3D Mapping of Mini-mental State Examination Performance in Clinical and Preclinical Alzheimer Disease

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Abstract: The Mini-mental State Examination (MMSE) is a brief cognitive screening instrument frequently used to track Alzheimer disease (AD) progression. We investigated the structural neuroimaging correlates of MMSE performance in patients with clinical and preclinical AD. We analyzed structural magnetic resonance imaging data from 29 probable AD and 5 MCI patients who later converted to probable AD using an advanced 3D cortical mapping technique. MMSE scores were entered as covariates in a general linear model that predicted the gray matter density at each cortical surface point. The results were corrected for multiple comparisons by permutation testing. The global permutation-corrected significance for the maps linking gray matter loss and cognitive decline was $P = 0.005$ for the left and $P = 0.012$ for the right hemisphere. Strongest correlations between MMSE score and gray matter integrity were seen in the entorhinal, parahippocampal, precuneus, superior parietal, and subgenual cingulate/orbitofrontal cortices. Significant correlations were also seen bilaterally in the temporal, the middle frontal and the left angular and supramarginal gyri. As a global cognitive measure, MMSE depends on the integrity of widely distributed cortical areas in both brain hemispheres with left-sided predominance.

Key Words: Alzheimer disease, Mini-mental state examination, MMSE, correlation, cortical atrophy, gray matter atrophy

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The Mini-mental State Examination (MMSE) is a brief cognitive screening test also used for tracking cognitive decline in patients with dementia.[1] This short battery tests orientation, language, short-term memory, construction, and attention. It is the most widely used cognitive instrument for evaluating patients with Alzheimer disease (AD).

AD progression manifests clinically with cognitive decline, structurally with brain atrophy and pathologically with progressive accumulation of neuritic plaques and neurofibrillary tangles. Advances in neuroimaging have revolutionized clinical neuropsychology by permitting brain-behavior correlations that provide insight into normal and abnormal cognition. Clinical trials in AD use various cognitive instruments including the MMSE. However, the association between MMSE and gray matter atrophy has rarely been investigated with techniques exploring the whole cortex. In this study we use an advanced 3D cortical analysis technique to study and visualize the associations between total MMSE score and cortical atrophy in clinical and preclinical AD. Our technique surveys the entire cerebral cortex while controlling for sulcal and gyral variability. It has been successfully employed in several neurodegenerative,[2–4] psychiatric,[5] and developmental studies.[6–9]

METHODS

Patients

Our study included 29 probable AD and 5 amnestic MCI subjects who later converted to probable AD. All subjects were participants in the UCLA Alzheimer's Disease Research Center database and were recruited and consented following the restrictions and policies of the UCLA Institutional Review Board. The diagnostic work-up consisted of a physician interview, general and neurologic examination, MMSE, tests of general intellectual functioning [Wechsler Adult Intelligence Scale (WAIS)—3rd ed[10]], verbal memory (California Verbal Learning Test—2nd ed[11]) and Wechsler Memory Scale—3rd edition (WMS-III): Logical Memory,[12] visuospatial function [Rey-Osterrieth Complex Figure test (ROCFT)–copy][13], visual memory (WMS-III: Visual reproduction[12] and ROCFT delayed recall[13]), language (Boston Naming Test[14] and Controlled Oral Word Association Test[15]), attention (WAIS digit symbol, Trails A[16]), and executive function (Trails B,[16] the Stroop test,[17] and the Wisconsin Card Sorting Test[18]). Diagnoses

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were reached by consensus decision among neurologists, psychiatrists, and neuropsychologists and were based on the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD[19] and the Petersen criteria for amnestic MCI.[20] All 5 MCI patients met NINCDS-ADRDA criteria for probable AD on a subsequent annual follow-up visit. Additional inclusion criteria were age 55 to 90 years, no evidence of concurrent general medical condition of sufficient severity to impact cognition, no history of drug or alcohol abuse, no concurrent psychiatric or other neurologic illness. We excluded subjects whose baseline images were acquired more than 6 months from the date of neuropsychologic evaluation and those with conditions precluding safe performance of magnetic resonance imaging (MRI).

