have coexisting pathologies.[5] One clinic-based study showed that both cortical AD pathology and subcortical cerebrovascular pathology overlap, resulting in reduced cortical volume.[6]

Our current study analyzed the associations between postmortem neuropathology findings and antemortem MRI-derived brain volumes in a cohort of prospectively-followed community-recruited subjects from the Framingham Heart Study (FHS). Using this cohort, we examined the relationship between MRI measures and both AD and cerebrovascular pathology. These MRI-pathology correlations extend findings from previously published clinical-MRI associations in the FHS cohort [7–10] by validating the pathology presumed to underlie these *in vivo* MRI studies.

Methods

Participants

The general design and demographics of the FHS have been previously described.[11] In brief, the FHS is a community-based population sample of individuals living in Framingham, Massachusetts. Currently, the FHS consists of multiple cohorts, the original participants of the study (Gen1) and their offspring (Gen2) as well as the spouses of their offspring. The original cohort of the FHS consisted of 5,209 participants who were enrolled into the study in 1948. At enrollment, the mean age was 44 years (range 28–62 years, 55% female). The offspring cohort includes 5,124 offspring of the original cohort and their spouses who were enrolled into the study in 1971. At enrollment, the mean age was 36 years (range 5–70 years, 52% female).

Participation in the FHS autopsy program is entirely voluntary and began in 1997. Of Gen1 participants, 35 were enrolled as potential brain donors, while 398 of Gen2 were similarly enrolled. This reflects 16% and 11% of surviving members of the Original and Offspring cohorts, respectively. All participants have extensive risk factor data and many also have antemortem imaging, neurological and/or neuropsychological assessment data. Of Gen 1 and Gen 2, 1,804 participants have died since the inception of the brain donation program, 186 of whom were enrolled. Of those participants enrolled, 74% (139) have come to autopsy. Those who had neuropsychological assessments within 2 years of death and at least 1 brain MRI were included in the current sample (n=59; 37 from Gen 1, 22 from Gen 2).

Data were obtained under a protocol approved by the Human Subjects Institutional Review Board of the Boston University School of Medicine. Written informed consent was obtained from all participants antemortem. Next of kin consented to autopsy at the time of death.

Definition of Clinical Diagnosis

Methods for the clinical surveillance of the FHS cohort have been described previously.[12–15] Participants receive regular clinical evaluations and individuals identified as having dementia satisfy DSM-IV criteria[16] by consensus review of all available clinical information.

Definition of Post-mortem Diagnosis

For each participant, family interviews are conducted with the closest next of kin after death. Questions from the Retrospective Clinical Dementia Rating (CDR) Scale[17] are included as part of this Family Interview enabling the determination of a CDR at or very near the time of death. Participants were determined to have dementia if the retrospective CDR value was 1 or higher. Change in cognitive status from the time of last MRI and death was used to further refine our analyses.

MRI acquisition, image analysis and measurement of MRI variables

MRIs were performed on participants from both the original cohort and the offspring cohort between March 1999 and June 2009. Methods for acquiring brain MRI in these participants have been described in detail.[10] Briefly, the majority of participants were imaged on a Siemens 1-T MR machine (Siemens Medical, Erlangen, Germany) with a T2-weighted double spin-echo coronal imaging sequence of 4 mm contiguous slices from nasion to occiput with a repetition time of 2,420 msec, echo time (TE) of TE1 20/TE2 90 msec; echo train length 8 msec; field of view 22 cm; and an acquisition matrix of 182 _ 256 interpolated to 256 _ 256 with one excitation. Digital information was post-processed by a central laboratory (CD), blinded to demographic and clinical information.

