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MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease

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Abstract

Background—Causes of cognitive impairment in subcortical ischemic vascular disease (SIVD) are less well understood than in AD, but have been thought to result from direct effects of subcortical lacunes and white matter lesions, perhaps related to disruption of important cortical-subcortical pathways.

Objective—To examine the relation between cognitive abilities and quantitative MRI measures of subcortical cerebrovascular disease and cortical and hippocampal atrophy.

Methods—Subjects were 157 participants in a multicenter study of SIVD and AD who included cognitively normal, cognitively impaired, and demented individuals with and without subcortical lacunar infarcts. Dependent variables were neuropsychological tests of global cognitive function, memory, language, and executive function. Independent variables were quantitative MRI measures of volume of lacunar infarcts in specific subcortical structures, volume of white matter lesion (WML), volume of cortical gray matter (cGM), and total hippocampal volume (HV). Multiple regression analyses were used to identify MRI predictors of cognition.

Results—Subcortical lacunes were not related to cognitive measures independent of effects of other MRI variables. WML was independently related to selected, timed measures. HV and cGM were strong and independent predictors of cognitive variables, with effects that did not differ in subjects with and without subcortical lacunes.

Conclusions—Results suggest that cognitive impairment associated with subcortical ischemic vascular disease is primarily a result of associated hippocampal and cortical changes.

There is an extensive literature on AD that describes a typical pattern of neuronal degeneration that explains the basic clinical features of the disease. Our understanding of contributions of subcortical ischemic vascular disease (SIVD) to cognitive impairment is much less developed. There is relative agreement dating to the seminal work of Tomlinson et al.[1] that multiple cortical infarcts can cause dementia. More recently, there is evidence that cerebrovascular

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disease amplifies the effects of pathologic changes of AD.[2,3] Disruption of frontal-subcortical circuits by strategically located infarcts is considered one important mechanism by which SIVD can result in symptoms of dementia,[4,5] and some have argued that single infarcts, strategically located, can cause dementia.[6-8] Subcortical small vessel ischemia in the absence of frank stroke is the defining feature of a dementia originally identified in the 19th century by Binswanger.[9] However, this cause for dementia is controversial and is explicitly recognized in one commonly used diagnostic ctiterion,[10] but not in two others.[11,12]

A recent study from our group[13] reported that global cognitive impairment and dementia in patients with SIVD were associated with atrophy of the hippocampus and cortical gray matter, but were only weakly influenced by white matter changes, and relatively unrelated to volume and location of subcortical lacunar infarcts. Patients with AD and demented patients with SIVD had hippocampal and cortical atrophy in common, though a somewhat different pattern of findings was observed in the two disorders.

The purpose of this study was to examine how quantitative MRI measures relate to more specific cognitive abilities in a sample with broad variability of cognitive impairment and SIVD. MRI volumetric measures of subcortical infarcts (lacunes), white matter lesions, hippocampus, and cortical gray matter were examined in relation to measures of global cognition, memory, language, and executive function.

Methods

Subjects

Participants in this study were recruited from three academic dementia centers and evaluated as part of a multicenter collaborative study examining contributions of SIVD and AD to cognitive impairment and dementia. All participants received a comprehensive clinical evaluation that included a detailed medical history, a neurologic exam, appropriate laboratory tests, and neuropsychological testing with a standardized test battery. In addition, participants received a MRI scan of the brain. Participants were diagnosed at a multidisciplinary case conference using the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) diagnostic criteria[14] for AD, and California Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) criteria[10] for ischemic vascular dementia. The Institutional Review Boards at all participating institutions approved this study. All subjects or their legal representatives gave written informed for participating.

Recruitment was targeted to fill six groups defined by three levels of cognitive impairment crossed with presence vs absence of subcortical lacunes. The levels of cognitive impairment were: 1) normal, defined by a Clinical Dementia Rating (CDR)[15,16] total score of 0.0; 2) impaired (CDR = 0.5); and 3) demented (CDR $\geq$ 1.0). Presence of lacunes was determined by an expert radiologist who viewed all MRI scans. Demographic characteristics and global cognitive function, as measured by the Mini-Mental State Examination (MMSE), are presented by recruitment group in table 1 for the 157 participants. The clinical diagnosis of demented subjects without lacunes was predominantly probable AD (n = 11, 76.9%). Clinical diagnoses of demented subjects with lacunes included possible or probable ischemic vascular dementia (n = 9, 52.9%), mixed AD/vascular disease (n = 5, 29.4%), and possible or probable AD (n = 3, 17.6%).