Imaging Data Acquisition and Analysis

MRI scans were acquired on a 1.5 T Signa MRI scanner (Milwaukee, Wisconsin) according to the following protocol: 3D SPGR (spoiled gradient echo), gapless coronal acquisition perpendicular to the long axis of the hippocampus, TR 28 ms, TE 6 ms, FOV 220 mm, 256×192 matrix, slice thickness 1.5 mm. We used a 9-parameter linear transformation for spatial normalization and scaling of each patient's image to the ICBM53 average brain imaging template.[21] To ascertain whether brain scaling has influenced our results by differentially scaling the gray matter and potentially negating the atrophy effects between our AD and MCI subjects we compared the native-space-to-ICBM transformation estimates for our AD and MCI patients (2 sample t test, $t = -0.53$; $P = 0.6$) and looked for a correlation between the subjects' transfomation estimates and their MMSE score (bivariate $r = 0.0193$; partial $r = 0.07$ corrected for age, sex, education, and race). Image intensity nonuniformity correction was applied to each image using a regularized tricubic B-spline approach.[22] The scalp and other extracerebral tissues were automatically removed. All volumes were visually inspected and mislabeled brain and nonbrain tissues manually corrected. After 3D hemispheric reconstruction, 38 sulci per hemisphere were traced according to a protocol with established interrater and intrarater reliability.[23,24] A group average sulcal map was computed. The parameterized, flattened hemispheric surfaces were warped to the average sulcal representations assuring explicit matching of corresponding gyri, as far as possible, before averaging of data on gray matter distribution across subjects. 3D maps of gray matter distribution were extracted[22] and mapped onto the corresponding parametric hemispheric model in exact spatial correspondence. As in many prior studies by our group and others, a commonly used measure of regional gray matter volume, known as gray matter density, was defined as the proportion of tissue segmenting as gray matter in a small spherical region (10 mm radius) around each point on each subject's cortical surface model (Wright et al,[25] Good et al,[26] Cannon et al,[27] Mechelli et al,[28] Thompson et al,[29] who have used similar measures). An average group 3D gray matter density map was created for all subjects in the study. Data on individual variations in gray matter density was computed and regressed against MMSE scores. MMSE scores were entered as covariates in a general linear model that predicted the 3D cortical map of gray matter density for each subject. This procedure yields a map of correlation coefficients (r-values) across the whole cortex, with each r-value representing the correlation between gray matter at that point and each subject's MMSE score. The results were corrected for multiple comparisons by permutation testing using a threshold of $P < 0.01$.[3] A detailed explanation of the permutation test is provided elsewhere.[30]

We additionally explored for possible confounding of the association between MMSE and gray matter density by age. We first explored this association by developing 3D correlations and statistical maps, which were corrected for multiple comparisons by permutation testing using a threshold of $P < 0.01$ (Fig. 2). We then developed a linear regression model with MMSE as the dependent and age as the predictor variable and a linear regression model with MMSE as the dependent and age and the mean regional gray matter density in the entorhinal, precuneus, and lateral parietal regions as independent predictors.

RESULTS

Demographic data on the subjects are provided in Table 1. The amnestic MCI subgroup had an average age of 70.8 years (SD 7.9), 16.5 years of education (SD 3.4 y), and a MMSE score of 28.8 (SD 0.96). The average neuropsychologic test scores for the amnestic MCI subgroup are provided in Table 2.

The global permutation-corrected significance for the maps associating MMSE performance with cortical atrophy was $P = 0.005$ for the left and $P = 0.012$ for the right hemisphere. The 3D statistical maps showed strong left-sided lateralization, with greater effect sizes and more extensive cortical areas linked to MMSE score in the left hemisphere (Fig. 1). MMSE score correlated strongly with gray matter integrity in the entorhinal and parahippocampal cortices [Brodmann area (BA) 28], precuneus (BA 7), superior parietal lobule (BA 7), and subgenual cingulate/orbitofrontal areas (BA 32 and 12). Strong correlations were also seen with the midposterior portions of the superior (BA 22), middle (BA 21), and inferior temporal (BA 20) gyri on the left and the

TABLE 1. Demographic Characteristics

Variable	Mean	Range	SD
Age (y)	76.6	52-89	8.7
Sex (M:F)	12:14	N/A	N/A
Education (y)	14.1	12-20	2.1
Race (W:AA:A)	26:1:2	N/A	N/A
MMSE	22.1	7-30	5.5

M indicates male; F, female; W, white; AA, African American; A, Asian.