Quantification was performed with a custom-written computer program operating on a UNIX, Solaris platform (Sun Microsystems, Santa Clara, California). The semiautomated segmentation protocol for quantifying total cranial volume (TCV), total cerebral brain volume (TCBV), temporal horn volume (THV), hippocampal volume (HPV), and white matter hyperintensities (WMH) has been described elsewhere,[10, 18–21] as have the interrater reliabilities for these methods.[10, 18, 22, 23] In brief, non-brain elements were manually removed from the image by operator-guided tracing of the dura matter within the cranial vault including the middle cranial fossa but above the posterior fossa and cerebellum. The resulting measure of the cranial vault was defined as the TCV and served as an estimate of head size to account for recognized sex differences. Quantification of TCBV and WMH required a multistep process that began with image segmentation to define brain matter from CSF.[19] For segmentation of brain from CSF, a difference image was created by subtracting the second from the first echo image. Image intensity non-uniformities were removed from the difference image,[21] and the resulting corrected image was modeled as a mixture of two Gaussian probability functions with the segmentation threshold determined at the minimum

probability between these two distributions.[18] For the present study, repeat analysis of intra- and inter-rater reliabilities were consistently above 0.90.[10]

Neuropathological assessment

Neuropathological evaluation of all autopsied brains was performed, blinded to all demographic and clinical information. Those methods have been previously reported in detail.[15] Briefly, the brains were received fresh and the gross neuropathological findings were recorded, including vascular lesions and the degree of atherosclerosis. The frontal, temporal and occipital poles were removed from one hemisphere and snap frozen at −80 C. The remaining tissue was fixed in 4% periodate-lysine-paraformaldehyde at 4°C for at least 2 weeks. Ten micron paraffin-embedded sections from 30 brain regions were collected, including the following: the olfactory bulb, brainstem, spinal cord and cerebellum; multiple neocortical regions; basal ganglia, thalamus, basal forebrain and the medial temporal lobe (MTL).

Histological stains and Immunohistochemistry

Histological stains included luxol fast blue, hematoxylin and eosin, Bielschowsky silver method, and immunocytochemistry for phosphorylated tau protein (Innogenetics, AT8, 1:2000) and amyloid-beta protein (Dako, 6F-3D, 1:500, pretreated in 90% formic acid for 2 minutes).

Quantitation of cortical pathology

Neurofibrillary tangles (NFTs)—The density of NFTs was rated semi-quantitatively in 14 regions using AT8 immunostained sections. In the neocortical regions, a rating of 1+ corresponds to a maximum density of 1 NFT per 20X field; 4+ corresponds to 10 NFT/ field. For the MTL structures, NFT were rated as follows: 1+: 1–10 NFT/ field; 4+ 31/ field. For NFT summary scores, the NFT density in the neocortical areas and MTL regions were tabulated. In addition, the NFTs were staged according to the hierarchy described by Braak and Braak.[24]

Neuritic plaques—The density of neuritic plaques (NPs) was determined in the same regions as NFTs by averaging the count in 3 fields as follows: a score of 1+ :1–9 plaques per 100X field; 4+: >32 plaques per field. The 1+ rating corresponded to a CERAD rating of sparse, a 2+ score corresponded to a CERAD rating of moderate, and a 3+ or 4+ score to a CERAD rating of frequent plaques.[25] Summary scores for NPs were tabulated from both the neocortex and medial temporal lobe structures.

Vascular and microvascular lesions

The FHS has been systematically documenting measures of vascular pathology and has developed a composite measure of vascular pathology derived using the National Alzheimer Coordinating Center and University of California at Los Angeles ischemia score protocols, and consistent with the Vascular Cognitive Impairment Harmonization guidelines.[26] The developed ischemic injury scale (IIS)[15] included assessments of hippocampal sclerosis, volume of chronic infarcts, number of lacunes and microinfarcts, degree of atherosclerosis,

arteriolosclerosis and white matter disease and gave an overall single IIS score for each brain. In addition, a subset analysis used the vascular ischemic score (VIS), which excluded hippocampal sclerosis and amyloid angiopathy from the IIS.

