

Perceived Loss of Memory Ability and Cerebral Metabolic Decline in Persons With the Apolipoprotein E-IV Genetic Risk for Alzheimer Disease

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Context: Concerns about age-related memory loss are greater in persons who have the apolipoprotein E-IV (*APOE4*) genetic risk for Alzheimer disease, but the correlation between the degree of concerns and future cerebral metabolic decline is unknown.

Objective: To investigate whether the degree of self-perceived memory loss is associated with regional cerebral metabolic decline.

Design: Longitudinal study.

Setting: Aging and Memory Research Center, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles.

Participants: Thirty right-handed, cognitively intact, middle-aged and older adults (age range, 50-82 years) with age-associated memory complaints, 14 of whom were carriers of the *apolipoprotein E-IV* allele, were recruited for longitudinal study.

Main Outcome Measures: At baseline, we administered a standardized neuropsychological battery and assessed self-appraisal of memory functioning using the Memory Functioning Questionnaire, which yields 4 factor scores indicating frequency of forgetting, serious-

ness of forgetting, retrospective functioning, and mnemonics use. Regional cerebral glucose metabolism was determined using fluorodeoxyglucose F18-positron emission tomography at baseline and after 2 years.

Results: At baseline, *APOE4* carriers and noncarriers did not differ significantly on objective memory measures or on Memory Functioning Questionnaire factor scores. However, the factor score for frequency of forgetting significantly correlated with global cerebral metabolic decline in all subjects regardless of *APOE4* genetic risk ($P=.01$). By contrast, the factor score for mnemonics use significantly correlated with metabolic decline in the temporal regions in *APOE4* carriers but not in noncarriers ($P=.03$).

Conclusions: The degree of perceived memory loss correlates with subsequent global cerebral metabolic decline for *APOE4* carriers and noncarriers; hence, memory complaints may reflect underlying cerebral metabolic changes. Compensatory strategies, as reflected by more frequent mnemonics use in *APOE4* carriers, may reflect underlying metabolic changes in the brain regions associated with prodromal Alzheimer disease. Self-reported mnemonics use may be helpful in identifying persons for clinical monitoring.

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MEMORY COMPLAINTS ARE common in middle-aged and older adults. In community-based studies, the prevalence of subjective memory complaints ranges from 22%^{1,2} to 56%,³ but rates may vary depending on the type of surveying, the affective status, and the demographics or composition of the sample.⁴

Memory complaints of patients are often brought to the attention of a physician, but whether increasing complaints signal future objective cognitive decline or dementia is controversial. Although the results of some longitudinal studies⁵⁻¹¹ indicate that memory complaints are associated with fu-

ture cognitive decline or dementia, the results of other studies^{3,12-17} do not. Discrepancies can be attributed to methodological factors, study design, and control of variables commonly associated with cognitive complaints or cognitive decline, such as age, education, and depression.^{3,4,7} Baseline cognitive functioning,^{5-7,16} psychological distress,¹⁵ physical deficits,³ and recency of onset of subjective memory complaints⁵ correlate with cognitive decline, sometimes more so than subjective memory complaints. The relationship between subjective memory complaints and change in cognition may vary as a function of ethnicity.³ The predictive validity of subjective memory complaints may depend on the sen-

sitivity of objective tests¹⁶ and on the extent to which objective tests measure the types of everyday difficulties assessed by subjective memory complaint measures.¹⁸

Physiological indexes of brain function or biological (genetic) markers for dementia risk offer an alternative approach to assessing the predictive validity of memory complaints. Few investigations have addressed the association between memory complaints and underlying brain function, but in one such study¹⁹ the patterns of cerebral activation during functional magnetic resonance (MR) imaging distinguished between diagnostic groups with subjective memory complaints. An association between subjective reports of increased use of memory aids and resting-state frontal lobe glucose metabolism in nondemented older adults has been found.^{20,21}

