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Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease

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Abstract

Objective—Although non-specific, cerebral atrophy and white matter hyperintensities (WMH) are features of the neurodegeneration associated with Alzheimer's disease (AD). The purpose of the current study was to determine if baseline measurements of cerebral atrophy and WMH predict the rate of future cognitive decline in AD.

Design—Data were drawn from the Predictors Study, a longitudinal study that enrolls mild AD patients and re-asseses them every six months with the Columbia modified Mini Mental State Examination (mMMS; 0–57). MR images were analyzed to determine the severity of WMH (Scheltens Scale) and the degree of atrophy (bicaudate ratio). Generalized estimating equations (GEE) were used to determine whether severity of baseline MRI measurements and their interaction predicted the rate of mMMS decline at subsequent visits.

Setting—Three university-based AD centers in the United States (Predictors Study).

Participants—Eighty-four AD patients from the Predictors Study received structural MRI at baseline and were selected for analysis. They had an average of 6 follow-up evaluations.

Main outcome measure—Cognitive (Columbia modified Mini-Mental State Examination).

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Author contributions

Study concept and design: Drs. Brickman, Honig, Scarmeas, and Stern. *Acquisition of data*: Drs. Brickman, Honig, Scarmeas, Albert, Brandt, Blacker, and Stern and Ms. Tatarina and Sanders. *Analysis and interpretation of the data*: Drs. Brickman, Honig, Scarmeas, and Stern. *Drafting of the manuscript*: Drs. Brickman and Scarmeas. *Critical revision of the manuscript for important intellectual content:* Drs. Honig, Scarmeas, Brandt, Blacker, and Stern. *Statistical analysis:* Drs. Brickman and Scarmeas. *Obtained funding*: Drs. Brickman and Stern. *Administrative, technical, and material support*: Drs. Honig, Brandt, Blacker, and Stern. Ms.Tatarina and Sanders. *Study supervision:* Drs. Scarmeas, Albert, Brandt, Blacker, and Stern.

Results—Generalized estimating equation models demonstrated that degree of baseline atrophy (β = −0.316, p = 0.036), severity of WMH (β = −0.173, p = 0.028), and their interaction (β = − 6.061, p = 0.018) predicted rate of decline in mMMS scores.

Conclusions—Both degree of cerebral atrophy and severity of WMH are associated with the rapidity of cognitive decline in AD. Atrophy and WMH may interact to have a synergistic effect on future decline, such that AD patients with a high degree of both have a particularly precipitous cognitive course. These findings lend further support to the hypothesis that cerebrovascular pathology contributes to the clinical syndrome of Alzheimer's disease.

Search Terms

Alzheimer's disease; MRI; neuropsychological assessment

In the absence of definitive diagnostic instruments for Alzheimer's disease (AD), structural magnetic resonance imaging (MRI) has emerged as an important tool for the characterization of morphological changes associated with the disease (for review, see[1]). Increased brain atrophy is a consistent structural neuroimaging findings that has emerged as a hallmark of AD[2, 3]. Longitudinal analyses revealed greater rates of brain atrophy among AD patients than among healthy adults[4–6] and a correlation between the severity of atrophic change and severity of cognitive deficits[2, 7]. These findings suggest that measures of cerebral atrophy provide a reasonable marker for disease staging in AD.

Areas of increased intensity on T2-weighted, including FLAIR, MRI sequences, termed "white matter hyperintensities" (WMH) are thought to reflect small vessel cerebrovascular disease[8–12] and may contribute to age-associated cognitive decline[13]. Similar to degree of cerebral atrophy, WMH are prevalent in AD[14] and the absence neuroradiologic markers of cerebrovascular disease among individuals with dementia is rare[13].

Whether evaluation of neuroimaging data at one point in time has prognostic value for determination of future cognitive decline remains an important question. Data from the Cardiovascular Health Study showed that baseline ventricular volumes were larger among individuals who progressed from neurological health to dementia over a four year period[15]. In one study[16], ventricular volume and severity of WMH both predicted rate of future decline among healthy older adults, but only ventricular volume predicted rate of decline among those with MCI and AD. However, only 39 AD patients were included and the investigators did not examine the interaction between ventricular volume and WMH severity. Examining the two phenomena together may help determine the relative importance of cerebrovascular disease in the course of AD and whether it synergistically interacts with disease state.

