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Association of Dementia Severity With Cortical Gray Matter and Abnormal White Matter Volumes in Dementia of the Alzheimer Type

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Objective: To examine associations between dementia severity and quantitative magnetic resonance imaging measures of cortical gray matter volume and abnormal white matter volume in 52 patients diagnosed with probable Alzheimer disease.

Design: Analysis of the relationship between magnetic resonance imaging volume measures and dementia severity using multiple regression and Pearson correlations.

Setting: Alzheimer's Disease Research Center, University of California, San Diego.

Participants: Twenty-three men and 29 women with probable Alzheimer disease (average age, 71.7 years; average education, 13.3 years).

Main Outcome Measures: The Mattis Dementia Rating Scale (MDRS) and the Mini-Mental State Examination.

Results: Using simultaneous multiple regression, magnetic resonance imaging volumetric measures of cortical gray matter and abnormal white matter were independently associated with dementia severity measured by either the MDRS or the Mini-Mental State Examination. Cortical gray matter volume and abnormal white matter volume also made independent contributions to performance in 4 of 5 cognitive domains assessed by the MDRS. Regional analysis indicated that limbic cortical gray matter volume and nonlimbic cortical gray matter volume were also correlated with the MDRS score; however, in the regression analysis the individual gray matter measures were not *independently* associated with MDRS performance. A similar analysis revealed statistically independent relationships of limbic gray matter volume and abnormal white matter volume, but not nonlimbic cortical gray matter volume, to Mini-Mental State Examination performance.

Conclusions: Quantitative magnetic resonance methods provided strong evidence that cortical gray matter volume, which may reflect atrophy, and abnormal white matter volume are independently related to dementia severity in probable Alzheimer disease: lower gray matter and higher abnormal white matter volumes are associated with more severe dementia.

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From the Alzheimer's Disease Research Center, University of California, San Diego (Drs Stout, Jernigan, and Salmon and Ms Archibald), and Veterans Affairs Medical Center (Drs Stout and Jernigan), San Diego, Calif. Dr Stout is now with Indiana University at Bloomington.

SEVERAL STUDIES have identified a relationship between gray matter atrophy revealed by in vivo brain images and the severity of cognitive impairment in Alzheimer disease (AD). For example, computed tomographic[1,2] and magnetic resonance imaging (MRI)[3] findings of hippocampal atrophy have been shown to be associated with memory complaints and impairments even in mildly impaired subjects.[4] Similarly, left superior temporal gyrus atrophy has been linked to severity of impairment in naming and category fluency.[5] In contrast to the consistently observed associations between gray matter atrophy and impairments in cognitive function, studies of the relationship of white matter abnormalities to cognitive dysfunction have produced variable results. While several studies[6-16] have failed to find associations between white matter abnormalities and cognitive function, other studies have detected such relationships. For example, Harrell et al[17] found that MRI measures of white matter abnormalities were associated with one estimate of global cognitive impairment, the Mattis Dementia Rating Scale (MDRS), but not with another, the

See Subjects and Methods on next page

SUBJECTS AND METHODS

SUBJECTS

Fifty-two participants in the Alzheimer's Disease Research Center of the University of California, San Diego, were studied. All were diagnosed with probable AD[24] using criteria from the National Institute of Neurological Disorders and Stroke (NINDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) and primary degenerative dementia according to the *Diagnostic and Statistical Manual for Mental Disorders, Third Edition, Revised*.[25] Patients with significant psychiatric or neurological histories (except probable AD), substance dependence, or major medical conditions were excluded. Only subjects with Hachinski[26] scores of 4 or less were considered for the diagnosis of probable AD; thus, patients whose dementia may have had a significant vascular component were not participants in the study.

Participants with possible frontal dementias were excluded from the diagnosis of probable AD based on informants' reports of personality change as a prominent early feature of the disease and/or the lack of an early, severe impairment in memory. To reduce the known clinical and pathological heterogeneity in this sample, 4 otherwise suitable participants were excluded from the analysis because they received clinical (n=3) or pathological (n=1) diagnoses of Lewy body variant of AD.[27] Participants were evaluated with medical and laboratory testing to rule out other possible causes of dementia. When data analysis was performed for the current report, all subjects had been studied for at least 3 years and had retained their diagnoses of probable AD. Informed consent was obtained from all participants.