TABLE 2. Neuropsychologic Data for the MCI Subgroup

Test	Mean Score	Range	SD
Verbal IQ	101.8	93-110	6.5
Performance IQ	98.2	84-135	21.1
Full scale IQ	100	89-127	15.7
Trails A	61.2 s	27-81	20.7
Trails B	186 s	63-349	112.2
Stroop C	184.2	115-236	53.3
Boston naming test	52.4	49-55	2.6
FAS	31.2	11-45	14.0
Animal fluency	13.8	7-19	4.4
Logical memory retention	72.6	52-90	14.5
ROCFT copy	30.6	21-36	5.9
CVLT trial 5	7.8	4-12	3.1
CVLT delayed recall	4.4	3-8	2.2
CVLT recognition	12.4	11-13	0.9
CVLT false positive	5.8	1-13	5.1

temporal pole (BA 38) and anterior portion of all 3 temporal gyri (BA 20, 21, and 22) on the right. The left angular (BA 39) and supramarginal gyrus (BA 40) correlated with MMSE on the left only. There were bilateral correlations with atrophy in the middle frontal gyrus (BA 46, 9, and 8) (Fig. 1).

Figure 2 shows the association between age and gray matter density. Significant age effects were seen bilaterally in the medial and lateral frontal and occipital association cortices, the lower portions of the sensorimotor strip, the superior temporal gyrus, as well as parts of the medial temporal, entorhinal, anterior and posterior cingulate, and superior parietal cortices on the left. The global permutation-corrected significance for the maps associating age with cortical atrophy was $P = 0.005$ for the left and $P = 0.04$ for the right hemisphere.

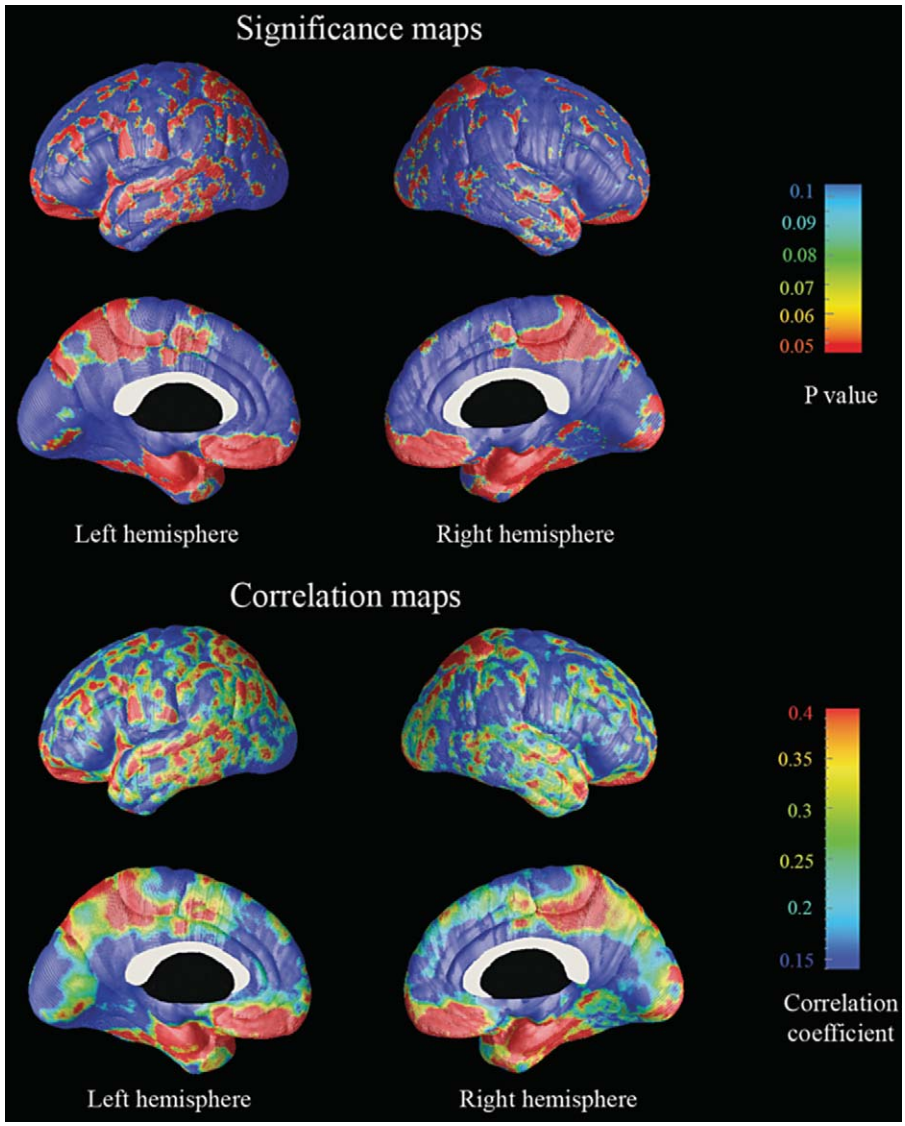

FIGURE 1. Statistical (top) and correlation maps (bottom) demonstrating the association between MMSE score and gray matter density in subjects with clinical and preclinical AD.