MRI methods

MRI variables of interest were computerized measures of volume of white matter lesions (WML), volume of cortical gray matter (cGM), total hippocampal volume (HV), and volume

of lacunes within specific structures: thalamus, putamen, caudate, globus pallidus, and white matter. All volumes were normalized to total intracranial volume (ICV).

Lacunes were small (>2 mm) areas of the brain with increased signal relative to CSF on proton density MRI in subcortical gray and white matter. Lacunes were differentiated from perivascular spaces, which can be particularly prominent below the anterior commissure and putamen and at bends in the course of penetrating arterioles. Isointense lesions on pseudo proton density MRI (as apposed to "true" proton density, which is obtained when extrapolated to TE = 0) at the level of the anterior commissure or inferior putamen were termed perivascular spaces; outside that region, they were defined as cavitated lacunes if they were ≥3 mm at maximum width.

Image acquisition and data management and transmission previously have been described.[13] A computerized segmentation algorithm was used to classify brain MRI pixels into cortical gray matter, subcortical gray matter, white matter, white matter lesions, ventricular CSF, and sulcal CSF. In addition, total intracranial volume was computed by summing over all pixels within the intracranial vault. Segmentation methods have been previously reported.[13] Intraclass correlation coefficients (n = 10) were 0.93 for percent of white matter; 0.99 for percent of white matter lesions; 0.95 for cortical gray matter; 0.99 for sulcal CSF; 0.99 for ventricular CSF.

The outline of the hippocampus was manually drawn on each 1.4 mm MRI slice and volumes were generated by a computer algorithm using previously reported methods.[13,17] An interrater reliability test (n = 18) using scans from normal controls yielded an *r* of 0.81 for total hippocampal volume. Accuracy of the manual ratings of hippocampal volume was subsequently evaluated by comparing manual volumes with volumes independently derived using an automated, computerized method (Surgical Navigator Systems, Boulder, CO) for determining hippocampal volume.[18,19] An analysis of variance approach (n = 92) showed that the automated ratings accounted for 78.8% of the variance in the manual ratings (standardized beta = 0.89), indicating a high level of correspondence between the manual and automated methods.

Neuropsychological tests

All participants received a standardized neuropsychological test battery from which neuropsychological variables used in this study were selected. The Mattis Dementia Rating Scale (MDRS)[20] was selected as a measure of global cognitive ability. The Initiation-Perseveration subscale of the MDRS (MDRS I-P) was chosen to measure of executive function, presumably mediated frontally. The Boston Naming Test (BNT)[21] was selected to measure language ability, conceptually linked to posterior cortical function. The List Recall score from the Word List Learning Test of the Memory Assessment Scales (MAS)[22] was used to measure memory, which is theoretically linked to the hippocampus. Finally, two fluency measures, the FAS test[23] and the Animal Category Fluency test,[24,25] were included. Both are timed and, consequently, should be sensitive to white matter pathology. Both have components of variation related to language and executive function. In addition, the FAS test has been linked to frontal lobe function.[26]

Data analysis

A multistage multiple regression approach was used to evaluate the relation between MRI variables and individual neuropsychological test variables. An initial baseline model used the demographic variables of sex, age, and education to predict each neuropsychological test. In the second stage, volumes of subcortical lacunes within the five specific structures were added as independent variables. WML was added as a predictor in Step 3, cGM in Step 4, and HV in

Step 5. The order of inclusion was chosen to first test effects of subcortical cerebrovascular changes alone and to then add cortical and hippocampal volumes as predictors.

Categorical analyses were also performed to address contributions of "abnormal" hippocampal volume, cortical gray matter volume, white matter lesion, and the presence of lacunes to cognitive impairment and dementia. Hippocampal and cortical gray matter volumes at or below the 10th percentile of the cognitively normal with no lacunes group were categorized as abnormal, as were white matter lesion volumes at or above the 90th percentile of this group. A multinomial logistic regression analysis was performed in which cognitive impairment group (normal, impaired, demented) was predicted by presence vs absence of lacunes, normal vs abnormal HV, normal vs abnormal cGM, and normal vs abnormal WML. A second analysis was performed in which terms were added to the model to represent the interactions of lacunes with HV, cGM volume, and WML.