Our study included only subjects with probable AD for whom a technically adequate MRI examination in conjunction with an Alzheimer's Disease Research Center annual examination was available. In effect, this excluded patients who were unable to tolerate the MRI without complications such as movement, and thus removed many of the most severely demented patients from the sample. The average interval separating neuropsychological testing and the MRI examination was 51 days. The final sample was 52 participants with the clinical diagnosis of probable AD (23 men, 29 women). The average age of the sample was 71.7 years (range, 56-84 years) and the average education was 13.3 years (range, 8-20 years). Examining neurologists obtained an estimated duration of illness by asking subjects' informants to estimate the year in which the earliest symptom of AD, such as forgetfulness, was first noted; average estimated duration of illness for the sample was 5.8 years (range, 2-12 years). At the time of the MRI and neuropsychological evaluations, 23 subjects were in the first year of the Alzheimer's Disease Research Center participation, 13 were in their second year, 11 in their third year, 3 in their fourth year, and 1 each in their fifth and sixth years.

PROCEDURES

Neuropsychological tests were administered during subjects' routine annual examinations at the Alzheimer's Disease Research Center. The MDRS[28] was administered and scored according to standard procedures, except that all test items were administered to every patient. The MDRS is a measure of global cognitive function designed for screening patients with possible dementia. In addition to assessing dementia severity, items within the MDRS are useful for making a brief assessment of 5 domains of cognitive function. Sums of scores for items in these domains make up the following subscales: (1) attention (37 possible points), (2) initiation and perseveration (37 possible points), (3) construction (6 possible points), (4) conceptualization (39 possible points), and (5) memory (25 possible points). Average performance on the MDRS in the current sample was 100.1 of 144 total points (range, 17-135 points), corresponding to a moderate to severe level of dementia.

The MMSE[29] was administered and scored according to standard procedures. The MMSE is a cognitive screening instrument that includes items assessing orientation, attention and concentration, language, constructional ability, and immediate and delayed recall memory. Performance on the MMSE is scored as the number of points correct of 30 possible points. Average performance on the MMSE was 18.4 of 30 possible points (range, 3-26 points).

MRI PROTOCOL

The MRIs were obtained using a 1.5-T superconducting magnet (Signa, General Electric, Milwaukee, Wis). An asymmetrical multiple-echo spin echo sequence was used to obtain axial images of the entire brain (repetition time, 2000 milliseconds; echo time, 25 and 70 milliseconds). Samples were made of 5-mm sections centered at 7.5-mm intervals. Two registered image sets were obtained, each highlighting different tissue characteristics; the proton density–weighted image effectively discriminated gray and white matter and T_2-weighted images discriminated brain and cerebrospinal fluid. **Figure 1** shows sample images from our standard research protocol.

IMAGE ANALYSIS

Details of the image analysis approach used in our study can be found in several articles[30-32] and are briefly summarized herein. To reduce experimenter bias in the anatomical analyses, images for our study were interspersed with

Continued on next page

Mini-Mental State Examination (MMSE). The computed tomographic studies have related leukoariosis to dementia severity, as measured by the Extended Scale for Dementia,[18] and to attention.[19] Periventricular white matter lesions visualized on MRI were associated with the Blessed Dementia Scale and the Folstein MMSE.[20] In addition, a recent MRI study[21] demonstrated that white matter abnormality was related to visuoconstructional, motor, tactile, and attentional performance, but not to global cognitive functioning.

There are several possible explanations for the inconsistencies among studies examining the association between white matter abnormalities and cognitive dysfunctions in AD. First, the studies have varied in criteria for subject inclusion; some studies have included subjects with cardiovascular risk factors, others have ex-

images from other studies in progress at that time, and image sets were stripped of all identifying information.