In the current study we used data from the Predictors cohort[17–19] to examine the prognostic utility of baseline measurements of atrophy and cerebrovascular disease on rates of cognitive decline among individuals with early AD. An overarching goal of the Predictors Study is to elucidate the determinants of the cognitive and functional course of AD. A subset of participants received standard MRI studies as part of their diagnostic workup. We used these data and rated the severity of cerebral atrophy and WMH to predict future decline in cognitive abilities. We predicted that both baseline atrophy WMH ratings would predict future decline in cognition and that the two measures would interact.

Methods

Sample characteristics

The sample was drawn from the Predictors cohort and included individuals with AD[20, 21]. Full inclusion criteria and details of the study are described elsewhere[17, 18]. Briefly,

participants met diagnostic criteria for dementia of the Alzheimer's type[21] and probable AD[20]. Exclusion criteria included parkinsonism, stroke, alcoholism, schizophrenia, schizoaffective disorder, and history of electroconvulsive treatments. Participants were recruited from three sites (Columbia University, Johns Hopkins School of Medicine, and Massachusetts General Hospital) between April 1989 and September 2005. The study was approved by local ethics committees. Neuroimaging was acquired for clinical diagnostic purposes and was available for 84 individuals in the study cohort. These subjects comprise the current study sample. The mean age at the time of the neuroimaging study was 73.24 (SD=8.02), 47.6% (n=40) was male, and 90.5% (n=76) was Caucasian. Mean number of years of education was 14.77 (SD=3.74). Participants were relatively mildly impaired at the time of their neuroimaging studies, as indicated by a mean mMMS of 41.29 (SD=7.11), which is comparable to a Mini Mental State Examination (MMSE)[22] score of about 22. The average number of follow-up visits, at approximate 6 month intervals was 5.76 (SD=2.99). Fifty percent (n=31, data available for 62 subjects) had the APOE-4 allele. At baseline, 9.5% (n=8) had self-reported history of diabetes, 16.7% (n=14) had dyslipidemia, 16.7% (n=14) had coronary artery disease (CAD), and 35.7% had hypertension (n=30). Compared to Predictors Study participants without available neuroimaging (n=456), the current study participants were similar in age, sex, number of evaluations, and proportion with the APOE-4 allele, diabetes, dyslipidemia, CAD, and hypertension. Those without neuroimaging had fewer years of education (13.43 ±3.52 vs. 14.77±3.740, t (537)=3.192,p=0.001).

Neuroimaging

Estimates of total brain atrophy were computed primarily from T1-weighted images, which were available for 53 (68%) of the 84 participants with neuroimaging data; atrophy measurements were computed for the remainder of participants on FLAIR-, proton-, or T2-weighted images. Findings did not change when we included image sequence as a dummy-coded covariate. Bicaudate ratios were derived on axially-acquired images as an estimate of total brain atrophy following established protocols[23–25]. To derive the bicaudate ratio, the axial slice on which the caudate nuclei produced the greatest amount of indentation on the lateral ventricles was identified and the distance in millimeters between the two caudate apices was measured. This value was divided by the maximum width of the skull at the same level of the caudate measurement (Figure 1). Using this approach, enlarged ventricles increase the distance between the two caudate nuclei resulting in a higher bicaudate ratio, so a larger value indicates a greater degree of atrophy. Bicaudate ratio measurements were made by two experienced raters (AMB, LH). Interrater reliability, computed on 12 images, was good for the bicaudate distance (intraclass correlation coefficient [ICC]=0.861), skull width (ICC=0.991), and bicaudate ratio (ICC=0.740). Further, in an independent sample of 17 dementia patients with digital T1-weighted MR images, we calculated bicaudate ratios and compared them to manually derived full relative brain volumes and found a strong relationship between the two measures (Spearman's Rho=−0.814,p<0.001). These findings suggest that the bicaudate ratio is a reliable and valid index of cerebral atrophy.

White matter hyperintensity severity ratings were made on FLAIR- and T2-weighted images using the Scheltens Scale[26]. The Scheltens Scale is a visual rating scale that includes anchored, 7-point severity ratings in periventricular (i.e., frontal horn, occipital horn, lateral bands), cortical (i.e., frontal lobe, temporal lobe, parietal lobe, occipital lobe), subcortical (i.e., caudate, putamen, globus pallidus, internal capsule, thalamus), and infratentorial (i.e., mesencephalon, pons, medulla, cerebellum) regions. The WMH severity measure for the current study was the summation of ratings in each of the four regions. All WMH ratings were performed by one rater (LSH). Intrarater reliability, computed on 12 images, was high (ICC=0.912).

