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Neuropathologic correlates of cognition in a population-based sample

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Abstract

Many cognitively normal older adults have underlying neuropathologic changes of Alzheimer's disease (AD), vascular brain injury (VBI), or Lewy body disease (LBD), which confer an increased risk of dementia. The current study focused on the association between multiple neuropathologic indices and performance on specific cognitive domains in a community sample of older adults. Of 438 participants in the Adult Changes in Thought population-based study of brain aging who were autopsied, 363 subjects had cognitive testing at their final study visit and were included. Associations were measured between performance on the Cognitive Abilities Screening Instrument prior to death and neuropathologic endpoints, including AD neuropathologic changes, LBD, cerebral amyloid angiopathy, and measures of VBI. Braak stage for neurofibrillary tangles, lower brain weight, and VBI as measured by cerebral cortical microvascular lesions (μ VBI) explained a significant proportion of the variance associated with global cognitive test performance ($R^2=0.31$, $p<0.0001$) both in the entire sample and when analysis was restricted to non-demented subjects ($R^2=0.23$, $p<0.0001$). Specific cognitive domains were differentially related to neuropathologic lesion type: memory and executive function with AD pathologic changes and cortical μ VBI, executive function with subcortical μ VBI, and visuospatial construction with LBD. Thus, neuropathologic lesions of LBD and μ VBI are associated with poorer cognitive performance over and above AD neuropathologic changes in subjects without dementia in this cohort. These findings underscore that cognitive impairment is a complex convergent trait that has important implications for clinical investigation and medical management of older adults.

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Keywords

Alzheimer's disease; brain; cerebrovascular disorders; cognition; dementia; Lewy bodies; pathologic processes

INTRODUCTION

Many studies of brain aging and dementia have observed that neuropathologic changes of Alzheimer's disease (AD), vascular brain injury (VBI), and/or Lewy body disease (LBD) are the major predictors of clinical dementia diagnosis in older individuals [1–3]. It is important to recognize that estimates of the relative contribution of these diseases to dementia and the extent of their co-morbidity varies significantly depending upon the cohort investigated, with discrepant results reported from research center cohorts versus population- or community-based cohorts, as well as variability due to difference in methodology and criteria [4, 5]. Although many clinical-pathological studies primarily focus on clinical dementia diagnosis as the primary cognitive outcome, others also have associated neuropathologic changes with various measures of cognitive performance. However, many of these investigations have relied on data gathered from research center cohorts, have small sample sizes, and/or focus primarily on AD neuropathologic changes [6–9]. There have been fewer large, community-based investigations attempting to associate a range of neuropathologic changes with cognitive performance, potentially limiting generalization of results from smaller research cohorts to the community. The primary goal of our study is to address these gaps in our knowledge.

The studies mentioned above and others have observed repeatedly that the neuropathologic features of AD, VBI, and LBD are variably present and commonly co-morbid among older adults without dementia or even without evidence of cognitive impairment. While clinical laboratory and radiologic evaluations have provided new insights into the natural history of apparently pre-clinical AD [10–12], a remaining advantage of autopsy evaluations is that they currently provide the most comprehensive assessment of brain diseases. We previously reported neuropathologic correlates of clinical dementia in the Adult Changes in Thought (ACT) cohort [13]. Given the current focus on the study of early cognitive changes that may signal latent and prodromal cerebral illnesses, we extend our findings here to address the association between neuropathologic changes and specific cognitive functions in older individuals without dementia.

MATERIALS AND METHODS

Participants

This study was approved by the Human Subjects Review Committees of the University of Washington and Group Health Research Institute. The study sample included autopsied participants from the ACT population-based cohort; detailed design and methods for ACT and for neuropathologic evaluation of ACT cases have been published previously [13–16]. In brief, the ACT cohort enrolls non-demented adults aged 65 and over, recruited from a random sample of Group Health Cooperative subscribers across the greater Seattle area. Cognitive screening, physical function, medical history review, and functional status assessments are administered to ACT participants at study entry and subsequently every two years unless, or until, a diagnosis of dementia is made. Participants who score below a cutoff of 86 out of 100 on the cognitive screening test (described below) or who are referred based on family and/or ACT interviewer concerns undergo a full dementia evaluation, which includes comprehensive cognitive and medical assessments. Dementia diagnosis is made by a consensus panel of experts using Diagnostic and Statistical Manual of Mental Disorders-

IV (DSM-IV) [17] and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [18] standard criteria.