The digital images were processed by trained image analysts using software developed in the laboratory on a personal computer platform. First, image analysts excluded all nonbrain pixels (eg, skull, scalp). Images were then subjected to digital filtration to reduce inhomogeneities in the images caused by nonbiological signal drift across images. Next, pixels were classified into categories including gray matter, white matter, cerebrospinal fluid, and signal hyperintensity (tissue abnormality). This was accomplished in 2 steps. First, 2 new linear combinations of pixel values were computed to optimize distinctions between gray and white matter and cerebrospinal fluid and brain, respectively. Second, classification criteria, which were based on the optimized pixel values and adjusted section by section based on white matter signal values (from samples chosen by image analysts), were applied to individual images. Image analysts then designated anatomical regions. Images were transformed spatially into a standard plane of section using corpus callosum and the interhemispheric fissure landmarks. Volume estimations for regions of interest were made by summing all pixels for a given measure across all sections, and these values were transformed to z scores normalized to a sample of age-matched and cranium size–matched healthy controls studied within the laboratory.

Volumetric measures of interest were total CGM, abnormal white matter (AWM), limbic (mesial temporal), and nonlimbic subregions of CGM. Total CGM included all gray matter that was visually determined to be part of the cerebral cortex and contained all gray matter within the frontal, parietal, temporal, and occipital lobes. This measure was obtained by summing all gray matter pixels left over after exclusion of gray matter pixels associated with subcortical structures. When boundaries between CGM and subcortical gray matter were ambiguous, image analysts referred to adjacent sections on filmed images. Abnormal white matter was defined as areas within either deep white matter or periventricular white matter that (1) were categorized by the tissue classification algorithm as frank signal hyperintensities (ie, had high signal values outside the ranges of gray matter, white matter, and cerebrospinal fluid) or (2) were categorized by the tissue classification algorithm as gray matter, but were located in areas in which the presence of gray matter could be ruled out. The presence of gray matter in these areas was ruled out by image analysts when inspection (using the filmed MRIs) of analogous regions on both adjacent sections revealed that no gray matter (eg, gyri) was present. This method classified all frank signal hyperintensities observable on proton density or T_2-weighted images as AWM, and also included additional pixels not obviously abnormal on the filmed images.

To designate subregions of the cerebral cortex, limbic CGM (L-CGM) was first isolated from the inferior mesial surface of the brain using a combination of stereotaxic and anatomical landmarks.[33,34] Within this limbic subregion were the amygdala, hippocampus, and most of the parahippocampal gyrus. Nonlimbic gray matter (NL-CGM) included all CGM not designated as L-CGM, ie, superior, inferior, anterior, posterior, peripheral, and mesial (**Figure 2**).

Pixel counts for each anatomical measure were corrected for age and cranium size using estimates derived from a large group of healthy control subjects studied within the laboratory. Volumes were expressed as z scores computed as the participants' deviations from age-matched and cranium size–matched healthy control values. The z scores for gray matter measures thus estimated brain atrophy. For the sample of 52 participants, average z scores (SDs and ranges) were −1.92 (SD, 2.02; range, −8.21 to 1.27) for total CGM; 0.69 (SD, 1.64; range, −1.81 to 8.65) for AWM; −0.98 (SD, 1.48; range, −4.31 to 2.23) for L-CGM; and −1.87 (SD, 1.96; range, −8.02 to 1.33) for NL-CGM matter. Thus, the studied group had, on average, lower gray matter and higher AWM volumes than healthy age-matched and cranium size–matched comparison subjects.

To reduce the influence of the several outliers within distributions of the neuropsychological and volumetric brain measures, distributions were normalized using an inverse normal density function.[35] This transformation converts the data into a normal distribution using the median value as the 0 point of the distribution and assigning all other cases according to their rank in the original distribution to points along a distribution closely fitting normality. As a result, extreme outlying values, such as z scores of +8.0 or −8.0, are brought into the tails of the normal distribution. This reduces the possibility of Type I error (finding statistical significance when the null hypothesis is true) and is necessary to satisfy assumptions for parametric analysis.