One biological marker of dementia that may be useful in assessing the predictive validity of memory complaints is the apolipoprotein E-IV (*APOE4*) allele. Possession of *APOE4* is a major risk factor for sporadic and familial late-onset²² and early-onset²³ Alzheimer disease (AD). *APOE* has 3 allelic variants (variants 2, 3, and 4) and 5 common genotypes (genotypes 2/2, 2/3, 3/3, 3/4, and 4/4). Possession of *APOE4* confers increased risk for AD in a dose-related fashion,²⁴ while possession of *APOE2* confers protection.²⁵

Several investigations have identified a relationship between *APOE4* genetic risk and cognitive complaints with respect to family history of AD,²⁶ depression,^{27,28} and cognition.^{29,30} Findings from a previous study²⁸ suggest that memory complaints in *APOE4* carriers may reflect underlying neurobiological determinants.

To our knowledge, no previous study has examined whether the degree of subjective memory complaints among nondemented persons with memory complaints is associated with future brain metabolic decline according to *APOE4* genetic risk. We investigated whether the degree of subjective memory complaint, as measured by Memory Functioning Questionnaire (MFQ) factor scores,³¹ *APOE4* genetic risk, and their interaction, were associated with regional cerebral metabolic decline in 30 nondemented persons who were followed up longitudinally.

METHODS

SUBJECTS

The 30 subjects were drawn from a larger longitudinal study³² of predictors of cognitive decline. Subjects were recruited irrespective of family history of AD and memory complaints. To increase the likelihood of obtaining *APOE4* carriers, some advertisements and physician referrals emphasized middle-aged and older persons with memory complaints and family histories of dementia in a first-degree relative. Subjects received neurological and psychiatric evaluations and routine screening laboratory tests to rule out treatable causes of cognitive impairment or potential cognitive confounding factors (eg, severe sensory deficits or nonpsychotropic medication interactions). All subjects were proficient in the English language. A neuropsychological battery was administered to quantify cognitive performance and to confirm the absence of a diagnosis of dementia or mild cognitive impairment.^{33,34} The 17-item Hamilton Rating Scale for Depression³⁵ was administered to assess mood.

Of 573 volunteers, we excluded 520 for various reasons (eg, medication use, concurrent use of psychotropic medications, con-

current medical or psychiatric illness, dementia or mild cognitive impairment, unclear or ambiguous family history of dementia, and presence of a neurological, medical, or major psychiatric condition that could affect memory or cognitive processing). Of the remaining 53 subjects, 35 returned for follow-up, but only 30 subjects had complete MFQ data. The other subjects did not return for follow-up for several reasons (eg, they were lost to follow-up, declined participation, developed exclusionary medical conditions, or started exclusionary medications).

We conducted an attrition analysis to determine if the 30 subjects who completed the study differed on demographic variables or on cognitive test results from the 23 subjects who did not complete the study. We found that the 2 groups did not differ significantly in age, sex, educational achievement, cognitive measures, or *APOE* genotype.

The final sample of subjects ranged in age from 50 to 82 years and was stratified according to *APOE4* genetic risk. Of the 30 subjects (27 white and 3 Asian), 14 were *APOE4* carriers and 16 were noncarriers. All *APOE4* carriers had the *APOE* 3/4 genotype. Of the 16 *APOE4* noncarriers, 2 had the *APOE* 2/3 genotype and 14 had the *APOE* 3/3 genotype. After complete description of the study to participants, we obtained written informed consent.

