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Dementia, Quantitative Neuroimaging, and Apolipoprotein E Genotype

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BACKGROUND AND PURPOSE: **Quantitative MR imaging differences in an elderly population of subjects with various clinical disorders (including dementia, particularly Alzheimer's disease and vascular dementia) and disorders of mild cognitive impairment were examined. Potential quantitative MR differences were assessed by presence or absence of the apolipoprotein E (*APOE*) ϵ4 allele and by level of cognitive deficit.**

METHODS: **One hundred eighty subjects with a diagnosis of dementia or other clinical disorders were identified from an eligible population of 5677 elderly individuals. Age, duration of disease, and head size (where appropriate) were considered as covariates. *APOE* genotype was determined by polymerase chain reaction using buccal material. Axial and coronal intermediate- and T2-weighted MR images were quantified using a multispectral segmentation algorithm. Cognitive status was assessed by means of a modified Mini-Mental Status Examination.**

RESULTS: **All types of dementing illness showed significant volume reductions in the majority of structures examined, particularly in the total brain, hippocampus, and white and gray matter, and increased CSF and ventricular volumes. Subjects with mild cognitive impairment showed fewer atrophic changes but were still distinguishable from the 24 control subjects. Presence of an ϵ4 allele was associated with smaller hippocampal volume in subjects with Alzheimer's disease and vascular dementia within just 1 year of disease onset. For other analyses, atrophy related to the presence of the ϵ4 allele disappeared after controlling for age and length of disease.**

CONCLUSION: **The effects of the ϵ4 allele on brain morphology may be subtly expressed early in the development of dementia, but do not specifically affect cerebral atrophy thereafter. Cognitive impairment is associated with atrophy irrespective of diagnosis and presence of ϵ4.**

A major public health concern is aging of the population and associated increases in the prevalence of various dementias, particularly Alzheimer's disease (AD) (1–3). Neuroimaging is a key procedure in the assessment of dementia, especially for differential diagnostic evaluations (4–10). Recently, interest has focused on quantitative methods for distinguishing normal aging from pathologic conditions and for differentiating the types of dementia, such as AD versus vascular dementia (VaD) (5, 6, 10–17). Few investigators, however, have had the opportunity to examine an entire population.

Recent dementia research has focused on the genetics of degenerative diseases (18). For example, numerous studies have shown an increased risk for AD, and potentially for VaD, associated with the allele ϵ4 at *APOE*, the polymorphic genetic locus for apolipoprotein E (19–33), but the relationship between AD, ϵ4, and neuroimaging findings remains uncertain (1, 2, 5, 10).

If the ϵ4 allele is associated with increased risk for AD and VaD, does it also predict degenerative, atrophic changes that are detectable by quantitative MR imaging techniques? To date, results in this area have been equivocal. In a preliminary study that included only a subset of the AD subjects reported herein, we found the ϵ4 allele to be associated with smaller total brain and hippocampal volumes, as well as with a larger ventricle-to-brain ratio (VBR) (34). Additionally, diminished cognitive performance (eg, on the modified Mini-Mental Status Examination, or 3MS) was related to degree of atrophy. However, when age and length of disease (LOD) were included as covariates, these ϵ4-associated differences in brain morphology were no longer evident. Jack et al (5, 35) recently reported no apparent *APOE* effect on hippocampal or temporal lobe volume, and Yasuda et al (20) found that

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AD patients with homozygous ε4 had the least amount of atrophy. Barber et al (36, 37) did not find medial temporal lobe atrophy or white matter lesions to be associated with *APOE* genotype. In contrast, Lehtovirta et al (38, 39) and Soininen and coworkers (40, 41) found smaller hippocampal volumes in AD subjects with an ε4 allele and smaller temporal lobe and associated structures that were ε4 dose-dependent (42). Plassman et al (43) also found smaller hippocampal volumes in nondemented, cognitively intact subjects with the ε4 allele, consistent with observations by Reiman et al (8) and Tohgi et al (44). None of these studies was population based, so sample variations may explain some of the discrepancy in the findings. Also, cerebral blood flow (CBF) studies have shown conflicting relationships between CBF and *APOE* genotype (45–49).

A new epidemiologic investigation of aging and dementia in the residents of Cache County, Utah, provided an opportunity to examine quantitative MR findings in an elderly population (including centenarians) with a continuum of cognitive functioning, all of whom had established *APOE* genotypes (50, 51). From a population of 5677 eligible elderly residents in the county, 5092 (90%) underwent a multistage evaluation process to detect and identify prevalent cases of AD, VaD, and other dementias (29) as well as cases of mild cognitive impairment (MCI) (52). The study also identified subjects with other clinical disorders that may affect cognition, such as Parkinson's disease, stroke, and neuropsychiatric disorders. A particular objective was to investigate the relationship between the *APOE* genotype and dementia. The increased AD risk associated with the ε4 allele was confirmed in the Cache County sample, although the association appeared to wane in extreme old age (50). A trend was also observed between the ε4 allele and VaD.

When possible, the dementia workup in the Cache County study included MR imaging of the brain. The MR images were interpreted clinically and then subjected to quantitative analysis (11, 12). We report herein the quantitative MR analyses in the first 180 patients with AD, VaD, and other clinical disorders, as well as in the 24 cognitively normal subjects, all with known *APOE* genotypes (53). The objectives of this investigation were fourfold: 1) to describe the quantitative findings of MR analyses in this population of subjects with various types of dementing illnesses and known *APOE* genotype; 2) to determine whether the ε4 allele was associated with any unique differences in brain morphology in this population of elderly and demented subjects; 3) to examine age and LOD variables on brain morphology in terms of the presence or absence of the ε4 allele and diagnostic classification; and 4) to examine quantitative MR findings, *APOE* classification, and cognitive impairment as assessed by a modified 3MS examination (54).