DATA ANALYSIS

Relationships between brain measures and each of the cognitive measures were analyzed using separate simultaneous regression equations supplemented with Pearson correlations to aid interpretation of the results. For all multiple regression analyses, an α of .05 was considered significant. For correlations, a cutoff α of .01 was used to reduce experimentwise error rate. Significant correlations were interpreted as describing simple relations among variables, while significant regression coefficients (β) were interpreted as showing independent effects of an independent variable given the values of other members of the set. For example, a significant β for AWM, when tested in a set with CGM, indicates that AWM contributes to dementia severity independently of any contribution of gray matter atrophy.

cluded such subjects, and some did not address these risk factors. Since cardiovascular risk factors are associated with a higher incidence of white matter disease,[13,22] inclusion of such subjects in the study sample may increase the range of white matter abnormality and could facilitate detection of a correlation between white matter abnormalities and cognitive dysfunction. However, this relationship might not be attributable to the pathological process of AD alone, but may also be related to white matter changes due to vascular disease. A second possible reason for the inconsistencies in the results of studies of white matter abnormalities and cognitive dysfunction in AD is that many studies have used only a small series of patients, and thus have had limited power to detect smaller effects. A third possible cause of inconsistencies is the problem of obtaining a reliable and objec-

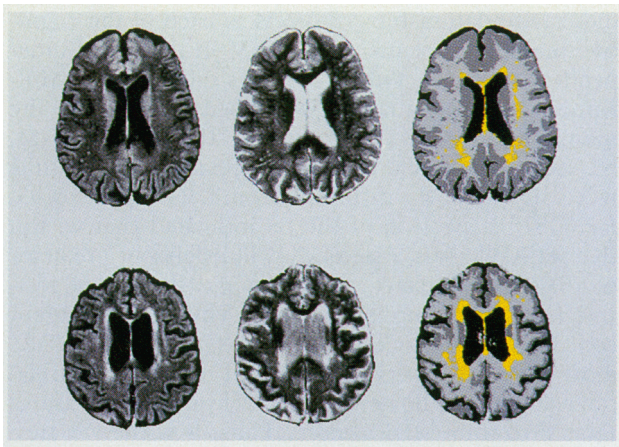

Figure 1. *The first and second columns highlight the standard protocol used in all magnetic resonance imaging examinations reported in our study. Each row represents 1 section from a single subject with the proton density–weighted images on the left, T_2-weighted images in the middle, and partially processed images highlighting (in yellow) pixels summed to obtain our measure of abnormal white matter at right. The image in the top row is from a 68-year-old healthy woman; bottom row, a 67-year-old woman with dementia of the Alzheimer type.*

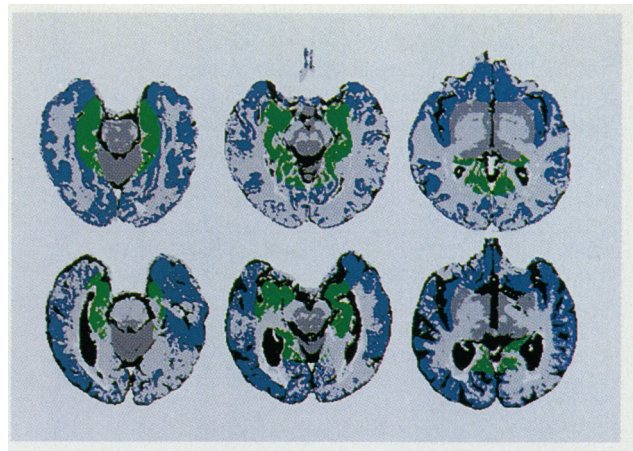

Figure 2. *Three representative axial sections through the ventral cerebrum showing the separation of limbic (green) and nonlimbic (blue) cortical gray matter. The top row is from a 71-year-old healthy woman; bottom row, a 74-year-old woman with probable dementia of the Alzheimer type.*

tive quantification of white matter abnormalities. Some studies that have failed to find a relationship between white matter abnormalities and cognitive function have used computed tomography, which is less sensitive to abnormalities in the white matter than MRI. Also, despite reliable semiquantitative methods for identifying and quantifying white matter hyperintensities on filmed images,[23] such methods may yield inconsistent results if imaging and filming techniques are not carefully controlled since variations in imaging parameters and even slight adjustments of the gray scale for filming can alter the appearance of hyperintensities. Because these methods rely on visual inspection, they are also limited by the ability of the human visual system to detect subtle differences in the shades of gray that indicate white matter hyperintensities, and abnormal signal values can easily be confused with partially volumed gray matter (eg, part of a gyrus that appeared on an adjacent section).