Statistical Analysis

Multivariate linear regression techniques were used to examine associations between pathology and MRI variables, using the MRI closest to time of death and adjusting for age at death, gender, and interval between MRI and death. The primary independent variables for the regression analysis were the summary scores for NFTs, NPs, microinfarcts, atherosclerosis, IIS and VIS. Secondary analyses include both NFTs and NP as covariates. Dependent variables were TCBV, LWMHV (the logarithm of the WMH volume), HPV and LTHV (logarithm of THV). Each of these volumes was analyzed as percent of TCV, and WMH and THV were log-transformed to normalize their distributions. In addition, for regional measures of either neuropathology (e.g. MTL NFTs) or MRI (e.g. HPV), summary measures from both hemispheres were used to simplify the analyses. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). The beta weight coefficients of the regression analyses of Table 4 are presented so that a difference of one level in neuropathological scale is associated with a corresponding standard deviation difference in MRI measure. For example, each increase in Braak and Braak stage is associated with a 0.15 SD reduction in TCBV. P-values <0.05 were considered statistically significant.

Results

Participant characteristics

Demographic characteristics of the participants in the study sample (n=59) are included in Table 1. The majority of participants were elderly with a mean age of 86.5±11.2 years (range 56.5–103.4 years old) at the time of death. The vast majority were non-demented at the time of final clinical diagnosis (81%). Most were male (56%) and well educated (53% with over 12 years of education). The average length of time between their last clinical visit and autopsy was 3.8±2.3 years (range 0.2–9.6 years). 31% of participants were either heterozygous or homozygous for the Apolipoprotein E4 polymorphism. Prevalence of vascular risk factors, average lipid profile and history of stroke at the last clinical visit are also included in Table 1. Other than the desire to volunteer for the autopsy study, there were no systematic differences in demographic or vascular risk factor variables between those who underwent autopsy and the remainder of the active participants.

Dementia Diagnosis

Comprehensive follow-up of the FHS cohorts allowed for assessment of dementia at both the time of clinical evaluation nearest the MRI and again at death. While no demented subject became non-demented during retrospective CDR assessment at death, an additional 19 subjects were determined to be clinically demented at the time of death. The average interval between MRI and death for this group was 4.73 ± 2.41 years, similar to the time from follow-up for demented subjects as a whole.

MRI characteristics

Table 2 summarizes the MRI findings in the participants. The participants with dementia at the time of death had a longer interval between the last MRI and brain autopsy, compared to non-demented participants. Their last MRI, on average, showed significantly lower TCBV and HPV. The demented participants also had significantly larger THV. WMH volumes and the prevalence of MRI infarcts did not differ between non-demented and demented participants.

Neuropathology findings

Table 3 summarizes the neuropathology findings. At autopsy, all participants (demented and non-demented) had some degree of NFT pathology, cerebrovascular pathology, or both. In a minority of cases, the degree to which these pathologies were present was not deemed to be sufficiently abnormal for age (i.e. these participants were thought to have normal brains). This included 3.5% of those with dementia at death. The participants with dementia had significantly smaller brain weights and significantly higher quantified degree of NFTs and NPs. The non-demented participants had more microinfarcts (total, cortical and subcortical), although this did not differ significantly from subjects demented at death. Moreover, while participants with dementia had a higher degree of cerebrovascular atherosclerosis and higher summary vascular and ischemic scores and amyloid angiopathy these differences were also not significant. Conversely, the prevalence of hippocampal sclerosis was substantially and significantly increased among demented versus non-demented subjects. Overall, participants with dementia appear to have MRI and neuropathology measures which are consistent with their dementia diagnosis at death.

Association between MRI measures of brain volume and neuropathology

Higher postmortem brain weight was associated with higher MRI brain volumes, as measured by both TCBV (beta 0.44 ± 0.07, p <0.001) and HPV (beta 0.003 ± 0.001, p<0.001). No significant association was found between brain weight and WMH volume (beta 0.002 ± 0.001, p = 0.145). Table 4 shows regression analyses of other neuropathology variables in association with various antemortem MRI brain volumes.