DNA ANALYSIS

We obtained DNA from blood samples. *APOE* genotypes were determined using standard techniques as previously described.²²

OBJECTIVE AND SUBJECTIVE MEMORY TESTS

A neuropsychological battery was administered to subjects as previously described,³² but we included only the objective tests of verbal and nonverbal memory for the present analyses. We included tests of immediate and delayed paragraph recall³⁶ (Wechsler Memory Scale-Revised logical memory), word list learning (Buschke-Fuld Selective Reminding Test total recall),³⁷ figure learning (Benton Visual Retention Test),³⁸ and delayed figure recall (Rey-Osterrieth Complex Figure).³⁹ We evaluated gross cognitive functioning using the Mini-Mental State Examination.⁴⁰

We assessed self-appraisal of everyday memory functioning using the MFQ, a popular instrument with high internal consistency and moderate concurrent validity with memory performance measures.⁴¹ The MFQ consists of 64 items rated on a 7-point scale and provides 4 unit-weight factor scores measuring frequency of forgetting, seriousness of forgetting, retrospective functioning (changes in current memory ability relative to earlier life), and mnemonics use (memory support techniques, mostly including external aids such as calendars and appointment books). Higher scores indicate higher (more favorable) levels of perceived memory functioning.

NEUROIMAGING

Subjects underwent positron emission tomography (PET) as previously described.^{42,43} In brief, they were imaged in the supine position with low ambient noise, and their eyes and ears were unoccluded. Intravenous lines were placed 10 to 15 minutes before tracer injection of 10 mCi of fluorodeoxyglucose F18. All imaging was performed 40 minutes after fluorodeoxyglucose F18 injection using the CTI/Seimens 831-08 EXACT HR (Seimens Corp, Hoffman Estates, Ill) or the CTI 962 EXACT HR+ scanner (15-63 image planes), and the duration of PET was 40 minutes. We acquired images of 21 subjects at baseline and follow-up using the 962 scanner; images of the 9 remaining subjects were acquired using the 831 scanner at baseline and the 962 scanner at follow-up. Because 2 scanners were used

to acquire images (because of scanner availability), computed tomographic images were reconstructed and axially smoothed to give comparable spatial resolution (full width at half-maximum, 0.65 cm in the axial plane and 0.8 cm in the image plane). The procedure has been previously described.³² Because the images from both scanners were reconstructed to have the same spatial resolution and because the same procedure was used for attenuation correction, no systematic differences are expected between images obtained from these 2 scanners. At baseline, 21.4% (3/14) of *APOE4* carriers and 37.5% (6/16) of *APOE4* noncarriers were imaged using the 831 scanner. At follow-up, all subjects were imaged using the 962 scanner. Images were acquired parallel to the canthomeatal line; a transmission measurement was used for attenuation correction.

Baseline brain MR images were obtained using a 1.5-T magnet or a 3-T magnet (General Electric MR Signa; General Electric Medical Systems, Milwaukee, Wis). At baseline, 21.4% (3/14) of *APOE4* carriers and 31.3% (5/16) of *APOE4* noncarriers were imaged using the 3-T magnet. At follow-up, all subjects were imaged using the 3-T magnet. Thirty-six transaxial planes were collected throughout the brain volume, superior to the cerebellum. For MR imaging registration (using PET for anatomical metabolic data localization with reference to individual structural anatomy), we acquired a dual-echo, fast spin-echo series using a 24-cm field of view and a 256 × 256-pixel matrix with 3-mm section thickness with no gaps between sections (repetition times, 6000 milliseconds [3-T magnet] and 2000 milliseconds [1.5-T magnet]; echo times, 17 milliseconds [first echo] and 85 milliseconds [second echo] [3-T magnet] and 30 milliseconds [first echo] and 90 milliseconds [second echo] [1.5-T magnet]). An intermodality image coregistration program⁴⁴ that performs image segmentation and simulation as preprocessing procedures was used to coregister PET and baseline MR images of each subject. Region of interest (ROI) analyses were then performed.

ROI ANALYSIS

Two persons blinded to clinical diagnosis and genotype manually drew the ROI in the axial plane on registered MR images for each subject. We assessed interrater reliability for the 2 persons drawing the ROIs by calculating the spatial overlap of ROIs drawn twice for 10 subjects to ensure that the mean ± SD reliability was 0.85 ± 0.04 or higher.