Autopsy sample

Of 4,530 ACT participants with at least one visit, 1,774 died; of those participants, 438 were autopsied. All autopsied participants provided written informed consent prior to death. As required by Washington state law, next-of-kin also provided informed postmortem consent prior to autopsy. Those who had cognitive testing at their final study visit (within two years of death for non-demented participants) and who underwent complete postmortem neuropathologic examination were included in the final analyses (cognitive sample, $n = 363$). Ninety percent ($n = 327$) of the cognitive sample had blood drawn for APOE genotyping prior to death, as previously described [14].

Autopsy procedures

Neuropathologic evaluations were conducted exactly as described previously [13, 16]. Neuropathologic measures (Fig. 1) included total brain weight; hallmark AD neuropathologic features (Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaques (NP) score [19] and Braak staging for neurofibrillary tangles (NFTs) as visualized by silver stain [20]); LBD as detected by Lewy bodies or Lewy neurites in the midbrain or cerebral cortex [13]; ranking of severity of cerebral amyloid angiopathy (CAA) [21]; and VBI from (i) large caliber vessels in the cerebrum as measured by remote gross (macroscopic) infarcts, including lacunar infarcts, and (ii) from small caliber vessels (microvascular brain injury or μ VBI) as measured by enumerating microvascular lesions (microinfarcts and microhemorrhages, although the vast majority are microinfarcts with rare bona fide microhemorrhages) in a standardized screening section of cerebral cortex and subcortical structures (cerebral white matter, basal ganglia, and thalamus) [13, 16] based on the method developed in the Honolulu Asia Aging Study [22] and recommended by a recent consensus panel appointed by the National Institute on Aging and the Alzheimer's Association [23, 24]. Other potentially informative markers of white matter injury, such as leukoariosis or leukoencephalopathy, were not collected as part of ACT. Given that acute microvascular lesions would have occurred subsequent to the final cognitive testing visit in most individuals, these lesions were excluded from analyses.

Cognitive examination

A cognitive screening test, the Cognitive Abilities Screening Instrument (CASI) [25], is administered to all ACT participants at their biennial study visit. The CASI consists of items from the Mini-Mental State Examination [26], the modified Mini Mental State Examination [27], and the Hasegawa Dementia Scale [28], and screens for impairments in a range of cognitive functions including attention, concentration, orientation, memory, language, visuospatial construction, verbal fluency, and abstraction. The CASI was originally developed as a cross-cultural dementia screen [25] and has been validated as a tool for the assessment of early to severe cognitive decline across populations [25, 29, 30].

Total CASI score as well as subscale scores reflecting performance in selected cognitive domains (executive function, verbal memory, visuospatial construction, and language) were calculated. Table 1 describes the test items that comprised each domain-specific score. Subdomains were determined as described by Teng et al. [25]; however, attention, concentration, abstraction, and verbal fluency items were combined to create a composite executive function index similar to the memory and language indices. To permit calculation of sub-domain scores and comparison of scores across domains, raw scores were converted to z-scores using the mean and standard deviation obtained from the entire, nondemented

cohort at baseline. These standard scores were then summed and averaged to create a composite z-score for each cognitive domain. Z-scores were also calculated for total CASI score to facilitate comparison with sub-domain scores. In addition, item response theory (IRT) scores have been generated for the ACT sample based on previously published findings that the CASI has curvilinear scaling properties (*e.g.*, a given number of standard CASI points are associated with variability depending upon such factors as age and education) [31]. IRT scores generated from previously published parameter estimates were found to produce less-biased estimates of global ability [32]. Thus, both CASI z-scores and CASI IRT scores were analyzed for the current study when examining global cognitive performance.