Association of brain volumes with NFTs

As summarized in table 4, there was a negative association between the degree of total and cortical NFTs in the postmortem brain and TCBV, which was maintained for analysis by the Braak stage of neurofibrillary disease. Conversely, there was a positive relationship between the logtransformedTHV (LTHV) and both the NFT score and Braak stage. These significant results remained even after covarying with the presence of NPs. There was no significant association between the NFT score or Braak NFT stage and LWMHV.

Association between brain volumes and amyloid plaques

Total and cortical NP counts also were negatively associated with TCBV (Table 4); however, cortical NP counts were no longer significantly associated with TCBV if covaried with NFT counts. Secondary analysis by quantile regression (data not shown) demonstrated a threshold effect between cortical NPs and TCBV, with a significant effect noted only

between the highest quintile of NP pathology in the cortex and TCBV. All measures of NPs (total, cortical and MTL) had positive associations with LTHV. Quantile regression analysis demonstrates that this effect was driven by the highest quantile of NP pathology (total, cortical and MTL). Similar to the relationship between TCBV and NPs, the association between NPs and LTHV was no longer significant when NFTs were included in the model. There was no significant association between LWMHV or HPV and overall NP counts. However, a significant threshold effect was found between the lowest quantile of the cortical NPs and and largest HPV, indicating that larger HPV was associated with lower pathology burden.

Vascular pathology and brain volumes

Summary measures of vascular disease (atherosclerosis score, IIS and VIS) did not show significant associations with antemortem MRI measures, though there are nonsignificant trends between higher vascular burden by these measures and lower TCBV and HPV, as well as larger LTHV (see table 4). Similar nonsignificant findings existed between MRI measures and the presence/absence of chronic infarcts, chronic lacunes and most measures of microinfarcts. A positive association was found between total subcortical and noncavitated microinfarcts and HPV. Secondary analysis towards a threshold effect (not shown) found a significant association between the highest tertile of total microinfarct pathology and HPV. However, there was a strong negative association between the presence of hippocampal sclerosis (HS) and hippocampal volume (Table 4) where the presence of HS was associated with approximately 1.2 SD reduction in size of the hippocampus. While there was no significant association between temporal horn of the lateral ventricle volume and HS, both the hippocampal (-1.41 ± 0.29; p <0.001) and temporal horn of the lateral ventricle 0.64 ± 0.30 (0.034) relationships with HS became stronger when medial temporal lobe NP and NFT were included in the models.

Discussion

This study was one of the first to examine the associations between both AD and non-AD postmortem neuropathology and antemortem MRI measurements in a community-based cohort of longitudinally-characterized elderly participants, the majority of whom (81%) were non-demented at their last clinical visit. In this cohort, higher AD neuropathology burdens were associated with lower total brain volumes, lower hippocampal volumes and increased size of the temporal horn of the lateral ventricles. This was consistent with another recent study of mostly demented individuals which looked at a summary variable of both tangle and plaque pathology and demonstrated that this summary AD pathology variable correlated well with both cortical gray matter and hippocampal volumes.[6] Our study analyzed tangles and plaques separately and demonstrated that the MRI volume correlates were strongest with NFTs, as opposed to NPs. Moreover, in a combined model, NFTs remained significantly associated with MRI volumes, whereas NPs were no longer significant. This finding is not surprising, given that the stage of NFT pathology more strongly correlates with the cognitive severity of dementia due to AD,[27] and given that other studies of MRI-pathology correlates show that tangles are highly associated with hippocampal volume.[2-4, 28] These findings also support recent data from amyloid imaging

studies that suggest the presence of amyloid pathology may have only modest effects on brain structure and function.[29–32] Our findings, in addition to prior studies examining MRI neuropathological associations, emphasize that anatomical changes in the antemortem brain, particularly generalized brain atrophy, most likely occur because of underlying neuropathology, and these changes are detectable by volumetric MRI techniques. Furthermore, MRI findings correlate with cognitive change as measured on standardized neuropsychological testing in the Framingham population. [9, 33, 34] Studies of MRI-pathology correlations are therefore important biological markers for *in vivo* associations between presumed neuropathology and cognitive decline.