Methods

The Cache County Study

A detailed description of the Cache County elderly population and the study methods used have been published elsewhere (50, 51). Briefly, a multistage screening and assessment protocol to ascertain the population's prevalence of dementia was used. This detection method is believed to yield 85% to 90% sensitivity (55). Individuals with dementia underwent a differential diagnostic evaluation that included a detailed history, a brief physical assessment, a standardized neurologic examination (all administered by specially trained nurses), and a 1-hour field battery of neuropsychological tests. All subjects who were capable completed a 10-minute cognitive screening instrument, the 3MS examination (54). The majority (84%) of subjects were subsequently examined by a board-certified gerontopsychiatrist and underwent neuroimaging. All data were then reviewed at a consensus diagnostic conference that included senior neuropsychologists and cognitive neuroscientists, gerontopsychiatrists, and board-certified neurologists. The year of disease onset was assigned retrospectively as the point at which subjects unambiguously met DSM-III-R criteria for dementia.

Subjects and Classification

Dementia was diagnosed in the 5092 study subjects by means of DSM-III-R criteria. AD diagnoses were based on NINCDS-ADRDA criteria (56), and VaD diagnoses were established by following NINDS-AIREN criteria (57, 58). Other diagnoses were made using standardized research criteria (50). A mild/ambiguous category was applied to those subjects who evidenced MCI or borderline impairment, suggestive of incipient AD, but who did not meet threshold criteria for specific dementia (52).

Ultimately, 335 cases of dementia were identified, of which 180 patients had MR imaging studies suitable for quantitative MR analysis. The various diagnostic categories to which the subjects were assigned are listed in Table 1. To simplify the parametric analyses, these categories were abridged to four classification groups: AD, MCI, clinical disorder not AD (including all disorders other than AD and MCI), and normal (including the 24 control subjects who underwent *APOE* genotyping, MR imaging, and the full assessment process). Subjects with AD constituted the largest group, followed by MCI and VaD subjects (see Table 1). Since ε4 has been associated with all three of these diagnostic categories (59–62), for several of the analyses, AD, VaD, and MCI subjects were combined into a single group and analyzed by presence or absence of the ε4 allele.

Because the influence of *APOE* may be apparent early in the evolution of AD, a finding substantiated in the Cache County population (50), one might expect to observe a differential distribution of *APOE* genotypes in demented subjects of varying ages. Furthermore, because the initial analysis of this population showed *APOE* effects related to AD and VaD subjects (22, 50, 62), AD and VaD subjects were combined in some analyses to increase the sample size and statistical power. Similarly, the MCI subjects were added to this analysis, because some had prodromal AD (63).

MR Imaging

MR imaging was performed at a regional medical center using a 0.5-T scanner with a quadrature head coil. The following imaging procedures were used: sagittal scans were T1-weighted with parameters of 500/15/2 (TR/TE/excitations), an acquisition matrix of 256 × 256, a field of view of 24 cm, and a section thickness of 5 mm with a 1-mm gap. Axial intermediate (proton density–weighted) and T2-weighted spin-echo images were acquired with parameters of 3148/31;90/1, a field of view of 22 cm, a matrix of 256 × 256, and a section

TABLE 1: Study demographics

	No.	Men	Women	Mean Age (SD)	Apolipoprotein E Genotype	
					$\in 4^-$	$\in 4^+$
Control group	24	11	13	77 (7.6)	15	9
Alzheimer disease	90	33	57	83 (6.8)	25	65
Mild cognitive impairment	39	20	19	83 (6.6)	12	27
Vascular dementia	21	8	13	83 (7.8)	15	6
Cerebrovascular disease	2	0	2	80 (2.1)	0	2
Frontal lobe dementia	3	1	2	81 (3.2)	1	2
Parkinson's disease	4	3	1	77 (3.9)	3	1
Psychiatric disorder	2	2	0	77 (15.6)	2	0
Dementia unknown	15	7	8	81 (7.4)	8	7
Alcohol dementia	2	2	0	84 (9.9)	2	0
Amnesic syndrome	2	0	2	80 (9.2)	1	1

thickness of 5 mm with a 1.5-mm gap. Coronal images obtained with a dual spin-echo technique (3046/30;90/1) were 3-mm thick with a 0.3-mm gap, a 22-cm field of view, and a matrix of 256 × 240.

Quantitative MR Imaging

Quantitative analyses were performed using well-established image analysis protocols, which have been published previously (11, 12, 43). Briefly, quantification was accomplished through multispectral segmentation of the proton density– and T2-weighted images, in which white and gray matter and CSF were separated from one other using ANALYZE software (64). Application of such multispectral segmentation permitted the volumetric quantification of the following structures: total intracranial volume (TICV); total brain volume; total brain CSF; and total ventricular, temporal horn, lateral ventricle, white matter, gray matter, and hippocampal volumes. The VBR was calculated on the basis of total ventricular and brain volume. With the exception of hippocampal volume, which was obtained in the coronal plane, all quantitative analyses were based on the axial images. All quantitative MR analyses were performed blinded to subjects' age, sex, *APOE* genotype, and diagnostic classification. The TICV measure was used to control for head size variation, except in VBR (11). Because the only MR scanner in Cache County was a 0.5-T unit and all our previous research had relied on images acquired at 1.5T on a different machine, we scanned four patients on both machines with comparable imaging protocols. We then subjected the digital data to identical multispectral image analyses, comparing the segmented images from the two systems. Raters had initially established ANALYZE intraclass reliability ($r > 0.9$) on images from the 1.5-T magnet, except for white and gray matter volumes, for which reliability was less ($r > 0.7$). These same raters found similar reliability coefficients when analyzing the subjects imaged on the two machines. Segmentation routines for white versus gray matter differentiation have some inherent variation based on operator classification. Since the contrast between brain parenchyma, CSF, and bone provides clear MR signal demarcation, the quantitative MR measures dependent on these tissue/compartment segmentations were more reliable (ie, TICV, total brain volume, CSF, and ventricular volumes). However, for whole-brain white and gray matter volumes, slight differences of even a pixel width result in variability when attempting to differentiate these tissues with this routine (65). Thus, although excellent inter- and intrarater reliabilities that exceeded $r = 0.9$ were achieved for TICV, VBR, whole brain, hippocampal volume, and all CSF and ventricular measures, the coefficients were approximately $r = 0.7$ for estimates of white and gray matter volume.