Analyses

T-tests and Fisher's exact tests were performed to examine differences between diagnostic groups (dementia, no dementia) on demographic variables and neuropathologic features. To evaluate the relationship between final cognitive performance and neuropathologic changes, linear regression was performed using total CASI score or CASI IRT score as the response variable and demographic and neuropathologic indices as predictors. Separate linear regression analyses were then performed by cognitive domain (CASI subscales measuring executive function, memory, visuospatial construction, and language), with demographic and neuropathology indices entered as predictors. Age, education, and gender were entered first in all regression models. Braak staging, CERAD score, and CAA were coded as ordinal scores based on standard criteria for each, LBD was coded as a binary variable (present versus absent), and brain weight, gross infarcts, and microvascular lesions were continuous data. Variance inflation factors were examined for each variable entered into the regression model to determine the presence or absence of multi-collinearity between the predictor variables. To determine whether *APOE 4* genotype was a significant predictor of cognitive performance over and above demographic and neuropathologic variables, secondary analyses were carried out on the subset of ACT participants who had undergone *APOE* genotyping prior to death. All statistical analyses were performed using Stata 12 (StataCorp., College Station, TX).

RESULTS

Participant characteristics

Sample characteristics are provided in Table 2. The sample included in this investigation did not differ from the total autopsy cohort with respect to demographic or neuropathologic measures. As we have observed previously [33], when the autopsy sample was compared to the entire ACT cohort who died, the autopsy group was older at death and had higher education than the group that did not undergo autopsy. Among those who underwent autopsy, the demented group was significantly older at death, had lower education level, had a lower final total CASI score, and was more likely to have neuropathologic changes across all indices than the non-demented group. As mentioned, biennial visits are discontinued once a participant is diagnosed with dementia in the ACT study; thus, there was a longer average period of time between final cognitive testing and autopsy for demented (~3.7 years) versus nondemented (~1 year) groups.

A substantial proportion of the cognitive sample had AD neuropathologic changes: 65% had Braak NFT staging of III to VI, and 47% had moderate or frequent CERAD score for NPs. Even when those who received a clinical diagnosis of dementia were excluded, one-half of the sample had Braak NFT stage of III to VI, and one-third had a moderate or frequent CERAD score for NPs. No differences were noted for those with a Braak stage III or less as compared with Braak stage IV–VI with regard to proportion of LBD, macroscopic infarcts,

or subcortical microvascular lesions. A lower proportion of participants classified as Braak stage none–III had cerebral cortical microvascular lesions (31%) and CAA (19%) as compared to those with Braak stage IV–VI (41% and 45%, respectively).

Global cognition and neuropathologic indices

Demographic factors alone accounted for 8% of the total variance in CASI score ($F(3,332)=9.46$, $p<0.0001$). When all neuropathologic indices were entered at once into the model, the total explained variance increased to 31% ($F(11,324)=13.04$, $p<0.0001$). Braak stage for NFTs, brain weight, and cerebral cortical μ VBI were significant predictors of total CASI score (p values ≤ 0.01) (Table 3). Low variable inflation factors (VIF range = 1.01–1.75) suggest that the magnitude of multi-collinearity between the predictors did not substantially impact the results. When CASI IRT scores were substituted for CASI total z-scores, the findings were similar, with a total explained variance of 37% ($F(11,322)=16.86$, $p<0.0001$). Again, Braak stage for NFTs, brain weight, and cerebral cortical microvascular lesions were significant predictors of CASI IRT scores. To determine if our results were largely influenced by subjects with dementia, analyses were re-run excluding those diagnosed with dementia during life. As with the total group, global cognitive function (total CASI score) was predicted by Braak stage for NFTs ($p=0.01$), brain weight ($p=0.04$), and cerebral cortical microvascular lesions ($p=0.02$) when all variables were entered into the model ($F(11,169)=4.59$, $p<0.0001$).

CASI subscales by cognitive domain and neuropathologic indices

Demographic factors alone accounted for only between 2–5% of the total variance in cognitive subdomain scores for the total group (Table 3). When all demographic and neuropathologic predictors were entered, age was associated with visuospatial construction, education with executive and memory functioning, and gender with memory. Brain weight was positively associated with performance across all cognitive domains.