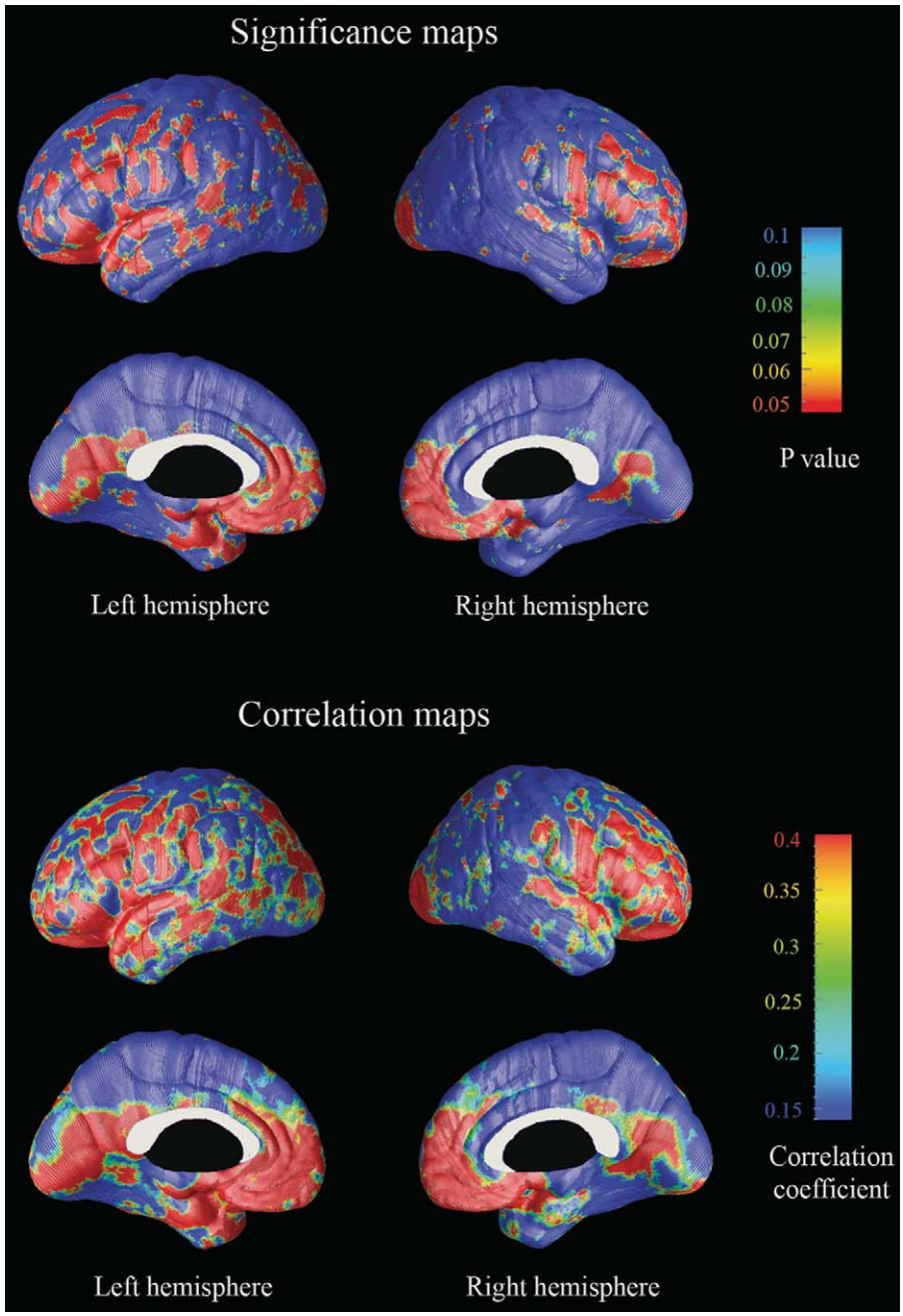

FIGURE 2. Statistical (top) and correlation maps (bottom) demonstrating the association between the age and gray matter density in subjects with clinical and preclinical AD.