Statistical Analysis

Owing to the multiple diagnostic categories and quantitative MR measures, the analysis of *APOE* genotype was simplified by combining $\epsilon 4$ homozygotes ($\epsilon 4/4$) and heterozygotes ($\epsilon 4/-$) into a single group, designated as $\epsilon 4+$, because a single copy of $\epsilon 4$ was sufficient to produce the association of $\epsilon 4$ to AD in this population (50). This type of *APOE* classification into $\epsilon 4+$ versus $\epsilon 4-$ has been used by others (36, 37, 63). The nine subjects who were $\epsilon 2/\epsilon 4$ were classified as $\epsilon 4+$, even though some evidence suggests that $\epsilon 2$ may be protective (66, 67). However, no such protection influence was seen in the Cache County cohort (50) nor in this study when $\epsilon 2/\epsilon 4$ subjects were included or excluded. Thus, quantitative MR findings were analyzed by *APOE* status ($\epsilon 4+$ versus $\epsilon 4-$) and four levels of diagnostic classification (control group, AD, MCI, and clinical disorder not AD; see Table 2). As mentioned earlier, in some of the analyses, AD, VaD, and MCI subjects were pooled together in a single group. The justification for including the MCI subjects was based on the fact that they do display mild cognitive deficits and this condition may be a prodrome for dementia (52, 63, 68). Furthermore, combining all subjects with various levels of cognitive impairment provides a single group with a continuum of cognitive deficits so that quantitative MR findings may be compared by presence or absence of $\epsilon 4$. In every case in which these three groups were combined, they were first analyzed separately. Separate analysis yielded no significant findings. Head size was controlled by using TICV as a covariate in analyses of covariance, which allowed for heterogeneous regression slopes among groups (ANCOHET' 69). Other covariates included age at assessment and time since onset of dementia (when present) as a measure of LOD. Since the hippocampal volume calculations relied on separate images obtained in the coronal plane, there were two fewer hippocampal volumetric analyses than available for other structures, which were all obtained in the axial plane. Temporal horn and hippocampal volumes were calculated separately for left and right as well as a combined mean for each. In all, 17 quantitative analyses were performed. For simplicity in data analysis and presentation, we chose the following three representative measures for graphic depiction of test results: total brain volume (brain), total hippocampal volume (hippocampus), and VBR.

Results

Demographics and Descriptive Findings: Quantitative MR × Diagnosis × **APOE** *Classification*

Table 1 summarizes group composition by sex and *APOE* classification. Graphic depiction of the

TABLE 2: Quantitative MR findings in brain parenchyma

	Control Group		Alzheimer's Disease		Mild Cognitive Impairment		Clinical Disorder, Not Alzheimer's Disease	
Sample Size	$\epsilon 4^-$ n = 15, Mean (SD)	$\epsilon 4^+$ n = 9, Mean (SD)	$\epsilon 4^-$ n = 25, Mean (SD)	$\epsilon 4^+$ n = 65, Mean (SD)	$\epsilon 4^-$ n = 12, Mean (SD)	$\epsilon 4^+$ n = 27, Mean (SD)	$\epsilon 4^-$ n = 32, Mean (SD)	$\epsilon 4^+$ n = 19, Mean (SD)
Age*	76.73 (8.06)	78.89 (6.55)	85.32 (6.88)	81.86 (6.46)	82.92 (6.57)	72.19 (6.82)	82.06 (8.00)	79.63 (6.14)
GM	676.08 (68.50)	710.15 (59.20)	592.91 (84.03)	568.60 (89.64)	581.26 (127.20)	579.03 (76.43)	553.27 (111.54)	549.61 (109.94)
WM	473.99 (45.83)	457.45 (58.47)	434.33 (105.20)	393.90 (107.65)	429.49 (71.02)	442.92 (128.28)	454.32 (130.81)	457.61 (115.18)
Brain	1150.07 (102.51)	1167.61 (101.70)	1027.23 (136.55)	962.50 (120.04)	1010.75 (137.09)	1021.95 (108.82)	1007.58 (135.66)	1007.22 (161.75)
TICV	1380.26 (128.90)	1460.78 (137.86)	1392.35 (146.53)	1316.79 (124.70)	1353.84 (148.29)	1334.98 (120.66)	1359.03 (167.59)	1348.36 (175.85)
VBR	3.70 (2.08)	4.25 (2.20)	7.11 (3.07)	. . .	. . .	. . .	. . .	. . .

Note.—GM indicates gray matter; WM, white matter; brain, total brain volume; TICV, total intracranial volume; VBR, ventricle-to-brain ratio.
* Age at time of clinical assessment.

mean (± SD) for whole brain and hippocampal volumes along with VBR is presented in Figure 1 for each diagnostic category. As expected, control subjects had the highest brain volume, with the exception of one outlier with Parkinson's disease and two subjects who suffered from alcoholism. Likewise, VBR was smallest in control subjects, except for the person with Parkinson's disease. In contrast, hippocampal volume did not exhibit such a clear separation across groups. Two subjects with frontal lobe dementia and the subject with Parkinson disease had the smallest hippocampal volume, followed by the AD subjects. In regard to *APOE* effects, generally, $\epsilon 4+$ subjects had smaller hippocampal volumes, even among the control group. The smallest brain volumes were observed in AD and VaD subjects with at least one $\epsilon 4$ allele. However, none of the $\epsilon 4$-related effects remained significant after controlling for age.

Table 2 provides the quantitative MR results across the four broad diagnostic groups for each morphometric measure (Table 3). Comparing groups by diagnostic classification yielded the expected results, wherein the control subjects had significantly less atrophy than the others (F_{brain} = 6.13, df = 3, 184, P = .001; F_{VBR} = 3.26, df = 3, 184, P = .012; $F_{hippocampus}$ = 3.59, df = 3, 178, P = .008). As with Figure 1, inspection of Table 2 reveals that, in many comparisons, subjects with an $\epsilon 4$ allele had signs of greater atrophy; however, no significant *APOE* effects, either primary or interactive, were observed when age was controlled. On most quantitative MR measures, subjects in the AD, MCI, and clinical disorder not AD groups had significantly more atrophic changes than did control subjects, but they did not differ from one another.