When all neuropathologic and demographic variables were entered at once, total explained variance for the memory subdomain increased to 30% ($F(11,342)=13.09$, $p<0.0001$). Negative neuropathologic predictors of memory performance included Braak stage for NFTs ($p<0.0001$) and cerebral cortical microvascular lesions ($p=0.01$). When only the non-demented group was analyzed ($F(11,180)=4.42$, $p<0.0001$), only Braak stage for NFTs significantly predicted memory performance ($p<0.0001$).

Demographic and neuropathologic variables together accounted for 18% of the executive subdomain score ($F(11,351)=6.95$, $p<0.0001$). Lower performance on the executive function index was predicted strongly by higher Braak stage for NFTs ($p=0.006$), and subcortical microvascular lesions ($p=0.001$), and was less strongly associated with cerebral cortical microvascular lesions ($p=0.04$). When the nondemented group was examined alone, the total explained variance was 15% ($F(11,184)=2.96$, $p=0.001$). As with the total group, performance on the executive function index was negatively associated with both subcortical microvascular lesions ($p=0.06$, statistical trend) and Braak stage for NFTs ($p=0.07$, statistical trend), although the associations were less strong than when the entire group was included in the analyses.

Total variance explained by the model accounted for 15% of the variance of the visuospatial construction index score ($F(11,339)=5.46$, $p<0.0001$). Poorer visuospatial construction performance was primarily predicted by presence of LBD ($p<0.0001$), with a secondary association noted for cerebral cortical microvascular lesions ($p=0.05$). When the demented participants were excluded from analyses ($F(11,178)=2.67$, $p=0.003$), LBD continued to be a significant predictor of performance on visuospatial construction performance ($p=0.001$).

Only 9% of the language subdomain score variance was explained by the demographic and neuropathologic model ($F(11,338) = 3.08$, $p < 0.001$). Language performance negatively correlated with LBD ($p = 0.02$) and subcortical microvascular lesions ($p = 0.03$), and Braak stage for NFTs ($p = 0.04$). When the demented group was omitted from analyses, the total model remained associated with language performance ($F(11,177) = 2.07$, $p = 0.03$). Similar results were noted for LBD ($p = 0.005$), but not NFTs or subcortical microvascular lesions.

Because prior studies have found an association between gross or macroscopic infarcts and cognitive function [34], we ran follow up analyses to determine whether infarcts identified grossly were associated with cognitive outcomes when microvascular lesions were omitted from the multivariate analyses. Across all cognitive domains, gross infarcts were associated with performance on the executive subdomain ($p = 0.009$) but not with any other cognitive test performance.

APOE sample

In the sample of subjects with completed APOE genotype, demographic factors, including *APOE* genotype ($\epsilon 4+$, $\epsilon 4-$), accounted for 15% of the total variance in CASI score ($F(4,296) = 13.01$, $p < 0.0001$). When all neuropathologic indices were entered at once into the model, the total explained variance increased to 37% ($F(12,288) = 13.82$, $p < 0.0001$). As with the total cognitive sample when *APOE* was not included, Braak stage for NFTs ($p < 0.0001$) and cerebral microvascular lesions ($p = 0.006$) were associated with total CASI performance. Significant neuropathologic predictors for the cognitive subdomains were likewise unchanged as compared to the total cognitive sample. *APOE* genotype was not a significant predictor of cognitive performance over and above the other neuropathologic predictors.

DISCUSSION

In the present study, we examined the relationships among neuropathologic lesions and cognitive performance prior to death in the ACT study autopsy sample. We previously found that multiple lesion types were associated with clinical dementia diagnosis [13]; in the current study, we focused on associations between neuropathologic changes and specific cognitive functions in subjects with or without dementia. Although Braak stage for NFTs was a significant predictor of global cognitive function, our results also indicated that non-AD lesions contributed. Specifically, we found that type of neuropathologic lesion differentially predicts performance across and within specific cognitive domains.