We designated rules for ROI drawing based on the identification of sulcal and gyral landmarks using the atlas of Talairach and Tournoux.⁴⁵ As previously described,³² the ROIs pertaining to memory processing and AD involve the right and left hemispheres and comprise the following: (1) the inferoparietal cortex (bounded anteriorly by the postcentral sulcus, superiorly by the intraparietal sulcus, inferiorly by the Sylvian fissure, and posteriorly by the antero-occipital sulcus), (2) the posterior cingulate cortex (surrounded by the cingulate sulcus posterior to the corpus callosum [retrosplenial region]), (3) the dorsolateral prefrontal cortex (defined by the middle frontal gyrus and the gray matter surrounding the inferofrontal sulcus and corresponding approximately to Brodmann areas 9 and 46), (4) the inferotemporal cortex (surrounding the inferotemporal sulcus at the base of the temporal lobes), (5) the superotemporal cortex (located immediately posterior to the transverse temporal gyri, from the Sylvian fissure to the superotemporal sulcus), and (6) the mediotemporal cortex (defined by the section through the center of the long axis of the hippocampus that included the amygdala, hippocampus, and parahippocampal gyrus). All ROIs were identified in their entirety, but for each region we located the middle section across planes that best represented the ROI for each subject, to avoid partial volume effects and difficulties with bound-

ary demarcations between subjects. The whole-brain ROI, drawn manually around the brain on each axial plane, included cortex, subcortical gray matter, and the midbrain to the level of the pons and excluded the cerebellum.

Exclusion of white matter from the ROIs was done first by segmentation, then manually by tightly adhering to gray matter while drawing the ROI boundaries, and then by thresholding. For thresholding, only the pixel values within 30% of the maximal pixel value within each ROI were used when calculating the mean ROI values. The choice of the 30% threshold was made as a compromise between the need to minimize the effects of the statistical noise of the image and the variability of ROI drawing on the calculated ROI values.⁴⁶ The ROI values were normalized to the whole-brain value at that same level. Investigators (L.E., P.S., and S.-C.H.) blinded to clinical and genetic findings analyzed the image data.

Written informed consent was obtained in accord with the procedures set by the UCLA Human Subjects Protection Committee. Genetic test results were not released to participants.

STATISTICAL ANALYSIS

We screened data for outliers and violations of normality assumptions. *t* Tests and χ^2 tests were performed for comparisons of *APOE4* carriers and noncarriers on demographics, clinical variables, and MFQ factor scores (frequency of forgetting, seriousness of forgetting, retrospective functioning, and mnemonics use).

To study the associations between the 4 MFQ factor scores and changes on the 5 objective memory tests for *APOE4* carriers and noncarriers, we performed separate univariate analyses of variance, with change scores (follow-up scores minus baseline scores) for each memory test as the dependent variable. The MFQ factor scores, *APOE4* genetic risk, and their interaction were the independent variables. Age was a covariate in all analyses. Given the relationship between depression and subjective memory, we also controlled for depressive severity by including the Hamilton Rating Scale for Depression scores as covariates in all analyses. All tests were 2-tailed, and in follow-up univariate analyses we adopted a significance level of $P = .05$ after Bonferroni correction.

To study the associations between MFQ factor scores and metabolic changes (follow-up rates minus baseline rates), we computed a repeated-measures analysis of covariance with *APOE4* genetic risk as the intersubject classification variable and the ROIs (left and right) of each of the following regions as the intrasubject classification variable: dorsolateral prefrontal cortex, posterior cingulate cortex, inferoparietal cortex, and temporal cortex (mean of the mediotemporal, inferotemporal, and superotemporal regions). Separate models were fitted for each of the MFQ factor scores. Each factor score and its interaction with *APOE4* genetic risk were used as the independent variables in the repeated-measures analysis of variance. Age, educational achievement, and Hamilton Rating Scale for Depression scores were used as covariates. All tests were 2-tailed, and we adopted a significance level of $P = .05$.