Clinical Evaluation

Performance on the mMMS[27] was the primary outcome measure. The mMMS is an expanded version of the MMSE[22] and consists of attention/calculation, general knowledge, language, and construction tasks. The scale has a maximum score of 57. All Predictors Study participants were required to score 30 or higher for inclusion, which is equivalent to a score of about 16 on the MMSE. The mMMS was administered at each semi-annual visit and thus served as the indicator of cognitive change.

Additional risk factor clinical data included presence or absence of the following variables: APOE-e4 allele[28], diabetes, dyslipidemia, CAD, and hypertension, which were coded as present based on reported history of treatment or diagnosis.

Statistical approach

Baseline associations between MRI-derived measurements and cognition were evaluated with multiple linear regression analyses. First, baseline bicaudate ratio, age, sex, education, and risk factor variables were entered as independent variables and total score on the mMMS was the dependent variable. The model was re-run without the risk factors. Next, the same two regression analyses were run substituting Scheltens Scale WMH severity ratings for the bicaudate ratio. Finally, the same two regression analyses were run with WMH ratings, atrophy ratings, and their interaction term.

A similar approach was taken to evaluate the impact of baseline atrophy and WMH severity on longitudinal change in cognition. A series of generalized estimating equations (GEE)[29] models tested associations between baseline bicaudate ratio or WMH severity on change in mMMS score with and without risk factor covariates. This approach takes into account multiple visits per subject and the likelihood that characteristics of the same individuals over time are correlated. To establish the rate of cognitive decline, the first GEE model was run with mMMS score as the dependent variable and time (in years from baseline) as the independent variable. In all subsequent GEE models, mMMS score was the dependent variable and the MRI measurement (i.e., Scheltens score or bicaudate ratio), time, and an MRI measurement by time interaction term were included as predictors. All models included age, sex, and education as additional covariates. In a final GEE model, we included WMH severity ratings *and* bicaudate ratios, their interaction terms with time, and their 3-way interaction (i.e., bicaudate ratio by Scheltens score by time) to evaluate their combined effects on decline. The three models were run with and without risk factor variables as additional covariates. Significant main effects of MRI measurements would indicate a difference in cognitive performance for each unit of measurement. A significant time effect would indicate a change in test scores over time. A significant interaction term with time would indicate differential rates of change in cognition over time as a function of the MRI measurement. Finally, a significant three-way interaction would suggest an interaction of the two MRI measurements with time.

Results

Baseline associations with cognition

Mean bicaudate ratio and WMH ratings were 0.1602 (SD=0.018) and 3.79 (SD=4.55), respectively. The overall multiple regression model testing the baseline association of atrophy with cognition was significant ($F(9, 55)=2.357$, $p=0.028$), although only increased number of years of education entered into the model as a predictor of higher mMMS scores ($\beta=1.161$, $SE=0.307$, $p<0.001$).

The regression model testing the association of WMH severity on baseline cognition was not significant with ($F(9, 53)=1.981$, $p=0.065$) or without ($F(4, 76)=2.302$, $p=0.067$)risk factor

variables included. Similarly, when the two MRI measurements and their interaction terms were included, the model was not significant with ($F(11, 53)=1.898$, $p=0.067$) or without ($F(6, 76)=1.960$, $p=0.083$) risk factor variables.

In a separate bivariate correlational analysis, severity of WMH was not significantly associated with atrophy ratings, controlling for age ($r(74)=0.103$, $p=0.376$).

Longitudinal analysis

Modified Mini Mental State Examination scores declined an average of 3.5 points per year (estimated $\beta=-3.455$, $p<0.001$). Table 1 displays the primary results of the three GEE analyses. For every 1% difference (i.e., increase) in baseline bicaudate ratio, there was an additional associated 0.316 point decrease in mMMS score per year (significant time by bicaudate interaction). Increased age ($\beta=0.452$, $p=0.037$), being male ($\beta=5.263$, $p=0.041$), and lower education ($\beta=1.239$, $p<0.001$) were associated with poorer mMMS scores. The effect of bicaudate ratio on mMMS decline was similar when the vascular risk factors were excluded. Figure 2 displays the estimated rate of decline in mMMS scores in participants with low and high bicaudate ratio values, which was defined on the basis of a median split (i.e.,.1567).

A similar pattern emerged when examining the impact of baseline WMH severity on future decline. For each Scheltens Scale point (i.e., increase in WMH severity), there was an additional 0.173 point loss in mMMS score per visit (significant WMH by time interaction; see Figure 3). Being male ($\beta=4.801$, $p=0.039$) and lower education ($\beta=1.018$, $p=0.002$) was associated with lower mMMS scores. None of the risk factor variables reached significance for this model. When they were removed from the analysis, the findings remained essentially unchanged, although the significance of the time by WMH interaction was reduced to a trend level effect.