Recent efforts examining the relationship between neuropathologic changes and cognitive function have been undertaken, most notably in the combined analyses of the Religious Orders Study and Memory and Aging Project [34]. Similar to the current study, these investigators found that AD neuropathologic changes were related to memory in nondemented subjects; however, several differences exist between our findings. For example, we found that microvascular lesions were related to cognitive function independently from gross infarcts. This is consistent with findings reported by the Honolulu Asia Aging Study (which also utilizes the CASI to measure cognition) [35, 36], and underscores the importance of “silent” μ VBI on everyday functioning.

Further, our study differs from others in that we separated VBI according to whether the lesions were cerebral cortical or subcortical. While total CASI score and memory performance were predicted by cerebral cortical, but not subcortical, microvascular lesions, performance on executive function tasks was associated with both cerebral cortical and subcortical microvascular lesions. We speculate that while subcortical VBI may not be

associated with global cognitive functioning per se, such lesions may nonetheless result in subtle yet potentially meaningful changes in executive function among older individuals.

Visuospatial ability was primarily associated with LBD in this sample, consistent with the observation that visuospatial impairment is often one of the earliest cognitive symptoms in Parkinson's disease [37,38] and is a primary feature of LBD [39]. A recent community-based autopsy study also found an association between visuospatial task performance and LBD [40]; results from the current study extend this research by demonstrating that this association exists even when analysis is restricted to subjects without dementia. Our unique finding that LBD was associated with a simple visuo-construction task even in nondemented individuals underscores the importance of identifying early visuospatial impairments in older adults. Although the neuropathologic substrate of impaired visuospatial abilities in LBD-related conditions is not well understood, it is hypothesized to result from pathophysiologic processes that promote Lewy body accumulation in posterior cortical regions, asymmetric dopamine loss in the right basal ganglia, disruptions in the fronto-striatal loop, or impairments in the dorsolateral prefrontal pathways [41–45]. Unlike other cognitive domains, visuospatial abilities were not specifically related to AD lesions over and above other neuropathologic changes. This is perhaps not surprising, given the general relative sparing of pure visuospatial functions in early AD [46, 47], and suggests that impairment on visuospatial function alone may be a specific indicator for non-AD related pathology.

The total variance for the language subdomain that was explained by the neuropathologic and demographic model was less than that of the other variables. Language functions are quite variable and can be disrupted by multiple pathological processes. For example, semantic processing is commonly disrupted in AD patients, while subcortical μ VBI is associated with impairments in speech production, language processing, and naming [48–50]. LBD also is associated with disrupted language, but such impairments differ qualitatively from AD and may be influenced by reduced fluency, impaired sentence processing, and slowed speech [51, 52]. Unlike the other cognitive subdomains, language was not associated with cortical μ VBI. Given that many language-based cognitive processes are primarily cortical in nature, this finding is somewhat surprising. However, subcortical μ VBI is associated with impairments in speech production, language processing, and naming [48–50], consistent with our finding that subcortical microvascular lesions may be associated with reduced performance on the language composite.

A potential limitation of our study relates to the variability in time between cognitive testing and death, and the possibility that those who were non-demented at the time of their final visit could potentially have developed dementia during the months prior to death. In addition, we did not have information concerning the presence of mild cognitive impairment in this sample, so the nondemented group likely includes a substantial proportion of participants who had cognitive impairment but lacked sufficient functional impairment to meet criteria for a diagnosis of dementia. This is a particularly important point given the amount of AD neuropathologic changes present in the clinically non-demented group; prior research has suggested that subjects with no cognitive impairment have relatively little AD neuropathologic change [53]. Due to these limitations, we chose to analyze cognitive performance in relation to severity of neuropathologic changes but without regard to clinical diagnosis at the final visit. This approach, which has been used by others [40], provides increased statistical power and is consistent with the recent conceptual shift that distinguishes AD neuropathologic changes from clinical dementia diagnosis, in large part as a recognition of latent and prodromal stages of disease. To verify that the results were not solely related to clinical dementia diagnosis, we did secondary analyses of both global and

subdomain cognitive performances in the clinically non-demented group only; the results were generally similar to findings from the combined sample.