To avoid the problems that may have led to inconsistent findings in previous studies, the present study examined the relationship between dementia severity and the extent of gray matter atrophy and white matter hyperintensities in a relatively large cohort of well-characterized patients with AD, using computer-based quantitative image processing techniques. We hypothesized that the degree of cortical gray matter (CGM) atrophy would be associated with the severity of global cognitive dysfunction as measured by the MDRS and that the extent of white matter abnormality would also be related to the severity of cognitive dysfunction, independently of its relationship with CGM atrophy.

RESULTS

The major hypothesis of our study was that both gray matter atrophy and the amount of AWM would be related to dementia severity in dementia of the Alzheimer type (DAT). We also examined the relationship of these brain measures to individual cognitive functions measured by the MDRS (eg, memory, conceptualization). Finally, we examined whether separating CGM into its limbic and nonlimbic components would reveal differential contributions of these areas to cognitive impairment.

DEMENTIA SEVERITY

Separate standard multiple regression analyses were used to determine the magnitude of the independent effects of CGM volume and AWM volume on the total MDRS and MMSE scores. **Table 1** displays the simple correlations, standardized regression coefficients (β), R^2, and adjusted R^2. For the MDRS, the regression correlation coefficient (R) was significantly different from 0 ($F[2,51]=8.88$, $P=.005$). Both CGM and AWM were independently associated with the total MMSE score ($\beta=.31$, $P<.01$ and $\beta=-.38$, $P<.01$, respectively), and together the 2 variables accounted for 27% of the variability in MDRS scores (24% adjusted). For the MMSE, R for the regression was also significantly different from 0 ($F[2,51]=11.45$, $P=.001$). Again, both CGM and AWM were independently associated with MDRS ($\beta=.34$, $P<.01$ and $\beta=-.42$, $P<.001$, respectively). Altogether, the 2 variables accounted for 32% of the variability in MMSE scores (29% adjusted). Thus, both CGM atrophy and AWM related to dementia severity (ie, the simple correlations were significant) and each contributed independently to dementia severity (ie, their standardized βs were significant). These results support the main hypothesis of the study.

To determine to what extent AWM adds to the variability explained by CGM volume alone, hierarchical regression was used to determine the magnitude and significance of the increment added by AWM volume once CGM volume was already taken into account. For the total MDRS score, adding AWM incremented R^2 by 14%, which was statistically significant ($F[1,51]=9.63$, $P<.003$). Similarly, for the MMSE, adding AWM incremented R^2 by 17%, which

Table 1. Gray and White Matter Correlates of the Dementia Rating Scale (DRS) and the Mini-Mental State Examination (MMSE) Performance*

	Cortical Gray Matter		Abnormal White Matter				
	r	β	*r*	β	*R*	R^2	Adjusted R^2
DRS	0.34	.31†	−0.41‡	−.38§	0.52‡	0.27	0.24
MMSE	0.38§	.34†	−0.45‡	−.42§	0.56‡	0.32	0.29

**Significance for* r *and* R *with 2-tailed probabilities.* R *indicates regression correlation coefficient.*
†P<.05.
‡P<.001.
§P<.01.

was also statistically significant (F[1,51]=12.42, P<.001). Thus, AWM accounts for a rather small amount of the total variance in dementia severity, but adds significant explanatory power over CGM atrophy alone.

MDRS SUBSCALES

The second set of analyses examined the relationship of CGM and AWM to individual cognitive ability areas using each of the 5 MDRS subscales. **Table 2** displays the results of these correlation and regression analyses. For all subscales, *R* was significantly different from 0: F(2,51)=7.21, P=.002 for attention; F(2,51) =6.52, P=.003 for initiation and perseveration; F(2,51)=8.85, P=.001 for construction; F(2,51)=5.70, P=.006 for conceptualization; and F(2,51)=7.27, P=.002 for memory. Table 2 shows that both CGM and AWM were significantly related to all the subscales except 1. The exception was that the initiation and perseveration subscale was related to AWM while for CGM neither the simple correlation nor the regression coefficient was statistically significant. Thus, poorer attention, construction, conceptualization, and memory were related to CGM atrophy and AWM volume, but impairment in initiation and perseveration was significantly related only to AWM.