In addition to Alzheimer's pathology, our study examined the relationship between cerebrovascular pathology and MRI measures. Deep nuclei microinfarcts were significantly associated with larger white matter hyperintensity volume. Conversely, microinfarct measures (total non-cavitated and subcortical microinfarcts) were associated with larger HPV. Importantly, however, the presence of hippocampal sclerosis (HS) was very strongly associated with the presence of dementia as well as significantly and inversely associated with hippocampal volume. Similar to our results, the Ischemic Vascular Dementia (IVD) cohort study of MRI-pathology correlation showed no relationship between parenchymal cerebrovascular pathology and hippocampal volume,[6] though an inverse relationship was present between parenchymal cerebrovascular pathology and cortical gray matter volume, suggesting that in that cohort, cerebrovascular disease may play a role in cortical atrophy. Our autopsy cohort extends this observation to include a relatively high prevalence of HS (20%) among older individuals with a retrospective diagnosis of dementia. Furthermore, similar to associations with Alzheimer's pathology, these pathological features appeared to influence MRI prior to the onset of dementia. The finding of increased HS among similarly aged individuals has been previously reported [35]. Our findings, therefore, support the notion of mixed pathological processes in the setting of dementia among community based studies of older individuals[36, 37].

There are several limitations of our study. The measure of total cerebral brain volume was neither regionalized nor segmented into separate cortical and subcortical volumes. Studies of regional and cortical/subcortical pathology in comparison to corresponding MRI volumes may better validate use of MRI as a proxy for pathology. Given the lower prevalence of dementia in our autopsy cohort and the low prevalence of clinical stroke (8%, see table 1), our study may be underpowered to detect cerebrovascular disease. The original and offspring Framingham participants are predominantly of European ancestry and are relatively well educated, which may affect generalizability. The low brain autopsy cohort enrollment (11% for gen1, 16% for gen2) may also play a role in generalizability. However, the cohort autopsy rate of 74% is comparable to similar studies.[6, 38] The length of time between MRI and autopsy was longer for those with dementia than for those who were cognitively normal. Therefore, even analyses adjusted for length of time between MRI and autopsy could still result in weaker associations due to potential events, such as stroke or Alzheimer's dementia, occurring between the last MRI and death.

The strengths of the study lie in the community-based methods for recruitment into the Framingham study. The data was prospectively collected and the participants were

longitudinally characterized. At entry, all participants were healthy and non-demented, and at the last clinical evaluation, 81% remained non-demented. Therefore, any associations found are less likely to be driven by nonspecific changes associated with dementia. In addition, MRI and pathology ratings were blinded to clinical information, so data were independently determined.

Studies of MRI and pathology correlations are important to the understanding of how antemortem structural changes in the brain relate to cognitive decline and pathological brain aging. Brain MRI is a critical component of the clinical evaluation of the patient with memory complaints, so systematic evaluations of MRI brain volumes are clinically relevant. This analysis in the Framingham cohort is an early opportunity to examine the neuropathological underpinnings of MRI findings in a relatively healthy community-based cohort, enabling more generalizable conclusions to be drawn regarding the association between MRI and neuropathology.

Acknowledgments

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Table 1

Subject demographics and clinical data, n=59

	Mean ± SD [Range] (unless otherwise specified)
Age at death, years	86.5 ± 11.2 [56.5 – 103.4]
Interval between last clinical visit and autopsy, years	3.8 ± 2.3 [0.2–9.6]
Male gender, n (%)	33 (56%)
Education, n (%)	
High school degree (12 years)	20 (34%)
12 - <16 years	13 (22%)
16years	17 (29%)
Hypertension,[a] n (%)	40 (69%)
Diabetes mellitus,[b] n (%)	5 (13%)
Total Cholesterol, mg/dl	191 ± 33 [105–284]
Triglycerides, mg/dl	159 ± 123 [27–717]
Current smoker, n (%)	4 (7%)
History of stroke, n (%)	4 (8%)
Diagnosis of dementia,[c] n (%)	11 (19%)
Apolipoprotein E4 genotype, n (%)	18 (31%)

[a.] Hypertension is defined as having a systolic blood pressure 140mmHg or diastolic blood pressure 90mmHg, or being on treatment for hypertension at the time of the last clinical visit.