When we examined the combined impact of baseline atrophy and WMH severity on future decline, a significant three-way interaction indicated that individuals with the highest severity of WMH *and* greatest atrophy had the most precipitous rate of cognitive decline (see Table 1, Figure 4). Excluding the vascular risk factors, the three-way interaction remained statistically significant and baseline atrophy ratings significantly predicted rate of decline.

Comment

The current study sought to determine whether measures of cerebral atrophy and WMH were associated with cognitive function and the rate of future cognitive decline in AD. Several important findings emerged. First, when examined cross-sectionally, increased atrophy was modestly associated with poorer cognitive performance, but the relationship between severity of WMH and cognition was unremarkable. When examined longitudinally, both severity of baseline atrophy and severity of baseline WMH were associated with a faster rate of future cognitive decline. When both severity measures were considered in the same statistical model, they interacted and had an effect on future decline. Taken together, the findings suggest a synergistic interaction of AD pathology and small vessel vascular disease on the course of cognitive symptoms in AD.

The results add to a growing corpus of work examining the associations among measures of AD pathology, vascular disease, and their clinical expression. In most studies, atrophy is more prominent among AD patients than controls[1–3, 30] and is associated with more severe cognitive symptoms[31, 32]. Others have reported that increased atrophy is associated with future risk of developing AD[15, 33, 34] and that the rate of regional atrophy predicts decline in patients with mild cognitive impairment and AD[35, 36]. The current study extends these findings. Although cross-sectional associations with cognitive abilities were weak, global atrophy was robustly associated with a more precipitous cognitive decline. The findings

suggest that among individuals with mild AD, the severity of pathology-associated atrophy at one point in time has prognostic utility. Whole brain atrophy is not specific to the diagnosis of AD; however, within a sample of well-defined AD patients, it is a good marker of disease severity. Thus, the current study supports previous cognitive studies showing an accelerated rate of future decline among more severely affected patients with AD[37].

White matter hyperintensity burden has been reported to be more severe among patients with AD than nondemented elderly[3, 14, 38], although not all studies have shown this association[39, 40]. Further, some studies have shown that increased burden is associated with poorer cognitive abilities in AD[41, 42], while others have not[40, 43, 44], but the relationship between severity of WMH and cognitive abilities among older adults without dementia, has been more consistently demonstrated ([45–47] c.f. [42]). It is possible that small vessel vascular disease, reflected in the severity of WMH, significantly impacts cognitive abilities among individuals with no or very little AD pathology. Among those with more severe disease, AD pathology may play a more salient role in cognitive abilities, effectively concealing the impact of small vessel vascular disease. Our results partially support this idea: on a cross-sectional basis, the severity of WMH was not associated with severity of cognitive impairment.

Our findings are consistent with the idea that cerebrovascular pathology interacts with AD pathology. While both severity of baseline atrophy and severity of baseline WMH were associated with rate of cognitive decline, when the two measures were included in the same model, the interaction effect was significant and the individual main effects were not. The observation is reminiscent of autopsy studies that have shown that individuals with vascular disease and AD pathology were more likely to have clinical dementia compared to those without vascular disease[48] or findings that less AD pathology is required to produce the same degree of cognitive impairment when vascular disease is present[49]. Our findings are most consistent with a report[50] that demonstrated a significant interaction of WMH and medial temporal lobe atrophy in the classification of older adults as AD or normal; the risk associated with having both a high degree of atrophy and a high degree of WMH volume was greater than the risk incurred by the product of the two factors. Although we did not observe an interaction between degree of atrophy and WMH cross-sectionally, the significant effect on future decline suggests a synergistic interaction of the two pathologies on the course of AD.

From a mechanistic perspective, the interaction of cerebrovascular and AD pathology may be a reflection of β-amyloid (Aβ) peptide deposition, which comprises both the senile plaques characteristic of AD pathology (in the Aβ42 species) and cerebrovascular amyloid (in its Aβ40 form). Indeed plasma concentrations of Aβ40 peptide were associated with increased WMH volume among patients with AD and cerebral amyloid angiopathy in a clinic-based sample[51] and among participants in the population-based Rotterdam Study[52]. In the current study, WMH severity predicted rate of decline in AD only after statistical adjustment for common vascular risk factors (see Table 1), suggesting that the variance in WMH related to cognitive course in AD is not due to these risk factors. Rather, it is possible that WMH associated cerebrovascular Aβ deposition specifically accounts for this association. Future work should examine the association among concentrations of plasma Aβ, WMH, and longitudinal changes in cognition.