REGIONAL GRAY MATTER PREDICTORS OF MDRS, MMSE, AND MDRS SUBSCALES

Cortical gray matter was divided into 2 components, 1 L-CGM (mesial temporal cortex) and 1 NL-CGM (the entire CGM excluding the limbic cortex). The L-CGM measure was used to capture the early and specific changes associated with DAT and the NL-CGM was used as a more nonspecific measure of CGM atrophy. Nonlimbic CGM contained both association cortex, thought to be affected in AD, and primary sensory and motor cortices, which are affected less severely in AD.[36] Further anatomically based divisions of the CGM were not technically feasible with these image data. Simultaneous multiple regression analyses were used to examine the relationship of L-CGM and NL-CGM to dementia severity and to the individual cognitive ability areas. Because the previous analyses indicated relationships of AWM to each of the cognitive measures, we included AWM in the set of independent variables. **Table 3** shows these results. Multiple regression analysis was used to examine the magnitude of the independent effects of L-CGM, NL-CGM, and AWM on total MDRS score. The results were significantly different from 0 (F[3,48]=6.63, P=.008). Inspection of the βs indicated that within this set AWM was a significant independent predictor of MDRS performance; the 2 gray measures were positive in sign but nonsignificant. Thus, independent contributions of L-CGM and NL-CGM on total MDRS score were not observed. Results of the simple correlations suggested, however, that each of these measures related to total MDRS score. Thus, it is the variance that these 2 gray matter measures share that appears to be related to total MDRS score. This is not surprising given the highly significant correlation between these 2 brain regions (*r*[52]=0.48, P=.001). When multiple regression was used to examine the magnitude of the independent effects of AWM, L-CGM, and NL-CGM on the MMSE, *R* for the regression was significant (F[3,48]=9.64, P<.001). Significance tests of the standardized regression coefficients indicated independent relationships of AWM and L-CGM, but not of NL-CGM to the MMSE score. The correlation of NL-CGM and MMSE was also not significant. The data indicated that lower MMSE scores were associated with higher AWM and lower limbic gray matter volumes, but were not significantly related to NL-CGM volume.

The next set of analyses examined the relations between L-CGM and NL-CGM, and AWM and 4 MDRS subscales. Because the purpose of these analyses was to provide additional descriptive information to the relationships observed between CGM and the subscales, only those subscales that had shown a specific independent relationship to CGM (attention, construction, conceptualization, and memory) were included in this analysis. Results of these analyses are included in Table 3. For the MDRS *attention* subscale, *R* for the equation was significantly different than 0 (F[3,48]=4.64, P=.006), and attention was independently associated with NL-CGM and AWM but not with L-CGM. These results indicated that subjects with poor attention had relatively more NL-CGM atrophy and more AWM. For the MDRS *construction* subscale, *R* for the equation was significantly different from 0 (F[3,51]=6.18, P<.001); however, only AWM showed a specific independent relationship to the construction score. Neither NL-CGM nor L-CGM was significantly correlated with construction. These results suggested that poorer performance on the construction subscale of the MDRS was associated with higher AWM, while statistically significant relationships to *individual* CGM subregions were not demonstrated. Similar results were obtained for the MDRS conceptualization subscale; *R* for this equation was significantly different from 0 (F[3,51]=4.20, P=.01). Again, only AWM was significantly associated with performance on the conceptualization subscale. Thus, it was those patients with relatively more AWM who had poorer

Table 2. Gray and White Matter Correlates of the Dementia Rating Scale (DRS) Subscale Scores*

DRS Subscale	Cortical Gray Matter r	Cortical Gray Matter β	Abnormal White Matter r	Abnormal White Matter β	R†	R^2	Adjusted R^2
Attention	0.33	.30‡	−0.37§	−.34§	0.48	0.23	0.20
Initiation	0.21	.17	−0.42§	−.41§	0.46	0.21	0.18
Construction	0.30	.26‡	−0.45†	−.42§	0.52	0.27	0.24
Conceptualization	0.32	.29‡	−0.33	−.30‡	0.43	0.19	0.16
Memory	0.41†	.38§	−0.29	−.25‡	0.48	0.23	0.20

**Significance for* r *and* R *with 2-tailed probabilities.* R *indicates regression correlation coefficient.*
†P<.001.
‡P<.05.
§P<.01.