Results

Cognitive impairment groups significantly differed in age at evaluation ($p = 006$; mean (SEM) normal = 73.71 (0.80), impaired = 72.39 (1.25), demented = 78.22 (1.39); table 1). There were significant differences in education related to both cognitive impairment ($p = 0.005$; normal = 15.25 (0.32), impaired = 14.51 (0.51), demented = 13.12 (0.56)) and lacunes ($p = 0.02$; no lacunes = 14.99 (0.41), lacunes = 13.60 (0.37)). Sex did not significantly differ according to cognitive impairment group ($p = 0.07$) or presence vs absence of lacunes ($p = 0.06$). Because of these demographic differences, subsequent analyses included covariates to account for possible confounding effects of age, education, and sex on measures of association between MRI and cognitive outcomes. There were clear differences in mean MMSE scores related to cognitive impairment group ($p < 0.0001$; normal = 29.00 (0.22), impaired = 27.39 (0.34), demented = 19.55 (0.39)).

Quantitative MRI measures as predictors of cognitive function

When volumes of lacunes within specific subcortical structures were included as independent variables in the stage 2 regression model, only volume of thalamic lacunes was significantly related to neuropsychological test variables. Thalamic lacune volume had a significant independent effect for four neuropsychological test variables: MDRS ($p = 0.002$, standardized beta =–0.26), BNT ($p = 0.02$, standardized beta = –0.21), FAS ($p = 0.05$, standardized beta =–0.16), and Animals ($p = 0.03$ standardized beta = –0.19). The standardized betas allow for a direct assessment of strength of the independent contribution of thalamic lacune volume as a predictor of the neuropsychological tests. The square of the standardized beta coefficient can be interpreted as the percentage of variance in the dependent variable accounted for by the independent variable. Overall, volume of subcortical lacunes was a weak predictor of cognitive performance. Volume of thalamic lacunes accounted for 3 to 7% of the variance in the four variables where there was a significant effect.

Volume of thalamic lacunes (L-Thal) was retained along with demographic variables in the stage 3 model, but lacunes in other locations were dropped since they did not significantly predict cognitive performance in stage 2. WML was also added as an independent variable in the stage 3 model. With the addition of WML to the model, L-Thal was not significantly related to any dependent variable. However, WML significantly predicted MDRS ($p = 0.002$, standardized beta =–0.26), MDRS I-P ($p < 0.0001$, standardized beta =–0.35), List Recall ($p = 0.04$, standardized beta =–0.18), FAS ($p = 0.0004$, standardized beta = –0.29), and Animals ($p = 0.0005$, standardized beta = –0.29). These results show that WML independently predicted all dependent variables except BNT, with strongest relations with MDRS I-P, FAS, and Animals. Associations of L-Thal with dependent variables were not statistically independent of effects of WML.

Volume of cGM was added to the stage 4 model along with the variables included in the stage 3 analysis, and was significantly related ($p < 0.0005$) to all test variables (betas: MDRS = 0.58; MDRS I-P = 0.51; BNT = 0.48; List Recall = 0.56; FAS = 0.32; Animals = 0.37). Neither WML nor L-Thal had significant predictive effects independent of volume of cGM.

HV was added as a predictor in stage 5. Standardized betas and significance levels of effects from this analysis are shown in table 2. L-Thal was not independently related to any of the neuropsychological test variables. WML was significantly but weakly related to category fluency in Model 5. cGM was independently related to MDRS total score, MDRS I-P, BNT, and FAS. HV was the strongest predictor and was significantly related to all variables except FAS. HV was a particularly strong predictor of List Recall. Taken together, results indicate that memory is strongly predicted by HV. Global cognitive function, executive function, and confrontation naming were associated with both cGM and HV. WML was a significant predictor for one of the fluency tasks, a timed task, which may reflect an effect of WML on cognitive speed. The figure shows R^2 values associated with the stage 1 to 5 regression models for all neuropsychological test variables. These R^2 values show the amount of the variance in the dependent variable predicted by the regression model. Of particular note, addition of cGM and HV resulted in substantial increases in R^2, whereas lacunes and WML had modest effects.