While inconsistencies exist in the literature regarding the exact relationship among AD pathology, vascular pathology, and cognition, findings do converge in demonstrating that increased cerebrovascular disease burden is not beneficial and is most likely harmful. At present, there are no available disease-modifying treatments for AD. However, there are a number of potentially modifiable risk factors and behaviors for cerebrovascular disease[53–55]. The reduction of these conditions could have therapeutic effects for the treatment of the

cognitive symptoms associated with AD and further study of the determinants of WMH among patients with AD may highlight newer treatment targets.

This study has several limitations. First, neuroimaging was available for only a subset of participants in the Predictors Study, although participants with and without neuroimaging were similar to each other. Second, analyses were conducted on ratings of clinical MRI scans, as opposed to digital scans that were acquired uniformly and analyzed automatively. Because clinical scans were acquired in the axial orientation, our analyses focused on global atrophy as opposed to atrophy in areas more specific to AD, such as the medial temporal lobe, which would require scans oriented in the coronal plane. Newer protocols exist that are able to quantify regional atrophy and WMH signal with higher precision and accuracy. It should be noted, however, that rater reliability for both the bicaudate ratio and Scheltens scale was high and that estimates of atrophy from the bicaudate ratio were highly correlated with whole-brain atrophy measures derived in an independent sample. Third, while the study comprised well characterized longitudinal cognitive data, neuroimaging data were only available at one point in time, thus limiting inference about the emergence and evolution of the imaging markers themselves. Future studies should incorporate prospectively collected longitudinal clinical and neuroradiologic data.

This study also has a number of particular strengths. This is among the largest studies that have examined prognostic utility of baseline neuroimaging characteristics on future cognitive decline in AD. Patients were carefully diagnosed at academic medical centers with specific expertise in aging and dementia and diagnoses were based on uniform application of widely accepted criteria via consensus diagnosis procedures. Diagnoses from the Predictors Study are accurate. For example, 93% of patients that came to autopsy had pathologically confirmed AD at postmortem evaluation [56]. Patients were evaluated prospectively and relatively frequently (i.e., biannually). As participants were generally mildly demented at their baseline evaluation, we were able to capture a large range of progression over time.

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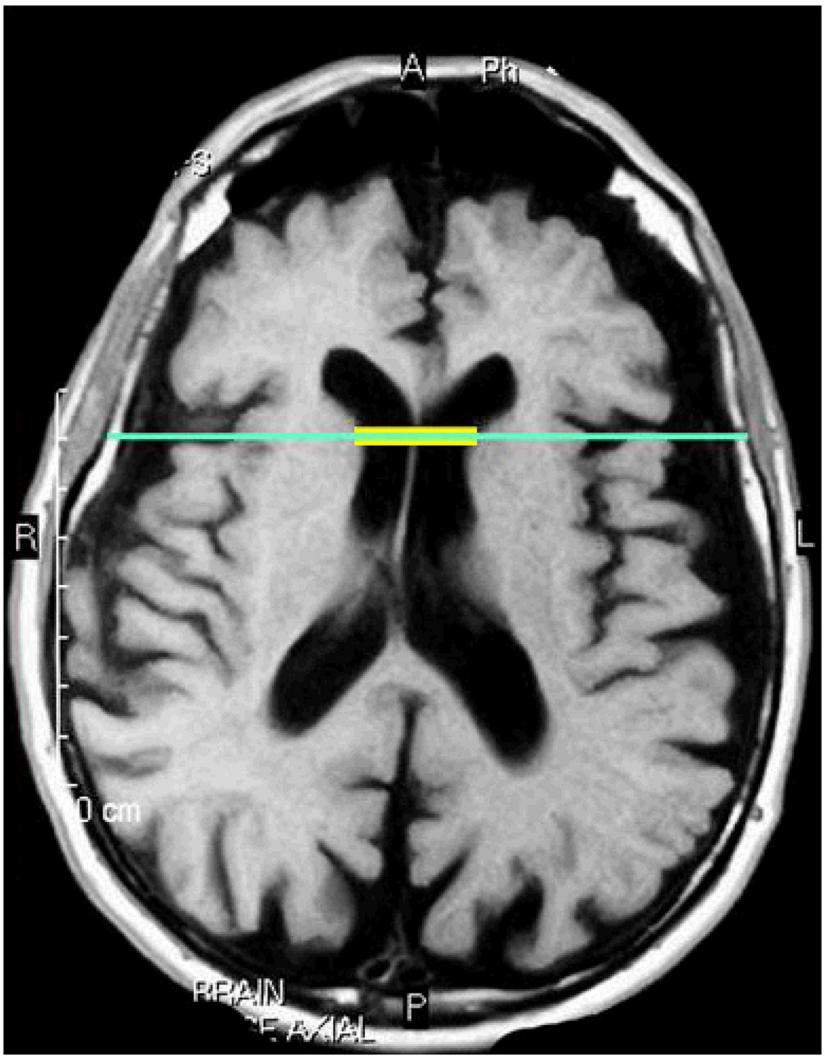