The correlation between age and MMSE ($r = -0.16$, $P = 0.37$) and a linear regression model of MMSE by age ($R^2 = 0.04$, $F = 1.185$, $P = 0.29$) were not significant. The linear regression model with MMSE as the dependent and age and the regional gray matter density of the entorhinal, precuneus, and lateral parietal regions as independent predictors yielded $R^2 = 0.47$, $F = 3.149$, $P = 0.016$. The correlation values between the regional gray matter density of the entorhinal, precuneus, and superior parietal regions and the MMSE score ranged between $r = 0.44$ and 0.6 (Table 3). Figure 3 shows the corresponding regression plots. The location, ICBM co-ordinates, and statistical significance of the regions showing the strongest associations of MMSE and gray matter atrophy can be found in Table 4.

DISCUSSION

As a global cognitive measure MMSE is thought to reflect the integrity of widely distributed cognitive networks situated in both hemispheres with left sided predominance. Using innovative 3D mapping techniques

TABLE 3. Bivariate and Age-adjusted Correlations Between the Mean Gray Matter Density of the Entorhinal, Precuneus, and Superior Parietal Regions and the MMSE Scores

Region	Pearson Correlation (*r*)	Significance (*P*)	Age Adjusted Partial Correlation (*r*)	Significance (*P*)
Left entorhinal	0.58	< 0.001	0.57	0.001
Right entorhinal	0.6	< 0.001	0.58	0.001
Left precuneus	0.45	0.009	0.48	0.005
Right precuneus	0.48	0.005	0.54	0.001
Left superior parietal	0.46	0.007	0.44	0.012
Right superior parietal	0.57	0.001	0.56	0.001

we were able to confirm that hypothesis, in the sense that widespread cortical atrophy was linked with MMSE decline. Strong linkage between MMSE score and gray matter integrity was observed in the mesial temporal, orbitofrontal, medial and lateral parietal, left more than right lateral temporal and middle frontal, and left inferior parietal cortical regions. The left-sided lateralization was expected as most items of the MMSE questionnaire rely on left hemispheric cognitive processing.

Using the cortical pattern matching technique our group compared the baseline and 18-month follow-up MRI data of 12 moderate AD (mean MMSE = 17.7) and