The previously described analyses included all study participants and did not differentiate those from different recruitment groups. Additional analyses were performed in which interaction terms were added to determine if effects of MRI variables were different in participants with lacunes in comparison to those without lacunes. None of the interaction effects were significant in any of the analyses (all $p > 0.28$), and results were essentially unchanged as a consequence of adding the interaction terms. This indicates that the relation of the MRI variables with neuropsychological test performance did not significantly differ for participants with and without lacunes.

An analysis was performed to assess the relation between the extent of subcortical ischemic vascular disease and cGM and HV. A regression model was used in which total volume of lacunes and WML were used to predict cGM and HV. cGM was strongly predicted by WML (beta = –0.56), but lacune volume was not significantly associated (beta = 0.02) independent of WML. HV was significantly but weakly predicted by WML ($p = 0.03$, beta =–0.19) but was not related to lacune volume (beta = 0.10). Interaction terms were added to assess whether WML was differentially associated with cGM and HV in the three cognitive impairment groups, the lacune and no-lacune groups, and the 3×2 interaction of these categories. None of these interaction effects approached significance, indicating that the relation of WML to cGM and HV did not systematically differ according to subject categorization groups.

Normal vs abnormal HV and cGM volume as predictors of dementia

A multinomial logistic regression analysis was performed in which cognitive impairment group membership (normal, impaired, demented) was predicted by presence vs absence of lacunes (LacGrp), normal vs abnormal hippocampal volume (HVGrp), normal vs abnormal cortical gray matter volume (cGMGrp), and normal vs abnormal white matter lesion (WMLGrp). The impaired group was selected as the reference group so that ability to discriminate this group from normal and demented groups could be evaluated. HVGrp ($p < 0.0001$) and cGMGrp ($p = 0.002$) significantly discriminated cognitive groups. HVGrp discriminated normal from impaired ($p < 0.0001$; OR = 11.1, 95% CI = 3.6 to 37.3), but not impaired and demented ($p = 0.59$). High HVGrp was associated with an eleven-fold increased likelihood of being in the normal group in comparison to the impaired group. In contrast, cGMGrp discriminated impaired and demented ($p = 0.02$; OR = 0.19, 95% CI = 0.04 to 0.78) but not normal and impaired ($p = 0.11$). Individuals in the high cGMGrp were approximately one-fifth as likely to be in the demented group as in the impaired group.

A second analysis was performed in which interaction terms were added for LacGrp with HVGrp, cGMGrp, and WMLGrp. None of these interactions were significant, and results were essentially unchanged. Finally, LacGrp and WMLGrp were dropped from the model and a HVGrp-by-cGMGrp interaction term was added. This interaction effect was also nonsignificant. Results also were unchanged when continuous MRI variables were used as predictors. These results indicate that abnormal HV and abnormal cGM volume make independent contributions to cognitive status. Low HV is the best discriminator of normal vs impaired status, whereas low cGM is the best discriminator of impaired vs demented status.

Discussion

Results of this study showed that neuropsychological test scores were most strongly associated with HV and cGM volume regardless of the specific neuropsychological domain being assessed. Abnormal white matter was weakly associated with cognitive performance, particularly for timed measures and measures of executive function. This pattern of results was essentially the same in participants with lacunes and without lacunes. Subcortical lacunes were weakly associated with cognitive performance.

Results from categorical data showed that hippocampal atrophy and cortical atrophy made independent and additive contributions to cognitive impairment and dementia. Dementia was much more likely in the presence of both cortical and hippocampal atrophy (82%), but was very uncommon in the absence of both (3%). Cognitive impairment not meeting criteria for dementia was observed with similar frequencies in all four combinations of normal vs abnormal HV and normal vs abnormal cGM volume. HV was most effective in differentiating normal and cognitively impaired cases, whereas cGM was a more important determinant of impaired vs demented.

These results converge with a previous report[13] to suggest that subcortical cerebrovascular disease has an indirect relation with cognitive impairment and dementia. Our results suggest that, as in AD, cognitive impairment in ischemic vascular dementia results from associated atrophy in the cGM and hippocampus. Thus, clearly different pathologic entities, such as AD and cerebrovascular disease, may both impact similar cortical structures and produce similar dementia syndromes, with the symptom profile and severity determined by the location and amount, rather than qualitative type, of pathology.