Table 3. Limbic and Nonlimbic Cortical Gray and White Matter Correlates of the Dementia Rating Scale (DRS) and the Mini-Mental State Examination (MMSE)*

	Limbic Gray Matter r	Limbic Gray Matter β	Nonlimbic Gray Matter r	Nonlimbic Gray Matter β	Abnormal White Matter r	Abnormal White Matter β	R†	R^2	Adjusted R^2
DRS, total	0.37‡	.22	0.33	.20	−0.41‡	−.36‡	0.54	0.29	0.25
MMSE, total	0.46†	.32§	0.35	.16	−0.45†	−.38‡	0.61	0.38	0.34
DRS subscale									
Attention	0.20	.00	0.32	.29§	−0.37‡	−.35‡	0.47	0.22	0.18
Construction	0.32	.17	0.27	.16	−0.45†	−.40‡	0.53	0.28	0.23
Conceptualization	0.32	.19	0.30	.19	−0.33	−.28§	0.46	0.21	0.16
Memory	0.48†	.34§	0.39†	.21	−0.29	−.22‖	0.55	0.31	0.26

**Significance for* r *and* R *with 2-tailed probabilities.* R *indicates regression correlation coefficient.*
†P<.001.
‡P<.01.
§P<.05.
‖P<.10.

conceptualization while relations between conceptualization and individual CGM regions did not meet criteria for statistical significance. For both the construction and conceptualization subscales, previous analyses demonstrated significant relationships to overall CGM atrophy (Table 2); the current subregion analysis failed to demonstrate independent effects of the L-CGM and NL-CGM subregions on these processes. Finally, the regression equation for the memory subscale was also significantly different from 0 ($F[3,51]=7.03$, $P<.001$). Only L-CGM was independently associated with the memory subscale. Independent associations of NL-CGM and AWM with the MDRS memory subscale were not demonstrated. The regression data showed a trend for AWM to be related to memory as well. Nonlimbic CGM was a significant correlate of memory but the β fell short of statistical significance.

CARDIOVASCULAR ILLNESS-FREE SUBGROUP

An exploratory analysis was conducted to determine whether dementia severity was related to CGM atrophy and AWM volume even in patients with AD who were free of current and past cardiovascular illness. For this analysis, subjects were excluded who had either medical history or physical examination findings of myocardial infarction, hypertension, rheumatic fever, cardiac surgery, or coronary artery disease. Of the remaining group of 27 subjects, 21 reported no cardiovascular problems, 4 reported only cardiac irregularities, 2 reported only angina on the medical history form, and all had normal cardiovascular function on physical examination. Separate multiple regression analyses were computed to determine the magnitude of the independent effects of CGM and AWM on the total MDRS and MMSE scores. **Table 4** displays the results. For the MDRS, *R* for the regression reached only the trend level for statistical significance ($F[2,24]=3.04$, $P=.07$). While CGM was not independently associated with total MDRS score in this subset ($\beta=.14$, $P>.10$), the standardized regression coefficient for AWM remained significant ($\beta=.44$, $P<.05$). Together, CGM and AWM accounted for 20% of the variance in MDRS scores (14% adjusted). For the MMSE, *R* for the regression was not significant, and neither CGM nor AWM was independently associated with MMSE scores. Thus, in the subgroup that was free of cardiovascular illness, the MDRS findings indicated that AWM volume was associated with dementia severity. In contrast, the MMSE analyses did not bear out this relationship.

COMMENT

Quantitative MRI measures of CGM volume loss and AWM were specifically associated with dementia

Table 4. Gray and White Matter Correlates of the Dementia Rating Scale (DRS) and the Mini-Mental State Examination (MMSE) Performance in the Cardiovascular Illness-Free Subset*

	Cortical Gray Matter		Abnormal White Matter				
	r	β	*r*	β	*R*	R^2	Adjusted R^2
DRS	0.11	.14	−0.43†	−.44†	0.45†	0.20	0.14
MMSE	0.09	.10	−0.23	−.23	0.25	0.06	−0.01

**Significance for r and R with 2-tailed probabilities. R indicates regression correlation coefficient.*

†P<.05.

severity in patients with DAT. These findings are consistent with those from previous imaging and autopsy studies[20,21,30,37,38] linking decreased gray matter volume and/or increased AWM to more severe dementia. The present study also demonstrated that CGM atrophy and AWM have statistically independent associations (indicated by the significance of the regression coefficients) with dementia severity. Thus, given the degree of patients' CGM atrophy, those with more AWM tended to have worse dementia. Similarly, given a particular level of AWM, patients with more CGM atrophy tended to be more severely demented. The present study is, to our knowledge, the first to demonstrate the independence of CGM atrophy and AWM in contributing to dementia severity, and suggests that the pathological processes that affect these measures may also be independent.