Age, Quantitative MR Findings, and **APOE**

For the analyses that follow, AD, VaD, and MCI subjects were combined, and Figure 2 shows scatter plots representing each data point by subjects' age for brain and hippocampal volumes and VBR. Each panel of the figure also shows two regression lines, representing $\epsilon 4+$ and $\epsilon 4-$ subjects, respectively. Inspection of Figure 2B shows that for $\epsilon 4+$ subjects, hippocampal volume was smallest in those between the ages of 65 and 75 years. The difference was significant (t = 3.92, df = 39, P = .0001). In addition, $\epsilon 4+$ subjects had slightly smaller total brain volume by age, although this difference was not significant. VBR was also greater in $\epsilon 4+$ subjects at younger ages, but two distinct outliers with severe cerebral atrophy were largely responsible for this finding (see Fig 2C). Identical analyses were performed by separating AD, VaD, and MCI subjects into separate groups. When examined independently, no significant findings were observed.

TABLE 3: Brain CSF quantitative MR findings

Sample Size	Control Group		Alzheimer's Disease		Mild Cognitive Impairment		Clinical Disorder, Not Alzheimer's Disease	
	ϵ_{4-} n = 15 Mean (SD)	ϵ_{4+} n = 9 Mean (SD)	ϵ_{4-} n = 25 Mean (SD)	ϵ_{4+} n = 65 Mean (SD)	ϵ_{4-} n = 12 Mean (SD)	ϵ_{4+} n = 27 Mean (SD)	ϵ_{4-} n = 32 Mean (SD)	ϵ_{4+} n = 19 Mean (SD)
CSF	230.19 (86.90)	293.16 (72.66)	365.12 (76.27)	354.30 (82.37)	343.09 (64.39)	313.03 (74.61)	351.45 (99.93)	341.14 (108.85)
IV	1.67 (0.63)	1.58 (0.32)	1.76 (0.62)	1.56 (0.80)	1.40 (0.48)	1.57 (0.75)	1.49 (0.71)	1.66 (0.51)
RTH	0.30 (0.36)	0.61 (0.80)	1.38 (1.37)	1.67 (1.74)	1.36 (1.42)	0.75 (0.79)	1.16 (0.82)	1.22 (0.99)
LTH	0.47 (0.45)	0.62 (0.92)	1.35 (1.20)	1.51 (1.44)	1.26 (1.64)	0.69 (0.62)	0.99 (1.05)	1.49 (1.25)
HORN	0.39 (0.37)	0.62 (0.84)	1.37 (1.21)	1.59 (1.54)	1.31 (1.52)	0.72 (0.66)	1.08 (0.86)	1.35 (1.08)
III	2.12 (0.88)	2.01 (0.74)	2.66 (0.83)	2.40 (0.82)	2.57 (1.05)	2.07 (0.89)	2.47 (0.95)	2.39 (0.81)
LAT	37.76 (21.72)	44.11 (20.89)	65.20 (29.72)	67.03 (32.61)	58.17 (30.01)	55.48 (31.47)	68.74 (32.92)	63.56 (38.13)
TVENT	42.32 (22.65)	48.94 (21.85)	72.35 (32.04)	74.17 (35.47)	64.76 (33.75)	60.55 (33.46)	74.85 (34.79)	70.31 (40.24)
SUBCSF	187.87 (69.31)	244.23 (56.80)	292.76 (59.53)	280.13 (67.20)	278.34 (58.81)	252.48 (57.09)	276.60 (79.19)	270.83 (92.10)

Note.—CSF indicates whole brain cerebrospinal fluid; IV, fourth ventricle; RTH, right temporal horn; LTH, left temporal horn; III, third ventricle; LAT, lateral ventricle; BRAIN, total brain; TVENT, total ventricular volume; SUBCSF, subarachnoid CSF; HORN, average temporal horn volume; HIPP, average hippocampal volume.

LOD, Quantitative MR Findings, **APOE,** *and Diagnostic Classification*

LOD was estimated for AD and VaD subjects. Combining AD and VaD subjects, Figure 3 offers a graphic summation of LOD effects in relation to total brain and hippocampal volumes and VBR by ϵ4 status. For those subjects with disease duration of less than 1 year, hippocampal volume was significantly smaller in ϵ4+ subjects ($t = 2.84$, $df = 6$, $P = .015$). All other comparisons and analyses yielded no significant *APOE* by LOD interaction effects. When AD and VaD subjects were assessed separately, no significant *APOE* $\times$ LOD effect was observed.

Cognitive Performance, Quantitative MR Findings, and **APOE**

To examine the relationship between 3MS examination performance and quantitative MR findings across the four major diagnostic groups, 3MS scores were divided into three groups: $\geq$ 91 (normal range), 71 to 90 (mild to moderate impairment), and $\leq$ 70 (moderate to severe impairment) to provide three levels of cognitive impairment for comparison. Results are summarized in Figure 4. In the majority of comparisons, 3MS performance was inversely related to degree of atrophy. Significant 3MS main effects on total brain volume ($F = 14.27$, $df = 2, 188$, $P = .0001$) and hippocampal volume ($F = 4.04$, $df = 2, 182$, $P = .001$) along with VBR ($F = 12.67$, $df = 2, 188$, $P = .001$) were found. However, there were no significant *APOE* effects.