RESULTS

Table 1 summarizes the demographic and clinical information. Baseline comparisons of *APOE4* carriers and noncarriers indicated no significant differences in age, sex, educational achievement, family history of AD, or Hamilton Rating Scale for Depression scores. The *APOE4* carriers and noncarriers did not differ significantly on objective memory test scores or on MFQ factor scores

Table 1. Baseline Demographic and Clinical Characteristics for Subject Groups*

Characteristic	APOE4 Allele Carriers (n = 14)	APOE4 Allele Noncarriers (n = 16)
Age, y	63.9 ± 9.8	66.6 ± 8.6
Education, y	15.3 ± 2.5	16.2 ± 2.9
Female sex, No. (%)	8 (57.1)	8 (50.0)
Mini-Mental State Examination score	28.6 ± 1.2	29.2 ± 1.1
Hamilton Rating Scale for Depression score	4.2 ± 2.8	3.1 ± 2.4
Alzheimer disease family history, No. (%)	9 (64.3)	7 (43.8)

Abbreviation: APOE4, apolipoprotein E-IV.

*Data are given as mean ± SD unless otherwise indicated.

(**Table 2**) at baseline. Although the groups did not differ significantly in age or baseline test performances, given the relationship between APOE4 genetic risk and age, we addressed the possibility that the slightly younger APOE4 carriers may have been mildly cognitively impaired compared with noncarriers. We conducted analyses of variance to determine if there was an interaction effect of age × APOE4 genetic risk on the results of the baseline memory tests and the Mini-Mental State Examination. Our findings indicated no significant interactions between age and genetic risk for any of these measures.

The APOE4 carriers and noncarriers did not differ significantly in baseline cerebral metabolism for any ROI (Table 2). After Bonferroni correction, there were no significant declines in regional metabolism in either genetic risk group after 2 years. For APOE4 noncarriers, only the right dorsolateral prefrontal cortex demonstrated a 2% decline after 2 years ($P = .04$), which was nonsignificant after Bonferroni correction.

The univariate analyses of variance examining the relationship between subjective memory complaints and objective memory test result changes showed that none of the MFQ factor scores was associated with memory test changes for either APOE4 genetic risk group. The repeated-measures analyses of covariance examining the relationship between subjective memory complaints and metabolic changes showed that frequency of forgetting was significantly correlated with global cerebral metabolic decline ($F_{1,23} = 8.34$, $P = .01$) regardless of APOE4 genetic risk (**Figure A**). With increasing complaints of frequency of forgetting, glucose metabolism (after 2 years) decreased in all regions. Furthermore, we found a significant interaction between mnemonics use and APOE4 genetic risk ($F_{1,23} = 5.47$, $P = .03$) with regional cerebral metabolic decline, which differed among APOE4 carriers vs noncarriers. For APOE4 carriers only, increased mnemonics use was significantly associated with a decline in cerebral metabolism over time ($t_{23} = 2.24$, $P = .03$).

We conducted separate analyses for the temporal, parietal, dorsolateral prefrontal, and posterior cingulate regions to assess which ROIs were associated with subjective memory complaints. The ROIs were averaged over the left and right hemispheres. For APOE4 carriers, increased mnemonics use at baseline was associated with