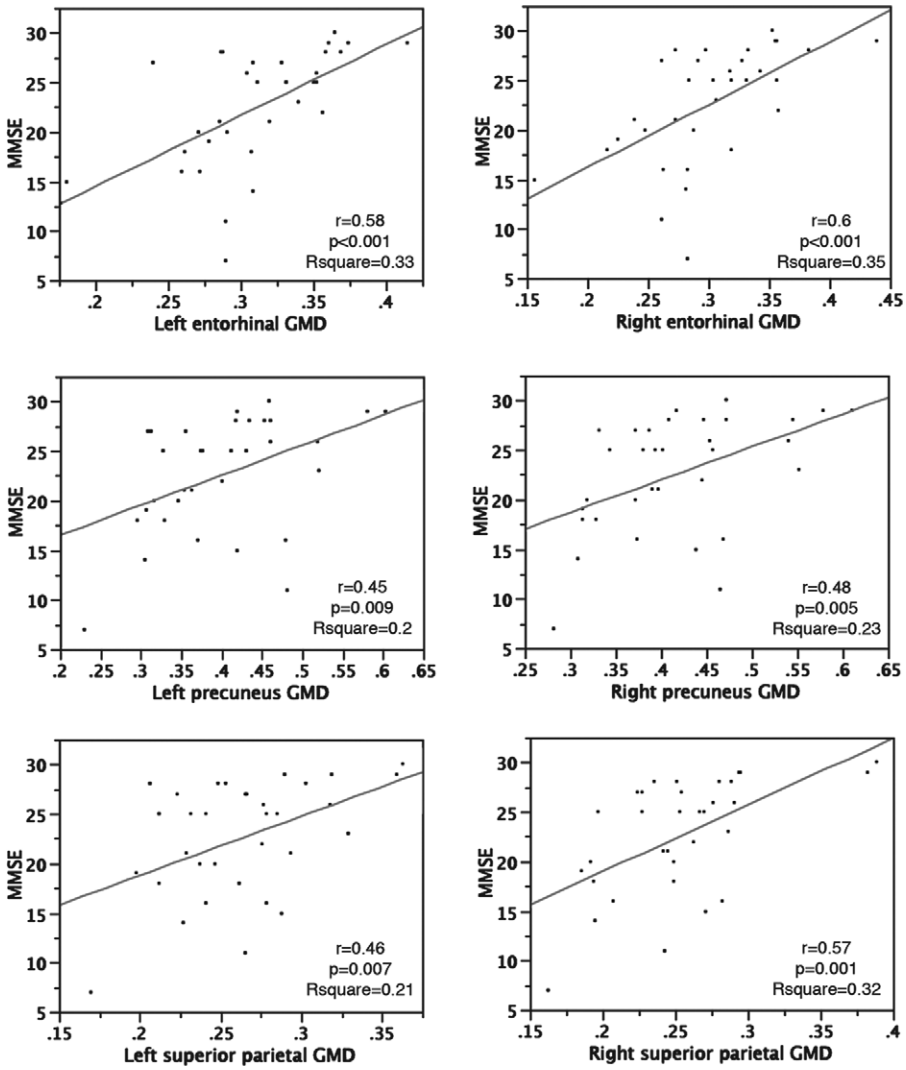

FIGURE 3. Regression plot of the individual mean gray matter density values and MMSE for the entorhinal, precuneus, and superior parietal regions.

TABLE 4. Location, ICBM Coordinates, and Statistical Significance of the Regions Showing the Strongest Associations of MMSE and Gray Matter Atrophy

Region	BA	Coordinates (mm)			*R* Value	*P*
		X	Y	Z		
Entorhinal/parahippocampal	Left BA 28	−19.0	−15.7	−28.1	0.59	< 0.001
	Right BA 28	20.0	−12.8	−30.2	0.59	< 0.001
Precuneus	Left BA 7	−2	−47.7	47.2	0.54	< 0.001
	Right BA 7	3	−43.6	49.4	0.56	< 0.001
Orbitofrontal cortex	Left BA 12	−2	40.9	−22.4	0.57	< 0.001
	Right BA 12	2	41.1	−20.2	0.54	< 0.001
Superior parietal cortex	Left BA 7	−29.5	−54	67	0.46	< 0.001
	Right BA 7	31	−66	57.1	0.58	< 0.001

14 age-matched normal controls. We explored the correlation between MMSE score and cortical density and found significant associations between gray matter atrophy and low MMSE scores in mesial and lateral temporal, parietal, and frontal association cortices. The associations showed a temporal gradient and were substantially stronger in follow-up in many of the above regions.[3] In the present study, we focused on clinical and preclinical AD in search for disease-specific associations. Longitudinal AD cognitive correlation maps may be of interest as they may show that the strength of the associations and perhaps even the regional correlation pattern is stage specific as a function of AD stage-dependent variability in the test measure (eg, MMSE) and gray matter integrity.

Using voxel-based morphometry in patients with AD, Frisoni et al[31] reported correlations between total MMSE score and somewhat surprisingly right more than left temporal, bilateral posterior cingulate/precuneus, and right superior parietal gray matter atrophy. Several other groups have investigated the association between global cognitive measures and regional brain volumes. The hippocampus, one of the first regions to be affected by AD, was reported to show almost as strong correlation with MMSE ($r = 0.47$) as we found for the gray matter regions in our study (Table 3).[32] In another longitudinal study, the correlation between MMSE decline and atrophy of the hippocampi and whole brain were, respectively, $r = 0.22$, $P > 0.05$ and $r = 0.38$, $P < 0.05$ in MCI and $r = 0.35$, $P < 0.05$ and $r = 0.47$, $P < 0.05$ in AD.[33] Using the magnetization transfer ratio (MTR) technique van der Flier et al[34] reported the following correlations of the relative peak MTR height with MMSE: whole brain $r = 0.58$, frontal lobe $r = 0.52$, and temporal lobe $r = 0.58$. Mean MTR, however, did not correlate with MMSE in any region. The strength of these correlations is comparable to ours.[34] Another group reported total cerebral volume to correlate strongly with another more accurate measure for AD severity-the sum of boxes Clinical Dementia Rating scale score ($r = -0.39$, $P = 0.006$).[35]

Our linear regression model with MMSE as the dependent and age and regional gray matter density of the entorhinal, precuneus, and lateral parietal regions as independent predictors was statistically significant ($R^2 = 0.47$, $F = 3.149$, $P = 0.016$). Our results are similar to those reported by Mouton et al[36] in a postmortem study of severe AD patients with mean MMSE 6.7 (SD 6.6) and normal elderly subjects. Their linear regression model with MMSE as the dependent and cortical volume and age as predictors yielded $R^2 = 0.58$, $F = 27.9$, $P = 0.0001$).[36] In their study, however, the gray matter volumes were estimated postmortem directly from sectioned brains and were devoid of imaging artifacts introduced by the MRI scanner, the skull, scalp, and other soft tissues. These factors probably contribute significantly to their better statistical significance.