Discussion

Our population-based study of dementia provides a quantitative description of brain morphology among subjects 65 years and older, all with known *APOE* genotype. As expected, quantitative MR findings showed distinct morphometric differences between healthy control subjects and those with dementia. Dementia, regardless of origin, was generally associated with demonstrable atrophy manifested by smaller brain and hippocampal volumes, along with larger ventricular volume. These observations are consistent with other studies (35, 36, 38–42). Level of cognitive impairment, as measured by 3MS performance, was inversely related to degree of atrophy. Of particular interest in this context was the group with ambiguous impairment or MCI. MCI subjects may be prodromal for AD (63), but at the time of initial assessment they did not meet criteria for diagnosis of AD (or any other dementing illness). As a group, the MCI subjects displayed global atrophic indicators intermediate to those observed in AD or VaD subjects, but distinctly more than those in control subjects. Unlike the AD and VaD subjects, however, the MCI group had hippocampal volumes similar to that of control subjects. For MCI subjects, it may be that structural

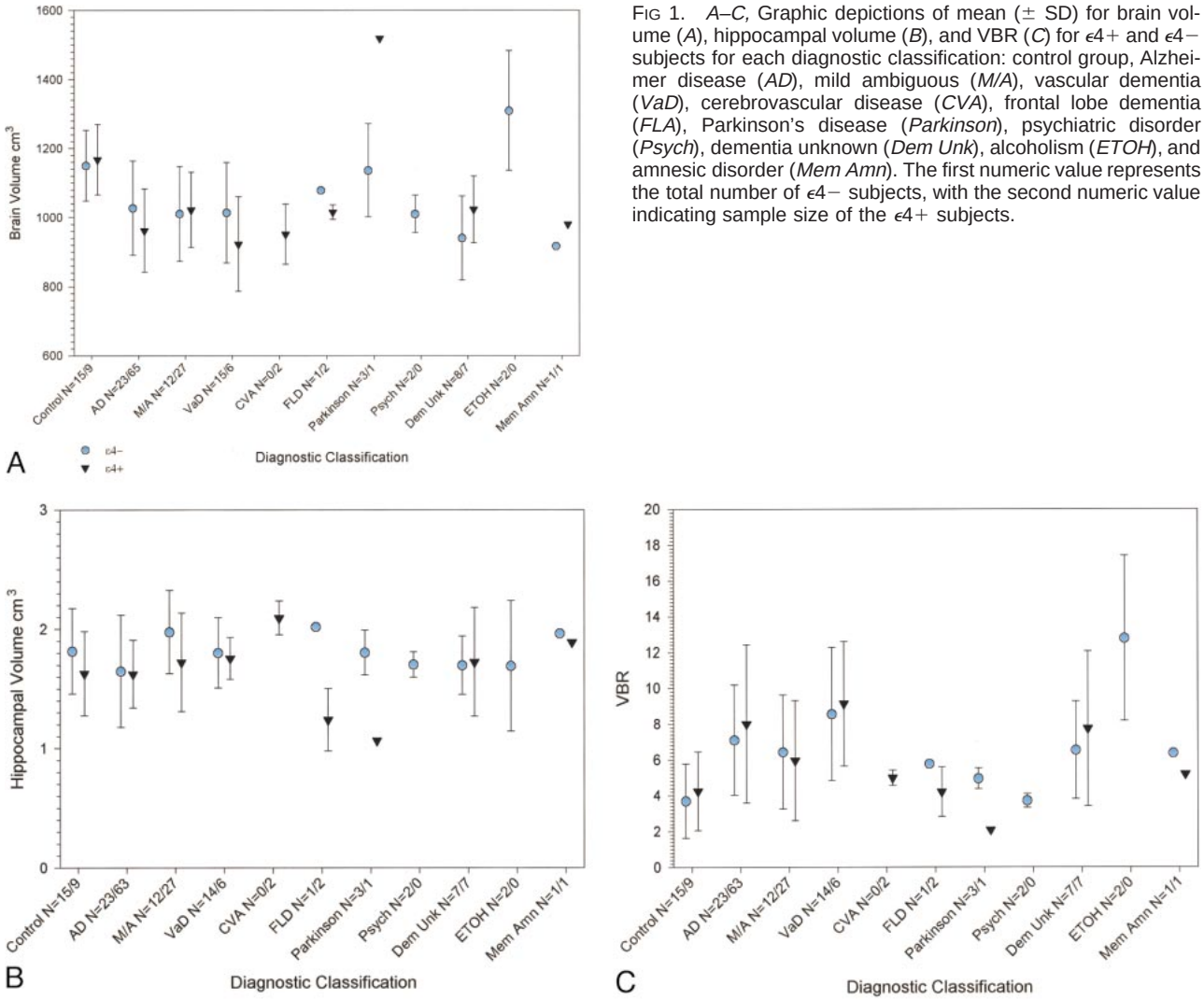

FIG 1. *A–C,* Graphic depictions of mean (± SD) for brain volume (*A*), hippocampal volume (*B*), and VBR (*C*) for ε4+ and ε4− subjects for each diagnostic classification: control group, Alzheimer disease (*AD*), mild ambiguous (*M/A*), vascular dementia (*VaD*), cerebrovascular disease (*CVA*), frontal lobe dementia (*FLA*), Parkinson's disease (*Parkinson*), psychiatric disorder (*Psych*), dementia unknown (*Dem Unk*), alcoholism (*ETOH*), and amnesic disorder (*Mem Amn*). The first numeric value represents the total number of ε4− subjects, with the second numeric value indicating sample size of the ε4+ subjects.

integrity of the hippocampus, even in the context of more global brain atrophy (elevated VBR and decreased brain volume), delays the frank expression of dementia. Recently, Jack et al (63) found that MCI patients who premorbidly had smaller hippocampal volume were more likely to progress to an AD classification (35, 70). Undoubtedly, such subjects are imbedded in our MCI population, and, on follow-up, will most likely meet criteria for AD (such an investigation in this population is currently underway). Taken together, these findings suggest that atrophy is a nonspecific effect of essentially all age-related disorders that may have a component of cognitive impairment or of actual dementia (71, 72). The intactness of the hippocampus may be critical in preserving cognitive status during the preclinical phase of AD.