An obvious explanation for the relation between cortical and hippocampal volume and cognition observed among patients with cerebrovascular disease is that these patients have concomitant AD.[27] The prevalence of both AD and cerebrovascular disease in the older population makes coincidence of the two pathologies likely in a significant proportion of dementia cases. Further, some have argued that cerebrovascular disease might be a risk factor for AD.[28]

Results from autopsied cases from this project suggest that concomitant AD pathology is unlikely as the sole explanation for cortical and hippocampal atrophy in patients with subcortical vascular lesions.[13] That study described three autopsied cases with dementia and lacunes. All three had a primary pathologic diagnosis of ischemic vascular disease, and none had neurofibrillary tangles in the neocortex. All three cases had both HV and cGM volume below the 10th percentile of the normal group. The number of neuropathologically diagnosed cases is small and replication of this study with neuropathologically diagnosed cases is critical, but results indicate that dementia with associated cortical and hippocampal atrophy can exist in the absence of significant AD.

There are several potential mechanisms that could explain structural changes in the cortex and hippocampus associated with SIVD. First, damage to subcortical neurons and demyelination

of axons could result in secondary structural changes in cortical or hippocampal neurons. Second, the cerebral cortex and hippocampus might suffer subclinical ischemic brain injury.[29] Microvascular changes in the cortex have been described as an important pathologic feature of vascular dementia.[30] Severe WML has been associated with deficient autoregulatory response[31] and increased oxygen extraction fraction[32-34] that could result in ischemic brain injury. The strong relation in this study between abnormal white matter and cortical volume loss supports a hypothesized link between white matter lesion and cortical ischemic injury, and may indicate that white matter change provides a useful marker for more extensive cerebrovascular disease. This was a robust relation that did not significantly differ across cognitive impairment groups, nor across those with and without lacunes.

WML clearly was a better indicator of cognitive impairment than subcortical lacunes. Current diagnostic criteria for vascular dementia emphasize the presence of radiologically documented infarcts. White matter disease is formally recognized only in the California ADDTC criteria and is not incorporated in either the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or the NINDS and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) diagnostic criteria for vascular dementia. These results suggest that white matter pathology may actually be a better marker for vascular dementia due to SIVD.

The finding that HV was the most sensitive discriminator of normal vs impaired cognitive status, and cGM volume best discriminated impaired and demented is of particular interest. In AD, there is an established progression of neurofibrillary pathology from medial temporal lobes to neocortex.[35] This helps to explain the early memory impairment as a result of hippocampal changes, and subsequent global dementia that presumably relates to broader neocortical changes. As previously discussed, there is also a rationale to explain the importance of cortical changes for dementia in cases where vascular disease is the primary etiology. The hippocampal influence on milder impairment associated with cerebrovascular disease is not as easy to explain and merits further study, especially given that HV was minimally correlated with lacunes and WML.

This study has a number of limitations. The study design was essentially correlational, which limits interpretations about causal mechanisms underlying cognitive impairment associated with vascular disease. MRI volumetric measures of more specific regions of cortical gray matter would be valuable, and measures of frontal lobe volume would appear to be particularly relevant given the theoretical relevance of frontal-subcortical circuits in ischemic vascular dementia. Similarly, more detailed examination of effects of lacunes in specific locations and of more specific types, and locations of WML might provide valuable information. The study sample was essentially a clinical sample of convenience and might not be representative of broader populations of patients with AD and cerebrovascular disease. Future studies using representative sampling methods are essential to enhance the generalizability and interpretation of studies of ischemic vascular disease with respect to dementia. Careful longitudinal studies with neuropathologically verified diagnoses will be important.

There is a growing body of literature examining additive or interactive effects of AD and cerebrovascular disease. A better understanding of how these common problems for older persons contribute alone and in combination to cognitive impairment and dementia is likely to be very important for a better understanding of dementia, and might also yield important clues for prevention and treatment of dementia.