Table 2. Baseline Test Scores for Subject Groups*

Measure	APOE4 Allele Carriers (n = 14)	APOE4 Allele Noncarriers (n = 16)
Memory Functioning Questionnaire		
Frequency of forgetting	150.5 ± 30.7	160.1 ± 33.6
Seriousness of forgetting	77.9 ± 21.2	82.4 ± 25.2
Retrospective functioning	14.7 ± 5.1	14.8 ± 4.1
Mnemonics use	25.5 ± 10.2	25.5 ± 8.5
Objective memory tests		
Buschke-Fuld Selective Reminding	96.6 ± 15.4	98.9 ± 19.7
Test total recall		
Wechsler Memory Scale-Revised	19.5 ± 7.4	21.7 ± 7.0
Logical Memory delayed†		
Benton Visual Retention Test errors	4.1 ± 1.9	4.9 ± 3.1
Rey-Osterrieth Complex Figure recall	18.3 ± 5.9	20.6 ± 6.2
Region of interest metabolism‡		
Temporal§	0.88 ± 0.03	0.88 ± 0.04
Inferoparietal	0.97 ± 0.04	0.98 ± 0.03
Dorsolateral prefrontal	1.00 ± 0.06	1.01 ± 0.04
Posterior cingulate	1.19 ± 0.05	1.20 ± 0.08

Abbreviation: APOE4, apolipoprotein E-IV.

*Data are given as mean ± SD.

†For APOE4 carriers, n = 13; for APOE4 noncarriers, n = 15.

‡Averaged over the left and right hemispheres.

§Mean of the mediotemporal, inferotemporal, and superotemporal regions.

metabolic decline in the temporal ROIs, while for APOE4 noncarriers there was no such association ($F_{1,23} = 4.53$, $P = .04$) (Figure B). No other MFQ factor score main effects or MFQ factor score × APOE4 genetic risk interactions reached statistical significance.

To assess scanner comparability, we reran the analyses with only the 21 subjects who were imaged using the same scanner at both periods. We found a significant relationship between greater complaints of frequency of forgetting at baseline and global decline over time for all subjects ($t_{14} = -14.7$, $P < .001$). A trend toward an association between greater mnemonics use at baseline and temporal lobe metabolic decline was found only for APOE4 carriers ($t_{14} = -1.8$, $P = .09$). Overall, the findings suggest that scanner differences did not affect the study results.

To ensure homogeneous group comparisons, we reran all analyses comparing only subjects having the APOE 3/3 genotype with subjects having the APOE 3/4 genotype. All results were identical to those conducted with the full sample.

At the time of the follow-up assessment, 1 subject was taking antidepressant medications. Analyses were rerun excluding this individual, and the findings were identical.

COMMENT

To our knowledge, the present findings are the first to indicate that the degree of self-awareness of memory difficulties is associated with longitudinal declines in underlying cerebral metabolism, as measured using fluorodeoxyglucose F18-PET. Complaints of greater frequency of forgetting at baseline are associated with global cerebral metabolic decline at follow-up for all subjects regardless of APOE4 genetic risk. Self-reports of increased use of compensatory memory strategies (ie, mnemonics use) corre-