[b.] Diabetes mellitus is defined by having a blood glucose 200mg/dl or fasting blood glucose 126 mg/dl, or being on treatment for diabetes mellitus at the time of the last clinical visit.

[c.] Refers to diagnosis of dementia at the time of the last clinical examination. Diagnosis of dementia is defined by Diagnostic and Statistical Manual, IV criteria.[16]

Table 2

Brain MRI data (mean ± SD % of TCV, unless specified) by clinical diagnosis.

	Retrospective Clinical diagnosis at time of autopsy		
	No dementia (n=29)[*]	Dementia (n=30)[*]	P-Value[**]
Interval between last MRI brain and autopsy, years	2.67 ± 1.76	4.82 ± 2.24	<0.001
TCV, cc	1290.29 ± 137.83	1201.20 ± 157.08	0.330
TCBV, %	73.52 ± 4.73	71.33 ± 4.01	0.012
LWMHV, %	−0.91 ± 1.43	−0.88 ± 1.30	0.902
HPV, %	0.27 ± 0.05	0.25 ± 0.07	0.041
LTHV, %	−2.17 ± 0.91	−1.54 ± 0.69	0.002
Large infarcts, number[**]	5	3	---
Small infarcts, number[**]	25	24	---

[**] MRI measures adjusted for age and gender

Abbreviations: MRI, magnetic resonance imaging; TCV, total cranial volume; cc, cubic centimeter; TCBV, total cerebral brain volume; LWMHV, logarithm of white matter hyperintensity volume; HPV, hippocampal volume; LTHV, logarithm of temporal horn volume

[*] Refers to diagnosis of dementia at the time of death determined by retrospective CDR).[17]

[**] Refers to number of infarcts in total sample.

Table 3

Neuropathological data (mean score ± SD or % prevalence, unless otherwise specified) by clinical diagnosis

	Retrospective Clinical diagnosis at time of autopsy		
	No dementia (n=29)[*]	Dementia (n=30)[*]	P
Brain weight, grams	1297.9 ± 170.2	1152.3 ± 163.4	0.002
Total NFT score[**]	10.9 ± 7.6	25.8 ± 14.4	<0.001
Cortical NFT score[**]	2.9 ± 4.1	11.4 ± 8.6	<0.001
MTL NFT score[**]	4.3 ± 2.1	7.3 ± 3.6	<0.001
Braak NFT stage	2.1 ± 1.4	3.8± 1.8	0.001
Total NP score[**]	7.1 ± 7.6	15.7 ± 11.1	0.001
Cortical NP score[**]	4.9 ± 5.1	10.4 ± 7.2	0.001
MTL NP score[**]	2.2 ± 2.9	5.3 ± 4.4	0.002
CERAD NP score	3.0 ± 0.9	2.2 ± 1.1	0.006
Atherosclerosis score	2.3 ± 3.0	3.5 ± 3.8	0.185
Ischemic Injury Score (IIS)	4.6 ± 4.0	5.7 ± 3.8	0.288
Vascular Injury Score (VIS)	3.8 ± 3.1	4.1 ± 3.5	0.752
Amyloid angiopathy score	0.4 ± 0.6	0.6 ± 0.6	0.158
Subjects with chronic infarcts (N)	4	7	---
Subjects with chronic lacunes	4	7	---
Total microinfarct score	2.7 ± 3.6	1.8 ± 3.0	0.303
Prevalence of microinfarcts (%)	58.6	43.3	0.240
Prevalence of hippocampal sclerosis (%)	6.9	20.0	<0.001

Abbreviations: NFT, neurofibrillary tangle; MTL, medial temporal lobe; NP, neuritic plaque; CERAD, Consortium to Establish a Registry for Alzheimer's Disease

[*] Refers to diagnosis at the time of death based on retrospective CDR.[17]

[**] Refers to the tabulated summary scoring of NFT and NP density.