A further limitation of the study involves the use of a single global cognitive test score and derived composites indexing different cognitive domains. Given that the CASI is designed as an enhanced screening instrument, the cognitive domain subscales produced a limited range of scores as well as ceiling effects. Unfortunately, because ceiling effects are present across all the subscales, our ability to assess the relationship between neuropathologic indices and cognition for those performing in the higher ranges was limited. Particularly given that this is a relatively highly educated sample, more sensitive neuropsychological measures of individual cognitive domains would have been preferable. However, our results with these less sensitive indices of cognition support the use of additional investigation of the relationship between specific cognitive domains and neuropathologic lesions in community-based samples. In addition to cognitive measures, the neuropathologic measures used may also have impacted our results. Our demographic and neuropathologic model accounted for 31% of the variance in total CASI score, and for varying lesser degrees on the cognitive subscales. Use of more quantitative measures of brain injury or disease burden may have increased the correlations with cognitive test scores. For example, only 65% of our sample had hippocampal sclerosis measured; of those, 80% were free from lesions. Thus, we did not have sufficient statistical power to detect the impact of these potentially important lesions. However, cognitive test performance may be affected by numerous environmental, genetic, and other biologic factors; thus it is likely that unmeasured (e.g., mood states, fatigue) or unknown factors also contributed to the variance associated with cognitive test performance. Finally, a limitation of this study, as well as most autopsy studies, is the relatively small proportion of the total sample that consents to and undergoes autopsy at death. Thus, we are constrained in our ability to generalize from these results to the population at large.

This study links cognitive subscales contained within a brief global screening measure to a variety of underlying neuropathologic indices in a non-clinically defined community sample. Although global functioning itself is related to certain (primarily AD) neuropathologic changes, directing attention to performance across specific cognitive domains permits more in-depth analysis of the potential impact of other, non-AD lesions, on cognition. In sum, our findings indicate that the type and quantity of neuropathologic lesions may be differentially related to cognitive domains affected by disease thus potentially highlighting different pathways to cognitive decline in older individuals.

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Fig. 1. Operationalization and levels of measurement of neuropathologic variables measured in the ACT cognitive sample.

Figure 2.
Neuropathologic variables that contribute to cognitive domains in the ACT study sample.

Table 1

Constituent CASI subtests by cognitive domain

Cognitive domain	CASI subtests
Executive function	attention, concentration, verbal fluency, abstraction
Memory	verbal list recall, object recall
Visuospatial construction	cube drawing
Language	command, reading, writing, naming

Table 2

Sample characteristics

Percentages in the table may not equal 100 due to rounding.

		Autopsy cohort (n = 438)	Total included sample (n = 363)	No Dementia (n = 196)	Dementia only (n = 167)	sig. [†]
Age at visit	mean (sd)	85.0 (6.6)	85.1 (6.5)	85.1 (7.2)	85.2 (5.8)	
Age at death	mean (sd)	87.4 (6.8)	87.4 (6.7)	86.0 (7.2)	89.0 (5.7)	***
Education	mean (sd)	14.3 (3.1)	14.2 (3.0)	14.5 (3.0)	13.9 (3.1)	*
Gender	% women	55.9	54.0	52.0	56.3	
Final CASI	mean (sd)	86.3 (10.5)	85.2 (10.7)	92.0 (5.7)	77.4 (9.9)	***
Braak stage for NFTs	% 0	4.1	3.9	5.6	1.8	
	% I/II	34.5	31.7	44.4	16.8	***
	% III/IV	33.6	33.6	39.3	27.0	
	% V/VI	27.9	30.9	10.7	54.5	
CERAD NP score	% None	22.8	22.3	29.1	14.4	
	% Sparse	30.6	30.9	37.8	22.8	***
	% Moderate	24.0	23.7	21.4	26.4	
	% Frequent	22.6	23.1	11.7	36.5	
Brain weight	mean (sd)	1214.2 (138.0)	1212.3 (137.3)	1240.2 (126.2)	1179.6 (142.9)	***
CAA ranking	% None	70.5	69.4	79.1	58.1	
	% Mild	14.8	15.7	11.7	20.4	***
	% Moderate	12.9	13.2	8.2	19.2	
	% Severe	1.8	1.7	1.0	2.4	
Lewy body disease	%	13.8	13.8	11.7	16.2	
Gross remote cerebral infarcts	%	30.3	31.7	22.5	42.5	***
Cortical microvascular lesions	%	34.6	35.5	27.0	45.5	***
Subcortical microvascular lesions	%	29.6	31.1	25.0	38.3	**

[†] significance reported for pairwise comparisons (t-tests and Fisher's exact tests) between dementia and no dementia groups.