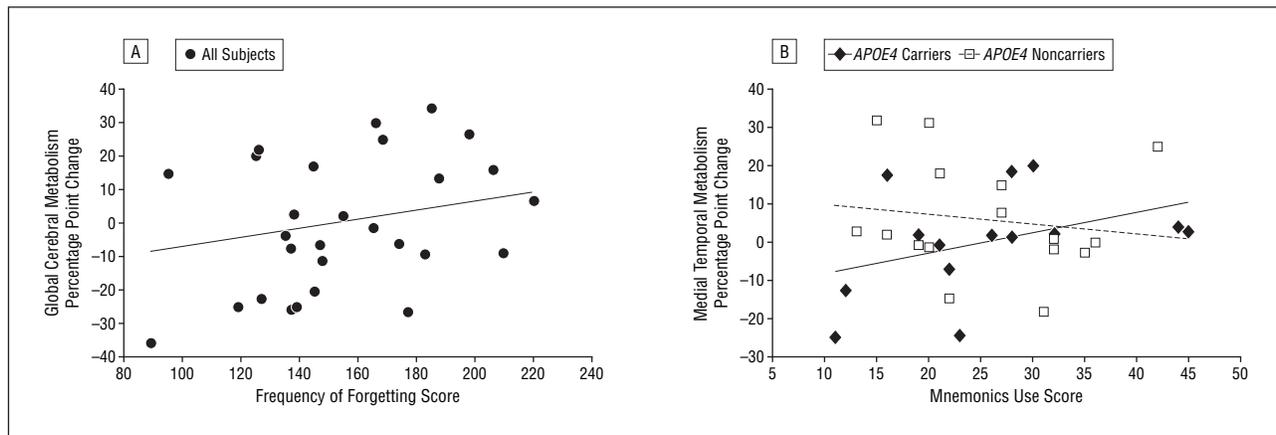


Figure 2. Correlation of baseline Memory Functioning Questionnaire factor scores with percentage point changes in cerebral metabolism over 2 years. A, A significant correlation between a higher degree of frequency of forgetting and percentage point decline in global cerebral metabolism was found for all subjects regardless of apolipoprotein E-IV (*APOE4*) genotype. B, A significant interaction was found between mnemonics use and *APOE4* status on percentage point change in medial temporal metabolism. For only *APOE4* carriers, greater mnemonics use was significantly associated with a decline in medial temporal metabolism.

late with glucose metabolic decline in the temporal brain regions in *APOE4* carriers but not in noncarriers. The findings suggest that the correlation between complaints of frequent forgetting and global decreases⁴⁷ in cortical metabolism is related to normal aging and not to underlying *APOE4* genetic risk of AD, as it was previously found that prefrontal decreases⁴⁸ occur in normal aging as well.

In contrast, the association between increasing mnemonics use and temporal metabolic decline suggests an awareness of underlying physiological deficits related to dementia risk. The temporal ROIs, which included medial temporal lobe and lateral temporal association cortices, are areas that subservise memory functions⁴⁹⁻⁵¹ and demonstrate neuropathological changes in preclinical and early AD.^{52,53} The temporal or temporal-parietal regions are among the earliest areas that demonstrate hypometabolism^{54,55} or hypoperfusion⁵⁶ in persons with AD, in unaffected relatives of persons with familial AD,⁵⁷ in unaffected monozygotic cotwins of persons with AD,⁵⁵ and in nondemented *APOE4* carriers.^{32,58} In longitudinal investigations, hypometabolism in the medial temporal, lateral temporal, or temporal-parietal regions has predicted the conversion of isolated memory impairment or mild cognitive impairment to AD,^{59,60} and *APOE4* carriers with declining cognitive function demonstrate temporal neocortical reductions in glucose metabolism.⁶¹ The prognostic implications would have been stronger if *APOE4* carriers in the present study had demonstrated objective cognitive impairment relative to noncarriers; however, carriers were highly educated, and neuropsychological tests may be less sensitive to subtle declines in such persons because of their high levels of cognitive reserve.⁶² In addition, neocortical hypometabolism may precede objective memory deficits because of the brain's compensatory abilities or cognitive reserve,⁵⁴ and it follows that such hypometabolism may have been ongoing in our *APOE4* carriers at the time of their enrollment in this study, although there were no significant group differences in baseline regional metabolism. Therefore, it is possible that persons with a genetic risk for AD may notice cognitive decline and use mnemonics to compensate for real memory changes before objective clinical detection.

Our results suggest differential predictive validity for metabolic decline depending on the type of memory complaint. In parallel, previous research indicates that some types of subjective memory self-ratings are more predictive of objective memory test performance than others.⁶³