Three positron emission tomography (PET) studies and one single photon emission computed tomography (SPECT) study investigated the correlation between MMSE and cortical metabolism. The 2 PET studies in AD showed correlations with frontal, temporal, and parietal metabolism.[37,38] The AD SPECT study reported an association between MMSE and left temporal perfusion.[39] In a cohort of MCI and normal elderly total MMSE score correlated with bilateral inferior frontal, medial and inferior temporal, anterior cingulate, as well as left superior temporal, precentral, parietal, and insular PET hypometabolism.[40] Our findings are consistent with those reported in the PET and SPECT literature and seem to conform to the pathologic distribution of AD pathology with involvement of the association and relative preservation of the primary cortices.

The strengths and limitations of our study need be recognized. We used a cross-sectional design that assured adequate heterogeneity, and sufficient breadth of disease burden, in our AD sample. However, a longitudinal design-if large enough to encompass symptomatic variability-may offer greater power to link disease progression with MMSE decline and allow for exploration of stage-specific phenomena. In the MCI subgroup, etiologic heterogeneity is unwelcome if we want to focus on understanding brain changes in the AD spectrum. We thus limited our selection to those MCI patients who subsequently met the stringent diagnostic criteria for probable AD. The diagnosis of definite AD requires pathologic examination, which is not available for our subjects. Finally, the entorhinal region is one of the most challenging areas for imaging analysis as it is highly variable in shape and highly susceptible to magnetic

susceptibility artifacts. With the present technique we have minimized possible errors by first using intensity normalization and then applying cortical pattern matching to control for entorhinal variability. The technique can be considered an extension of the VBM methodology where instead of smoothing we explicitly coregister cortical surface data using sulcal constraints. For the entorhinal and parahippocampal cortex we used the collateral sulcus laterally and the invagination toward the hippocampus medially.

AD is a relentlessly progressive neurodegenerative disorder with very high prevalence among the elderly. Its current economical impact is enormous and on a continuous rise.[41] AD researchers and the pharmaceutical industry are actively searching for efficient disease-modifying AD therapies. These compounds would ideally demonstrate both cognitive and structural evidence for slowing disease progression. Investigating the structural correlates of cognitive decline will not only provide important evidence about various cognitive networks; it will also provide an excellent foundation for the utility of neuroimaging as a surrogate biomarker in clinical trials. In that context, we would hope to not only demonstrate drug-induced slowing in cortical atrophy but also a strong correlation between these regional effects and clinical stability or improvement.