Figure 1.
Bicaudate ratio. The yellow represents the distance between the two apices of the caudate nuclei. The inner skull dimension is shown in turquoise. The bicaudate ratio is derived by dividing the ventricular dimension (yellow) by the inner skull dimension (turquoise). A higher ratio represents greater atrophy.

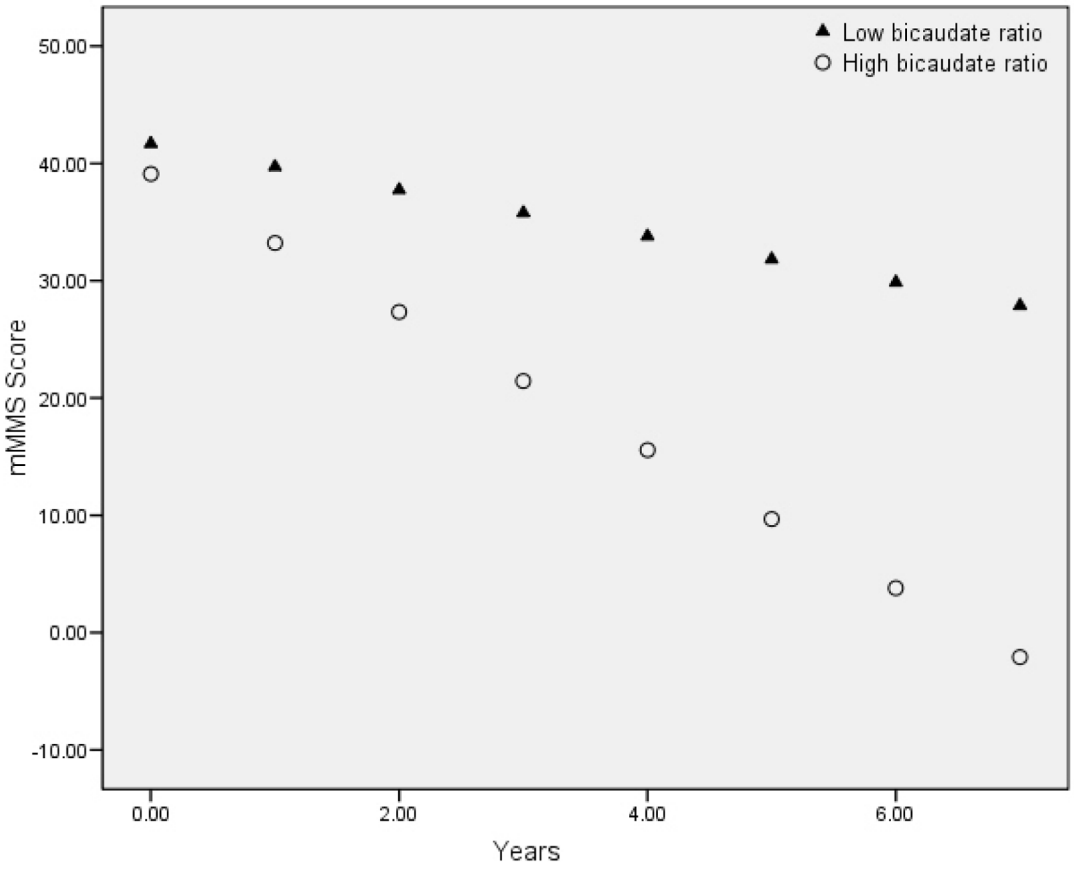

Figure 2.

Predicted rates of cognitive change based on baseline characterization of bicaudate ratio. For graphical presentation, baseline bicaudate ratio is presented as a dichotomous variable based on the median split of the entire sample (median=0.1567). Note that higher bicaudate ratio indicates greater amounts of atrophy. The results from the GEE analysis suggest that the greater the amount of atrophy at baseline, the greater the rate of cognitive decline.