As anticipated, age effects were apparent in this population of elderly subjects, who ranged from 65 to more than 100 years old (14, 35, 49, 73–75). Increased age was associated with decreased brain and hippocampal volumes along with increased VBR. For hippocampal volume, ε4+ subjects had smaller hippocampi than did ε4− subjects if they were under the age of 75. Over that age, no significant ε4 effect was observed. Likewise, ε4+ subjects who were early in the disease process (ie, 1 year or less) had the smallest hippocampal volumes. Since the AD risk effect of *APOE* may be mediated by age (76, 77), the morphometric change associated with presence of an ε4 allele may be expressed at a younger age and possibly in the mildest stage of illness. Bondi et al (78), Caselli et al (79), and Smith et al (80) found possession of an ε4 allele to be associated with cognitive impairment in nondemented subjects. Plassman et al (43), Reiman et al (8), and Tohgi et al (44) have all found smaller hippocampal volumes in cognitively normal ε4+ individuals. These observations would fit with an early rather than late expression of an *APOE* effect on brain morphology. Clearly, even if there is an early ε4 effect on brain morphology, the current study suggests that once the AD or VaD progresses to full expression or the AD

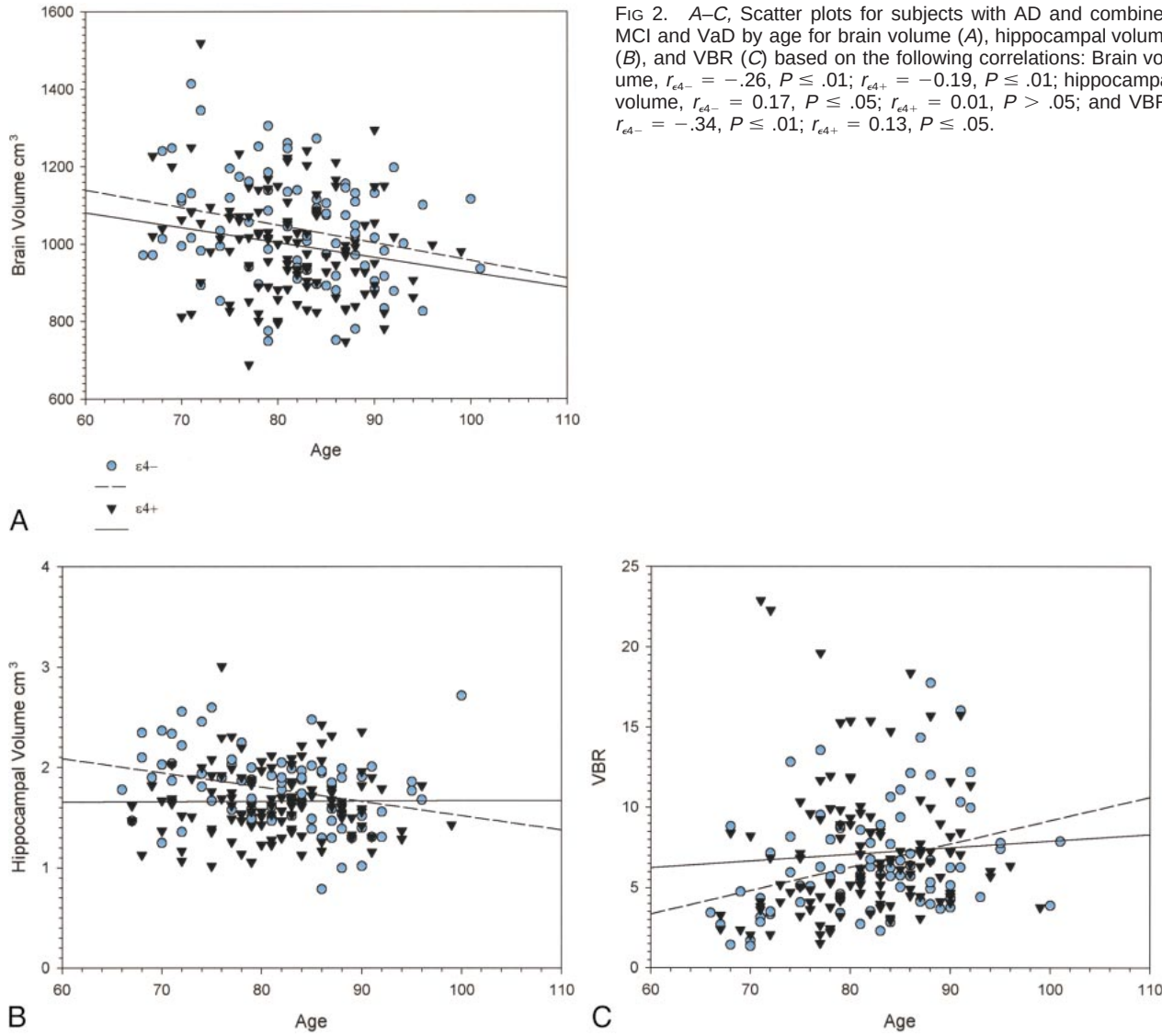

FIG 2. *A–C,* Scatter plots for subjects with AD and combined MCI and VaD by age for brain volume (*A*), hippocampal volume (*B*), and VBR (*C*) based on the following correlations: Brain volume, $r_{\epsilon 4-} = -.26$, $P \leq .01$; $r_{\epsilon 4+} = -0.19$, $P \leq .01$; hippocampal volume, $r_{\epsilon 4-} = 0.17$, $P \leq .05$; $r_{\epsilon 4+} = 0.01$, $P > .05$; and VBR, $r_{\epsilon 4-} = -.34$, $P \leq .01$; $r_{\epsilon 4+} = 0.13$, $P \leq .05$.

or VaD subject is beyond 75 years of age, *APOE* genotype probably does not systematically influence gross brain morphology. Potentially, this is an important finding of this investigation, as it confirms other studies that did not detect an $\epsilon 4$ effect on brain morphology with either advanced age or disease severity, yet raises the possibility of detecting morphologic differences earlier in life or in the disease process. Obviously, additional research is needed.

The standard limitations of the quantitative MR technique always are a concern in data interpretation (65) and must be taken into consideration when reviewing these observations. For example, the lack of effect may be due to measurement error or to insensitivity of the quantitative MR technique in discriminating hippocampal disease at the microstructural level (65). For instance, the segmentation method used to assess hippocampal volume is merely a global measure of hippocampal anatomy. While volume is related to neuronal cell count (81), it is nonetheless a crude measure of hippocampal integrity. Thus, the real proof of any *APOE* effect at the hippocampal level (or within any other brain structure) must await histologic examination or additional sensitive neuroimaging analyses of the hippocampus; eg, with high-resolution MR imaging, functional MR imaging, or spectroscopy (82, 83).