REFERENCES

1. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cogntive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
2. Ballmaier M, O'Brien JT, Burton EJ, et al. Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects. *Neuroimage*. 2004;23:325–335.
3. Thompson PM, Hayashi KM, de Zubicaray G, et al. Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci*. 2003; 23:994–1005.
4. Thompson PM, Dutton RA, Hayashi KM, et al. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. *Proc Natl Acad Sci USA*. 2005;102: 15647–15652.
5. Ballmaier M, Sowell ER, Thompson PM, et al. Mapping brain size and cortical gray matter changes in elderly depression. *Biol Psychiatry*. 2004;55:382–389.
6. Sowell ER, Peterson BS, Thompson PM, et al. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6:309–315.
7. Sowell ER, Thompson PM, Peterson BS, et al. Mapping cortical gray matter asymmetry patterns in adolescents with heavy prenatal alcohol exposure. *Neuroimage*. 2002;17:1807–1819.
8. Sowell ER, Thompson PM, Tessner KD, et al. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. *J Neurosci*. 2001;21:8819–8829.
9. Sowell ER, Thompson PM, Welcome SE, et al. Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet*. 2003;362:1699–1707.
10. Wechsler D. *WAIS-R Manual*. New York: The Psychological Corporation; 1981.
11. Delis DC, Kramer JH, Kaplan E, et al. *California Verbal Learning Test, Form II*. 2nd ed. San Antonio, TX: The Psychological Corporation; 1987.
12. Wechsler D. *Wechsler Memory Scale-Revised*. San Antonio, TX: The Psycholocical Corporation; 1987.
13. Corwin J, Bylsma FW. Translations of excerpts from the Andre Rey's psychological examination of traumatic encephalopathy and P.A. Osterreith's The Complex Figure Copy Test. *Clin Neuropsychologist*. 1993;7:3–15.
14. Kaplan EF, Goodgalss H, Weintraub S. *The Boston Naming Test*. Philadelphia: Lea&Febiger; 1983.
15. Benton AL, Hamsher KD. *Multilingual Apahasia Examination*. Iowa City, Iowa: AJA Associates; 1989.
16. Kelland DZ, Lewis R, Gurevitch D. Evaluation of the repeatable cognitive-perceptual-motor battery: reliability, validity and sensitivity to diazepam. *J Clin Exp Neuropsychol*. 1992;14:65 (abstract).
17. Stroop JR. Studies in interference of serial verbal reactions. *J Exp Psychol*. 1935;18:643–662.
18. Berg L. A simple objective treatment for measuring flexibility in thinking. *J Gen Psychol*. 1948;39:15–22.
19. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology*. 1984;34:939–944.
20. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58:1985–1992.
21. Collins DL, Neelin P, Peters TM, et al. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr*. 1994;18:192–205.
22. Shattuck DW, Sandor-Leahy SR, Schaper KA, et al. Magnetic resonance image tissue classification using a partial volume model. *Neuroimage*. 2001;13:856–876.
23. Hayashi KMTP, Mega MS, Zoumalan CI. Medial hemispheric surface gyral pattern delineation in 3D: surface curve protocol. Available at: http://www.loni.ucla.edu/~khayashi/Public/Medial_suface/MedialLinesProtocol.
24. Sowell ER TP, Mega MS, Zoumalan CI, et al. Gyral pattern delineation in 3D: surface curve protocol. Available at: www.loni.ucla.edu/~esowell/new_sulcvar.html.
25. Wright IC, McGuire PK, Poline JB, et al. A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *Neuroimage*. 1995;2:244–252.
26. Good CD, Johnsrude IS, Ashburner J, et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*. 2001;14(Pt 1):21–36.
27. Cannon TD, Thompson PM, van Erp TG, et al. Mapping heritability and molecular genetic associations with cortical features using probabilistic brain atlases: methods and applications to schizophrenia. *Neuroinformatics*. 2006;4:5–19.
28. Mechelli A, Friston KJ, Frackowiak RS, et al. Structural covariance in the human cortex. *J Neurosci*. 2005;25: 8303–8310.
29. Thompson PM, Hayashi KM, Sowell ER, et al. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. *Neuroimage*. 2004;23(suppl 1):S2–S18.
30. Apostolova LG, Dinov ID, Dutton RA, et al. 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. *Brain*. 2006. In press, published online October 3, 2006; doi: 10.1093/brain/awl274.
31. Frisoni GB, Testa C, Zorzan A, et al. Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry. *J Neurol Neurosurg Psychiatry*. 2002;73:657–664.
32. Jack CR Jr, Dickson DW, Parisi JE, et al. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology*. 2002;58:750–757.
33. Jack CR Jr, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology*. 2004;62:591–600.
34. van der Flier WM, van den Heuvel DM, Weverling-Rijnsburger AW, et al. Magnetization transfer imaging in normal aging, mild cognitive impairment, and Alzheimer's disease. *Ann Neurol*. 2002;52:62–67.
35. Csernansky JG, Wang L, Swank J, et al. Preclinical detection of Alzheimer's disease: hippocampal shape and volume predict dementia onset in the elderly. *Neuroimage*. 2005;25:783–792.

36. Mouton PR, Martin LJ, Calhoun ME, et al. Cognitive decline strongly correlates with cortical atrophy in Alzheimer's dementia. *Neurobiol Aging*. 1998;19:371–377.
37. Kawano M, Ichimiya A, Ogomori K, et al. Relationship between both IQ and Mini-Mental State Examination and the regional cerebral glucose metabolism in clinically diagnosed Alzheimer's disease: a PET study. *Dement Geriatr Cogn Disord*. 2001;12:171–176.
38. Ushijima Y, Okuyama C, Mori S, et al. Relationship between cognitive function and regional cerebral blood flow in Alzheimer's disease. *Nucl Med Commun*. 2002;23:779–784.
39. Lampl Y, Sadeh M, Laker O, et al. Correlation of neuropsychological evaluation and SPECT imaging in patients with Alzheimer's disease. *Int J Geriartr Psychiatry*. 2003;18: 288–291.
40. Cao Q, Jiang K, Zhang M, et al. Brain glucose metabolism and neuropsychological test in patients with mild cognitive impairment. *Chin Med J (England)*. 2003;116:1235–1238.
41. Schumock GT. Economic considerations in the treatment and management of Alzheimer's disease. *Am J Health-Syst Pharmacy*. 1998;55(suppl 2):S17–S21.