The present study expands on previous investigations of subjective memory complaints and underlying brain function in persons at risk for cognitive decline. Patterns of activation involving the lateral and medial temporal regions during performance of an episodic memory task, as assessed by functional MR imaging, distinguished between persons with memory complaints with early AD or major depression and healthy controls without memory complaints.¹⁹ The patients with AD demonstrated decreased activation in the medial, mid, and lateral temporal regions compared with controls, particularly in the right hippocampus, compared with patients with major depression. Previous cross-sectional studies^{20,21} examined the relationship between MFQ factor scores and cerebral metabolism in a sample of persons with and without a family history of AD who had age-associated memory impairment. Consistent with the present findings, group differences in resting-state regional cerebral glucose metabolism and memory measures were minimal. Few objective memory measures correlated with metabolic rates. Less frequent mnemonics use correlated with increased frontal metabolic activity, suggesting that memory complaints may be a more sensitive indicator of decreased frontal lobe activity than objective memory tests. In the previous cross-sectional studies,^{20,21} *APOE4* genetic risk was not a variable, which may explain why the present study did not replicate the frontal metabolic finding. Overall, the present results are consistent with previous findings that subjective memory complaints are sensitive indicators of underlying brain function and extend the findings to support that memory complaints are associated with regional glucose metabolic decline in *APOE4* carriers.¹⁹⁻²¹

In the present study, *APOE4* carriers did not differ significantly from noncarriers in subjective memory complaints, which was inconsistent with some previous reports. The *APOE4* allele may be overrepresented in persons with memory complaints and a family history of AD,²⁶ in

persons with memory complaints and age-related cognitive decline,²⁹ and in older depressed adults.²⁷ In the present study, family histories of dementia were not significantly different between *APOE4* carriers and noncarriers, subjects in the present investigation were less cognitively impaired (mean Mini-Mental State Examination score, >28.5) compared with persons with age-related cognitive decline in the study by Blesa et al²⁹ (mean Mini-Mental State Examination score, 24.4), and our subjects were not depressed. In another study³⁰ of *APOE4* carriers, subjective memory complaints were associated with accelerated cognitive decline on a test assessing the speed of information processing but not on tests of immediate or delayed recall. In the present study, *APOE4* carriers and noncarriers did not differ in the prevalence of memory complaints or in the rate of decline on tests of immediate or delayed memory. Findings in a previous cross-sectional study⁶⁴ among a slightly larger overlapping sample demonstrated that *APOE4* carriers had significantly more complaints about retrospective functioning than noncarriers. Discrepancies may be due to sample composition and uncorrected statistical test results in the previous study. As emphasized in the previous study,^{64(p1037)} although results were statistically significant, group differences on the MFQ factor scores were small, and 95% confidence intervals for the means overlapped between groups.

There are several limitations of the present study. The sample was not representative of the general clinical population, as most subjects were highly educated and white. Only 30 (5.2%) of 573 persons who volunteered for the study were included. Volunteers with other possible health risk factors for cognitive impairment, including those that may interact with the *APOE4* genetic risk to increase the risk for dementia (eg, cerebral vascular disease), were excluded. It is possible that very mild cases of dementia were undetected, which may have affected metabolic rate findings, although detailed screenings were conducted at baseline to rule out dementia or mild cognitive impairment. Because this is a naturalistic study, we cannot rule out that right censoring may have occurred, meaning that *APOE4* carriers were more highly represented among those excluded because of baseline cognitive deficits (eg, mild cognitive impairment) compared with noncarriers. Finally, the present study is the first known report of a correlation between subjective memory complaints and subsequent cerebral metabolic decline in genetically at-risk persons, and replication of these findings is warranted.

Our results support the validity of memory complaints for individuals by indicating that the degree of memory complaints is reflected in objective metabolic changes and suggest that complaints should be taken seriously. Regardless of *APOE4* genetic risk, complaints of increased frequency of forgetting predicted global cerebral metabolic decline, and such metabolic changes may be indicative of normal aging. Specific memory complaints related to the use of compensatory strategies in *APOE4* carriers may provide additional information regarding the potential for metabolic decline in the regions that subserve memory and that are associated with AD. Self-reported use of compensatory strategies may be useful in identifying persons for further study or for increased clinical monitoring. Distinguishing between general complaints and behavioral com-

pensation may be important in future studies assessing the validity of memory complaints.

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