Braak NFT stage comparisons: 0, I, II versus III, IV, V, VI; CERAD NP score comparisons: none/sparse versus moderate/frequent; CAA ranking comparisons: none/mild versus moderate/severe; LBD, gross cerebral infarcts, cortical and subcortical microvascular lesion comparisons: present versus absent.

p < 0.001
**
p < 0.01
*
p < 0.05.

Table 3

Linear regression results for total CASI score, cognitive subdomains, and neuropathology variables

Variables	CASI (total)		Executive		Memory		Construction		Language	
	Total group	Non-demented	Total group	Non-demented	Total group	Non-demented	Total group	Non-demented	Total group	Non-demented
Demographic model	R ² =0.08 ***	R ² =0.14 ***	R ² =0.05 ***	R ² =0.08 **	R ² =0.03 *	R ² =0.10 ***	R ² =0.05 ***	R ² =0.07 **	R ² =0.02 [‡]	R ² =0.02
Age	-2.90 **	-3.38 ***	-2.34 *	-3.31 ***	-2.44 *	-3.05 **	-4.25 ***	-3.61 ***	-2.51 *	-2.20 *
Gender	0.54	0.97	-1.25	-0.70	0.68	2.88 **	0.24	0.09	0.01	-0.68
Education	4.47 ***	4.72 ***	2.99 **	1.66 [‡]	2.15 *	1.96 *	-0.29	-0.14	1.09	-0.64
Total model	R ² =0.31 ***	R ² =0.25 ***	R ² =0.18 ***	R ² =0.15 ***	R ² =0.30 ***	R ² =0.21 ***	R ² =0.15 ***	R ² =0.15 **	R ² =0.09 ***	
Age	-1.20	-1.49	-0.78	-1.68 [‡]	-0.54	-1.24	-3.01 **	-2.58 **	-1.34	-0.97
Gender	2.54 **	2.80 **	0.39	0.15	2.82 **	3.03 **	1.38	0.74	0.80	-0.53
Education	3.95 ***	3.55 ***	2.30 *	1.05	1.68 [‡]	1.93 [‡]	-0.78	-0.35	0.58	-0.97
Brain weight	3.43 ***	2.10 *	3.13 **	2.26 *	3.03 **	0.75	3.04 **	1.71 [‡]	1.89 [‡]	0.71
CERAD NP score	-1.11	0.26	-0.12	-0.30	-0.55	0.76	-1.56	-0.56	0.14	-0.71
Braak stage for NFTs	-5.30 ***	-2.60 **	-2.79 **	-1.84 [‡]	-6.87 ***	-3.65 ***	-0.37	-0.11	-2.11 *	-1.59
Cerebral amyloid angiopathy	-1.17	-0.48	0.28	1.47	-1.24	-1.25	0.36	-0.05	0.76	0.58
Lewy body disease	-0.85	0.35	-0.77	-0.30	-1.22	-1.43	-4.04 ***	-3.33 ***	-2.37 *	-2.86 **
Gross remote cerebral infarcts	0.71	1.20	-0.52	0.77	1.16	0.86	0.68	0.40	0.27	0.30
Cortical microvascular lesions	-2.46 **	-2.28 *	-2.03 *	-0.25	-2.52 **	-1.60	-1.93 *	-0.57	-1.14	0.00
Subcortical microvascular lesions	-1.10	-0.61	-3.47 ***	-1.93 [‡]	-0.56	-1.64	-1.06	0.75	-2.22 *	-1.21

Results are expressed as t-scores.

p 0.001

**
p 0.01

*
p 0.05

[‡]
p < 0.10