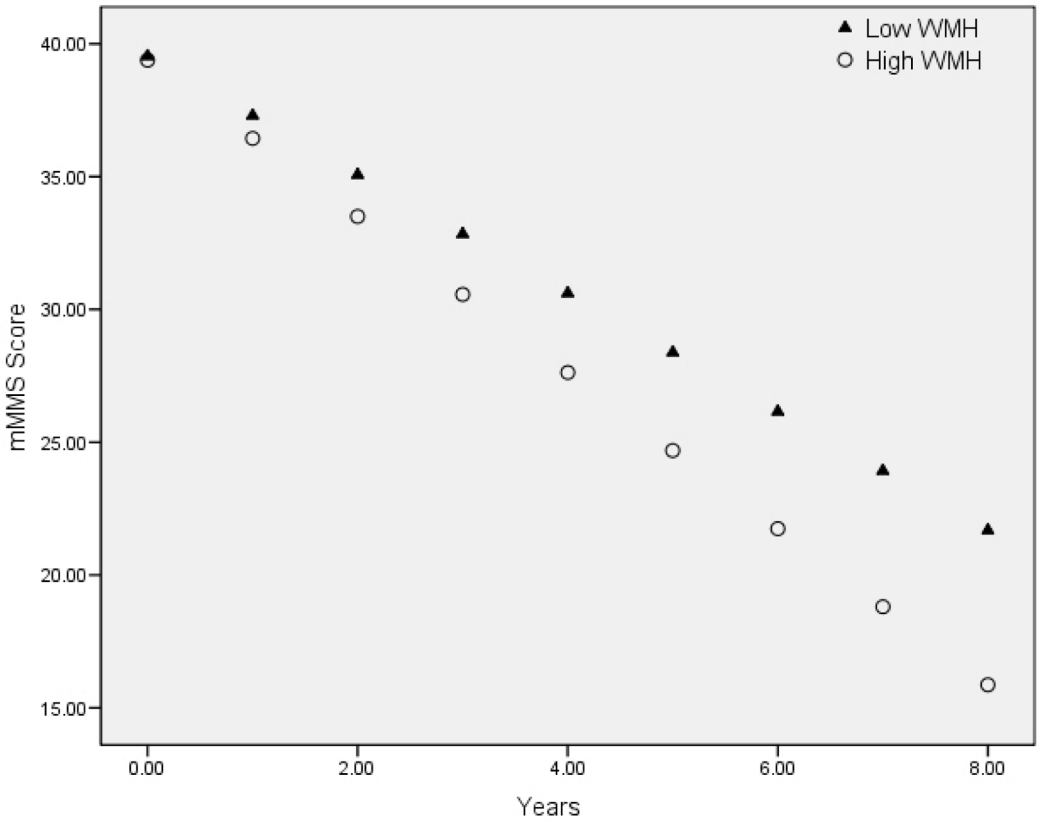

Figure 3.
Predicted rates of cognitive change based on baseline characterization of WMH severity. For graphical presentation, the baseline Scheltens Scale score is presented as a dichotomous variable based on the median split of the entire sample (median = 3.0). Note that higher "High WMH" refers to more severe WMH. The results from the GEE analysis suggest that the greater the more severe the baseline WMH, the greater the rate of cognitive decline.