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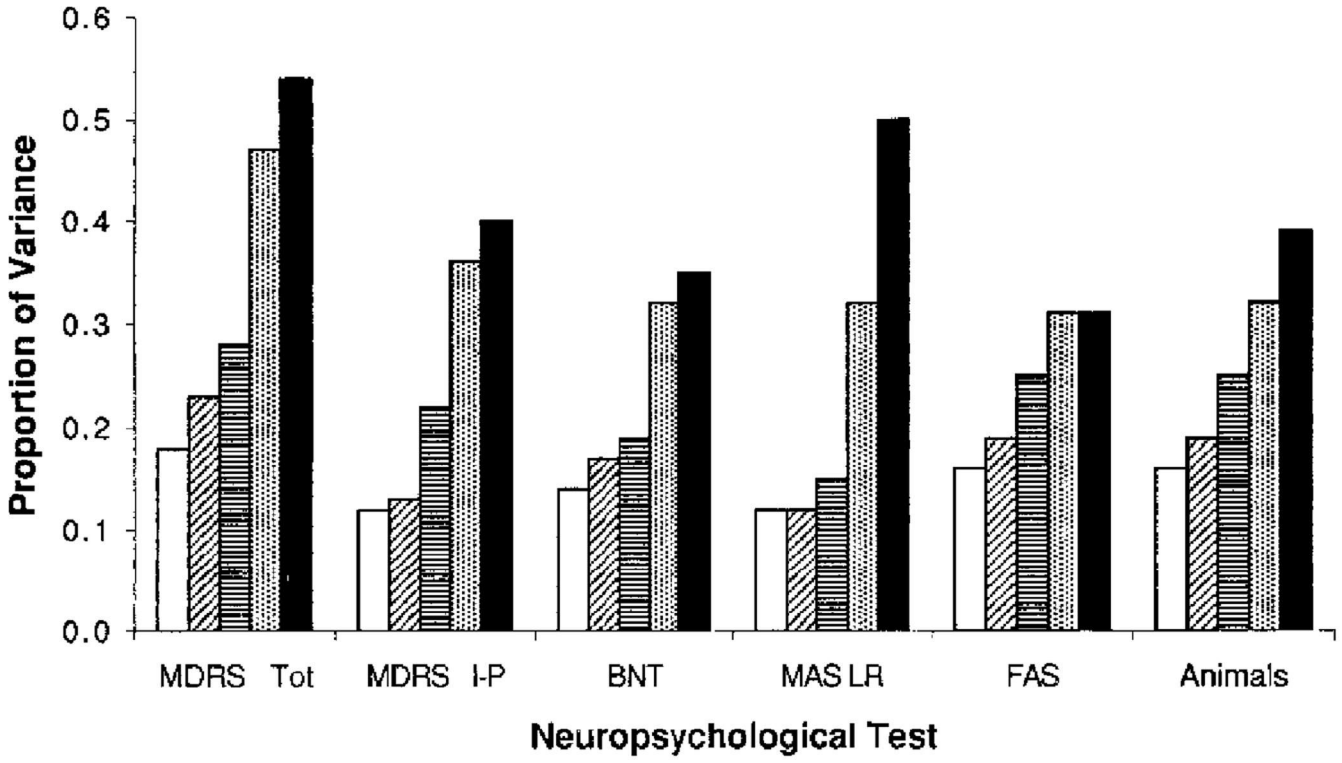

Figure.

Percent of total variance (R^2) of neuropsychological test variables explained by sequential regression models. Demographic variables (D) alone were included in the first model. Volume of thalamic lacunes was added in model 2, volume of white matter lesion (WML) was added in model 3, volume of cortical gray matter (cGM) in model 4, and hippocampal volume (HV) in model 5. For each neuropsychological test, each bar shows the amount of variance accounted for by all of the effects in that specific model. Differences between adjacent bars correspond to the incremental explanatory power associated with the addition of the last variable. In general, results show slight improvement in prediction associated with thalamic lacunes, modest effects associated with WML, and robust improvement in prediction when cGM and HV were added. (Neuropsychological tests: MDRS Tot = Mattis Dementia Rating Scale total score; MDRS I-P = Initiation-Perseveration subscale of the Mattis Dementia Rating Scale; BNT = Boston Naming Test; MAS LR = List recall trial of the World List Learning Test of the Memory Assessment Scales; FAS = FAS letter fluency total score; Animals = animal category fluency total score.) □ = demographic (D); ▨ = D + Lac; ▤ = D + Lac + WML; ▩ = D + Lac + WML + cGM; ■ = D + Lac + WML + cGM + HV.