Another limitation is that the current study was not longitudinal. Since presence of $\epsilon 4$ confers increased risk and earlier onset of AD, any potential *APOE* effect on brain morphology may only be seen in the earliest stage of the disease (maybe even prodromally) and may only be discovered by tracking quantitative MR findings in the at-risk population from prodromal stages through diagnosis of dementia. Such longitudinal investigations combined with regional analyses (4, 5, 9, 83–86), in particular, hippocampal volume in the context of other temporal lobe morphologic measures (63, 72, 83), may be critical in establishing any *APOE* ef-

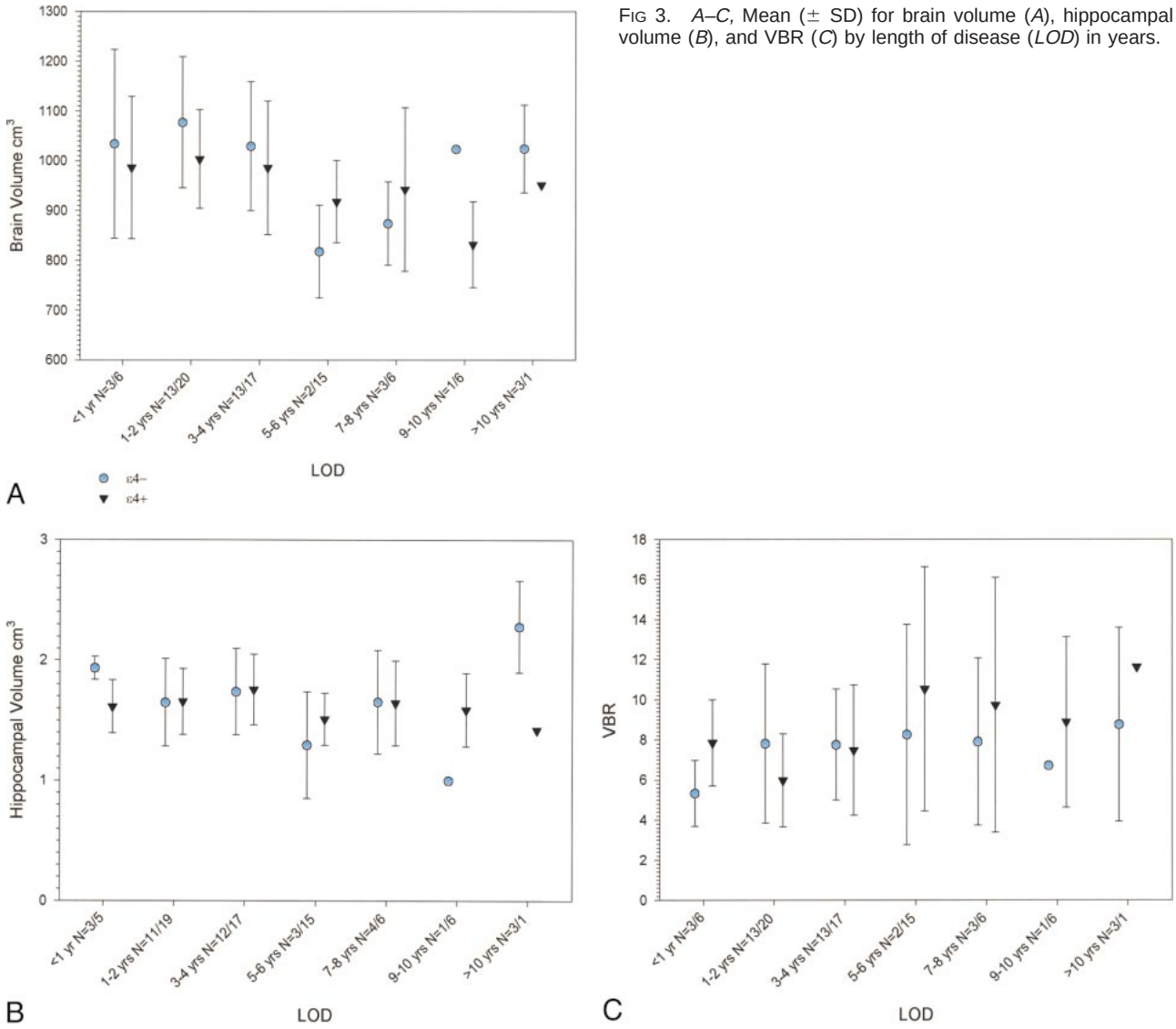

FIG 3. *A–C*, Mean (± SD) for brain volume (*A*), hippocampal volume (*B*), and VBR (*C*) by length of disease (*LOD*) in years.

fects that can be determined by neuroimaging analysis.

Like other epidemiologic studies of dementia, the Cache County study shows an enhanced risk and younger age of AD onset in subjects who possess at least one copy of the ϵ4 allele (50). Several lines of evidence point to a role of *APOE* in neuronal maintenance and repair (77, 87, 88), and a number of studies have shown that the presence of the ϵ4 allele is associated with development of β-amyloid and neurofibrillary tangles (24, 89–91). Additionally, the ϵ4 allele at *APOE* may be associated with vascular angiopathy (30) and ischemic vascular disease (92); hence, the relationship between *APOE* ϵ4 and VaD. Heuristically, the presence of the ϵ4 allele, if it is associated with some form of impaired neuronal maintenance, could be a pathologic factor associated with the development of AD and VaD (59). However, while this as well as other epidemiologic studies have shown age-related *APOE* effects, more than half the Cache County population of elderly who had an ϵ4 allele did not develop AD by age 100. Obviously, other factors in addition to *APOE* genotype participate in the development of AD (27, 28, 31), such as other susceptibility genes (93) or environmental modifiers (eg, head injury) (94, 95). The overriding finding of this investigation is that once dementia is expressed, *APOE* genotype does not appear to play a unique or major role in the degree of cerebral atrophy.