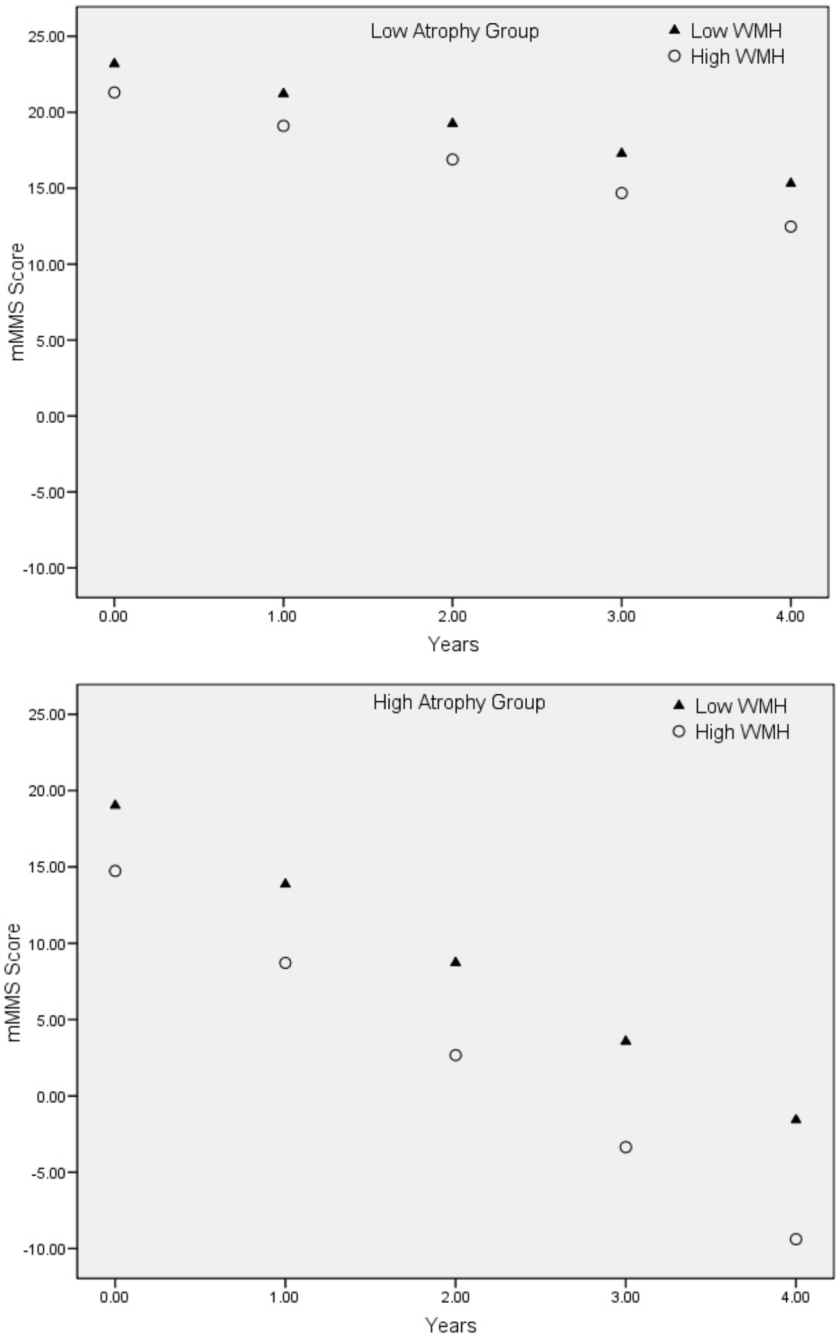

Figure 4.

Graphical representation of the significant Time by baseline WMH by baseline atrophy interaction. For the purpose of graphical presentation, WMH severity (circles and triangles) and degree of atrophy (upper and lower panel) are displayed in high and low groups based on the median severity. Note that the predicted mMMS scores decline most precipitously among individuals with greater level of atrophy *and* the greater baseline WMH burden (lower panel, circles).

Table 1

Results from the three GEE analyses testing the associations between baseline measures of Atrophy, WMH, and their combined effects on rate of cognitive decline. Each analysis was run with (Model 1) and without (Model 2) vascular risk factor variables. The main effect of "Time" shows the rate of mMMS change per 1 year interval. Interactions involving Time show the annualized rate of change on mMMS as a function of each unit of the independent variable. For example, the "Time X Bicaudate Ratio" interaction shows the impact of baseline atrophy measures on rate of annualized mMMS change (i.e., for every 1% increase in baseline bicaudate ratio, there is an associated 0.316 point decrease in mMMS score per year).

GEE Analysis	Variable of Interest	Model 1*		Model 2¥	
		β	P	β	P
Atrophy	Time	1.619	0.485	2.964	0.116
	Bicaudate Ratio	−0.786	0.023	−0.497	0.092
	Time X Bicaudate ratio	−0.316	0.036	−0.415	<0.001
WMH	Time	−2.706	<0.001	−3.160	<0.001
	Scheltens Score	−0.082	0.683	−0.106	0.558
	Time X Scheltens Score	−0.173	0.028	−0.122	0.71
Atrophy + WMH	Time	−1.988	0.295	0.977	0.504
	Bicaudate Ratio	−0.445	0.148	−0.427	0.121
	Scheltens Score	−0.224	0.245	−0.145	0.360
	Time X Bicaudate Ratio	−6.277	0.620	−0.278	0.003
	Time X Scheltens Score	0.968	0.049	0.512	0.094
	Time X Bicaudate Ratio X Scheltens Score	−6.061	0.018	−3.250	0.050

*Model adjusted for Age, Sex, Education, APOE4, Diabetes, Dyslipidemia, CAD, and Hypertension

¥Model adjusted for Age, Sex, and Education