Performance in 4 of 5 cognitive domains assessed by the MDRS received significant independent contributions from both CGM atrophy and volume of AWM. The initiation and perseveration subscale had a somewhat different result in that CGM atrophy was associated only with AWM volume. Overall, then, AWM and CGM are both related to most of the subareas tested in the MDRS.

Given that in many studies[6-10,13-16] when AWM is detected clinically significant behavioral effects have *not* been apparent, it was interesting that our measure of AWM was such a significant and reliable predictor of dementia severity. Perhaps the increased sensitivity of our method of measuring AWM over that of clinical assessment, and/or the sensitivity of our methods of measuring dementia, improved the sensitivity with which such a relationship could be detected.

Recent summaries of neuropathologic studies[35,39] suggest that the changes in the limbic cortex are early, severe, and strongly related to memory loss, while it is the neocortical changes, thought to occur with progression, that are required for dementia to become apparent. This would suggest that while limbic cortex atrophy may be related to severity of memory impairment, dementia severity would be more strongly associated with neocortical atrophy. It is also likely that given the early and severe damage to the limbic system, little variability in these measures may exist in later stages of DAT (ie, a floor effect), making a relationship of limbic cortex to memory undetectable. In the present study, measures of dementia severity and brain volumes were relatively free of identifiable floor or ceiling effects and had ranges sufficient for correlation-based analyses. Our findings demonstrated significant and specific contributions of CGM *and* AWM volume to dementia severity. However, when both L-CGM and NL-CGM measures were examined together, neither was a significant independent contributor to MDRS score, and only the L-CGM measure had a significant independent relationship with the MMSE score. This *does not* indicate the lack of a significant relationship between the CGM measures and dementia severity; this pattern of findings suggests that it is primarily the variance shared between these gray matter measures that is associated with MDRS performance, rather than the nonshared variance. That is, although CGM atrophy has been shown to contribute significantly to dementia severity, independent contributions of atrophy in the 2 cortical subregions could not be demonstrated. One limitation of our NL-CGM was that it summed together a large area of neocortex without dividing areas thought to be more severely affected in DAT (ie, association cortices) from those less affected (ie, primary sensory and motor cortices). This limited the sensitivity of this measure as a predictor of dementia severity.

The finding of a specific association between L-CGM and the MMSE may have occurred because 9 (40%) of the 30 points on the MMSE are memory and orientation points. The MDRS has only 25 (17%) of 144 points for memory items; thus, the MDRS has a lower loading of memory items, probably making MDRS performance less reliant on an intact temporolimbic memory system.

A limitation of the present study is that it does not contain non-DAT demented groups, thus precluding the assessment of the specificity of these brain-behavior relationships. Thus, we cannot say whether the present results generalize to other types of dementia or are specific to DAT. Also, while our method of detecting and quantifying AWM has several features that improve its sensitivity and reliability over semiquantitative assessments of white matter pathology used in other imaging studies, it does not contain sufficient information to allow localization of abnormalities as being either within the deep white matter or in periventricular regions. Finally, while our analysis of the cardiovascular illness-free subset of subjects suggests that abnormalities in the white matter are associated with dementia severity even in the absence of cardiovascular illness, these findings are somewhat inconsistent in the current sample. That is, one measure of dementia severity (the MDRS) showed this relationship while the other (the MMSE) did not. Therefore, this issue must be clarified by future studies that use a larger group of subjects without cardiovascular illness to increase power for detecting such effects.

In summary, the current study provides strong evidence using volumetric MRI that atrophy in the gray matter and abnormalities in the white matter play independent roles in determining severity in DAT.

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