Table 4

Linear regression model of neuropathology and brain MRI results, adjusted for age, interval between MRI and autopsy, and gender (n = 59, significant values in bold).

Pathology		TCBV beta±SE	p-value	LWMHV beta±SE	p-value	HPV beta±SE	p-value	LTHV beta±SE	p-value
NFT	Total	−0.02±0.01	**0.003**	0.01±0.01	0.409	−0.02±0.01	0.079	**0.03±0.01**	**0.001**
	Cortical	−0.04±0.01	**0.004**	0.01±0.01	0.641	**−0.03±0.02**	**0.044**	**0.05±0.01**	**0.001**
	MTL	−0.06±0.04	0.080	0.04±0.04	0.257	−0.03±0.04	0.500	**0.11±0.04**	**0.003**
Braak stage		**−0.15±0.06**	**0.016**	0.03±0.06	0.567	−0.11±07	0.123	**0.22±0.06**	**0.001**
NP	Total	**−0.03±0.01**	**0.010**	−0.001±0.01	0.895	−0.02±0.01	0.124	**0.03±0.01**	**0.001**
	Cortical	**−0.04±0.01**	**0.004**	−0.001±0.02	0.934	−0.03±0.02	0.110	**0.06±0.02**	**0.001**
	MTL	−0.05±0.03	0.073	−0.01±0.03	0.844	−0.04±0.03	0.204	**0.07±0.03**	**0.013**
Atherosclerosis		−0.05±0.03	0.099	−0.01±0.03	0.802	−0.03±0.04	0.489	0.05±0.03	0.154
IIS		−0.20±0.12	0.105	−0.01±0.12	0.948	−0.22±0.14	0.110	0.20±0.13	0.142
VIS		−0.12±0.13	0.364	0.03±0.12	0.832	−0.001±0.14	0.995	0.10±0.14	0.453
Chronic infarcts*		−0.21±0.35	0.554	0.06±0.34	0.859	0.02±0.39	0.964	0.13±0.38	0.727
Chronic lacunes*		−0.10±0.29	0.728	−0.22±0.28	0.437	−0.06±0.33	0.863	0.01±0.31	0.964
Total micro-infarcts*		−0.19±0.22	0.380	0.24±0.21	0.261	0.39±0.24	0.106	−0.20±0.23	0.394
Noncavitated microinfarcts*		−0.03±0.24	0.899	0.08±0.24	0.732	**0.64±0.26**	**0.015**	−0.39±0.26	0.138
Cavitated microinfarcts*		−0.17±0.22	0.440	0.25±0.21	0.245	0.35±0.24	0.149	−0.11±0.24	0.653
Cortical micro-infarcts*		−0.02±0.25	0.943	−0.09±0.24	0.706	0.31±0.27	0.249	−0.16±0.26	0.534
Subcortical microinfarcts*		−0.11±0.25	0.670	0.004±0.24	0.987	**0.57±0.27**	**0.036**	−0.32±0.26	0.225
Deep nucleii microinfarcts*		−0.10±0.23	0.669	**0.53±0.21**	**0.016**	0.26±0.26	0.308	−0.09±0.25	0.715
Hippocampal Sclerosis*		---	---	---	---	−1.23 ± 0.30	<0.001	0.44±0.33	0.179

Abbreviations: MRI, magnetic resonance imaging; NFT, neurofibrillary tangle; MTL, medial temporal lobe; CERAD, Consortium to Establish a Registry of Alzheimer's disease; TCBV, total cerebral brain volume; LWMHV, logarithm of white matter hyperintensity volume; HPV, hippocampal volume; LTHV, logarithm of temporal horn volume; NP, neuritic plaque; IIS, ischemic injury score; VIS, vascular ischemic score

*
Given the distribution of scores, these pathology variables were analyzed as present or absent.