Table 1

Number of subjects, demographic characteristics, and MMSE score by recruitment category (CDR category by presence vs absence of lacunes)

Recruitment group	n	Mean education, y (SD)	Mean age, y (SD)	Mean MMSE (SD)	Sex, % female
CDR = 0.0, no lacunes	50	15.5 (2.8)	72.4 (8.0)	29.4 (0.7)	60.0
CDR = 0.5, no lacunes	16	15.3 (2.0)	72.6 (5.9)	26.8 (2.6)	43.8
CDR ≥ 1.0, no lacunes	13	14.2 (3.7)	78.1 (7.1)	19.8 (3.3)	53.8
CDR = 0.0, lacunes	40	15.0 (3.1)	75.0 (6.3)	28.5 (2.0)	47.5
CDR = 0.5, lacunes	21	13.8 (3.4)	72.2 (9.4)	27.8 (1.8)	23.8
CDR ≥ 1.0 lacunes	17	12.0 (3.2)	78.3 (8.1)	19.3 (3.6)	47.1
Total	157	14.6 (3.2)	74.2 (7.8)	26.8 (4.2)	48.4

MMSE = Mini-Mental State Examination.

Table 2

Standardized beta values for demographic covariates and quantitative MRI measures as predictors of neuropsychological test variables

	Neuropsychological test					
Independent variable	**Mattis DRS total**	**Mattis DRS I-P**	**Boston Naming Test**	**MAS list recall**	**Letter fluency (FAS)**	**Category fluency (animals)**
Sex (male)	−0.02	−0.10	0.17*	−0.01	−0.07	0.01
Education	0.27§	0.22‡	0.23‡	0.21‡	0.33§	0.25‡
Age	0.01	0.08	−0.07	0.05	0.11	−0.04
Thalamus lacune volume	−0.12	0.10	−0.11	−0.02	−0.04	−0.07
Abnormal white matter volume	−0.05	−0.16	0.03	−0.04	−0.16	−0.20*
Cortical gray matter volume	0.34‡	0.33†	0.30†	0.16	0.26*	0.11
Hippocampal volume	0.34§	0.25†	0.24†	0.55§	0.09	0.35§

Standardized beta represents the correlation of the predictor variable with the dependent variable independent of the effects of the other predictor variables.

Mattis DRS total = Mattis Dementia Rating Scale total score; Mattis DRS I-P = initiation-perseveration subscale of the Mattis DRS.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

§ $p < 0.0001$.

Table 3

Frequency (percentage) of individuals in each category defined by the cross tabulation of normal vs abnormal hippocampal volume, normal vs abnormal cortical gray matter volume, and presence vs absence of lacunes who were normal, impaired, and demented

	Normal HV Normal cGM	Abnormal HV Normal cGM	Normal HV Abnormal cGM	Abnormal HV Abnormal cGM
Not demented				
No lacunes	42 (89.4)	4 (40.0)	3 (50.0)	1 (6.3)
Lacunes	27 (61.3)	2 (25.0)	7 (44.4)	0 (0.0)
Combined	69 (75.8)	6 (33.3)	7 (46.7)	1 (6.3)
Impaired				
No lacunes	5 (10.6)	1 (10.0)	2 (33.3)	1 (6.3)
Lacunes	12 (27.3)	4 (50.0)	3 (33.3)	4 (23.5)
Combined	17 (18.7)	5 (27.8)	5 (33.3)	5 (15.1)
Demented				
No lacunes	0 (0.0)	5 (50.0)	1 (16.7)	14 (87.5)
Lacunes	5 (11.4)	2 (25.0)	2 (22.2)	13 (76.5)
Combined	5 (5.5)	7 (38.9)	3 (20.0)	27 (81.8)

Normal HV = normalized hippocampal volume > 10th percentile of cognitively normal participants without lacunes; abnormal HV = normalized hippocampal volume < 10th percentile; normal cGM = normalized cortical gray matter volume > 10th percentile; abnormal cGM = cortical gray matter volume < 10th percentile.