Yasuda et al (20) made an interesting observation in a cross-sectional, clinical sample of AD subjects recruited from a hospital dementia service in Japan. While all subjects with AD had significantly reduced brain volume as compared with control subjects, AD subjects with ϵ4/4 genotype actually had the least degree of brain atrophy. These investigators interpreted this observation to mean that ϵ4+ subjects incurred the disease early and, owing to their relatively young age, the ravages of a degenerative disease interacting with age had not

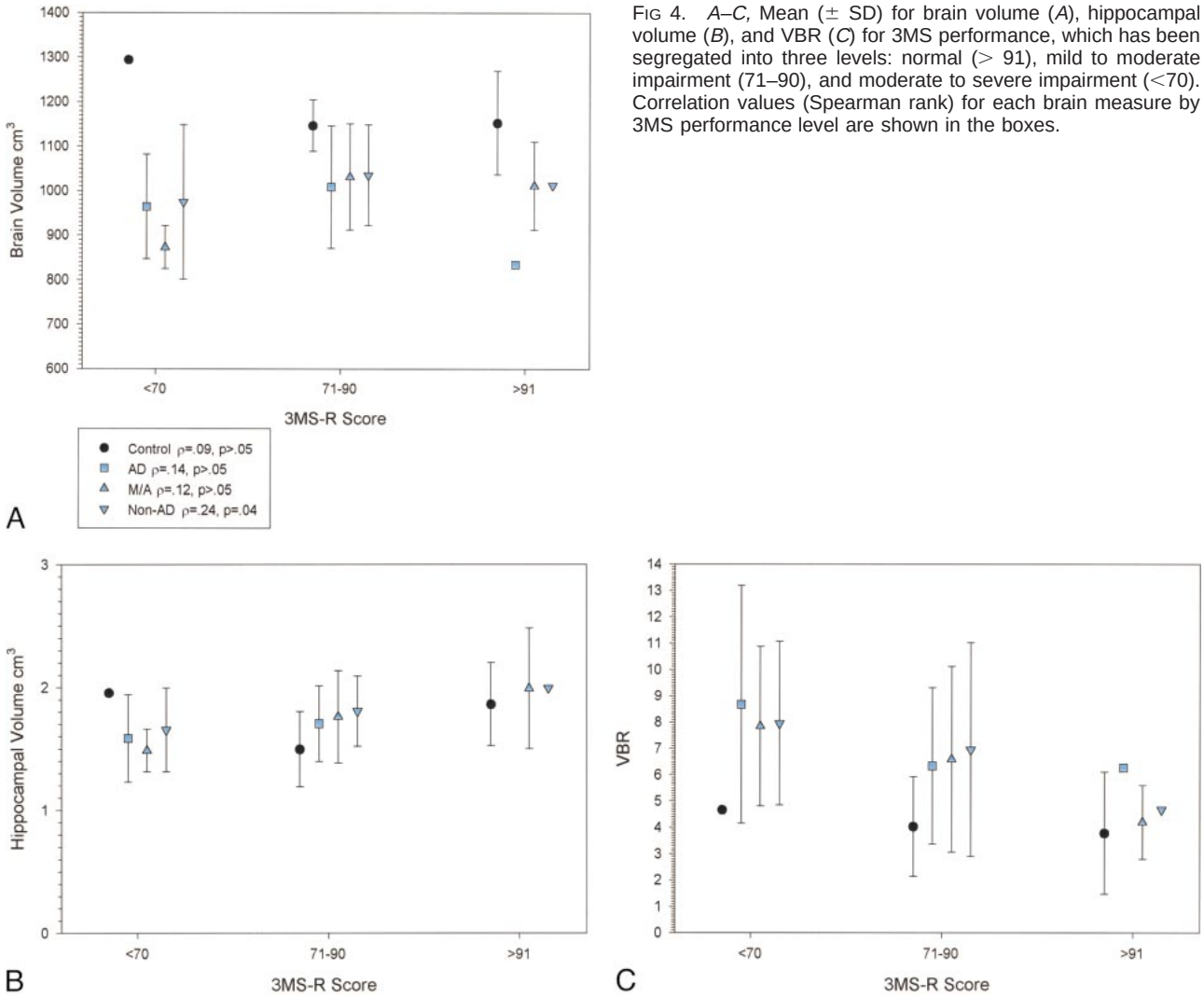

FIG 4. *A–C,* Mean (± SD) for brain volume (*A*), hippocampal volume (*B*), and VBR (*C*) for 3MS performance, which has been segregated into three levels: normal (> 91), mild to moderate impairment (71–90), and moderate to severe impairment (<70). Correlation values (Spearman rank) for each brain measure by 3MS performance level are shown in the boxes.

reached their peak. Hence, there was less atrophy in these younger ϵ4+ AD subjects. Yasuda et al used a sample of convenience, and the mean age of their ϵ4/4 subjects was 70 years. In contrast, the ϵ4+ group in the Cache County study, while younger (see Table 1) than the ϵ4− subjects, were considerably older (mean age, 80+ years) than the subjects studied by Yasuda et al (20). Although symptom duration was reported, the volumetric findings in the study by Yasuda et al were not analyzed by disease duration. Jack et al (5), controlling for disease duration, found no difference in hippocampal volume between ϵ4+ and ϵ4− AD subjects.

Conclusion

We found generalized atrophy to be ubiquitous across all forms of dementia and associated disorders investigated in this population-based study. A subtle *APOE* ϵ4 effect may be present early in the AD and/or VaD disease process, wherein quantitative MR analysis of hippocampal volume shows greater hippocampal atrophy. However, once an individual is advanced in age or in progression of disease, any *APOE* effect on gross brain morphology is mitigated. Accordingly, there appear to be no lasting morphologic effects detected by quantitative MR imaging that are associated with presence or absence of the ϵ4 allele. This observation is consistent with other recent reports (36, 37). In addition, degree of brain atrophy is inversely related to 3MS performance, irrespective of *APOE* genotype.

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