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Authors

Protas, Hillary D
Chen, Kewei
Langbaum, Jessica BS
et al.

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Posterior Cingulate Glucose Metabolism, Hippocampal Glucose Metabolism, and Hippocampal Volume in Cognitively Normal, Late-Middle-Aged Persons at 3 Levels of Genetic Risk for Alzheimer Disease

Dr. Hillary D. Protas, PhD, **Dr. Kewei Chen, PhD**, **Dr. Jessica B. S. Langbaum, PhD**, **Dr. Adam S. Fleisher, MD**, **Dr. Gene E. Alexander, PhD**, **Ms. Wendy Lee, MS**, **Mr. Daniel Bandy, MS**, **Dr. Mony J. de Leon, EdD**, **Dr. Lisa Mosconi, PhD**, **Mss. Shannon Buckley, BA**, **Mss. Diana Truran-Sacrey, BA**, **Dr. Norbert Schuff, PhD**, **Dr. Michael W. Weiner, MD**, **Dr. Richard J. Caselli, MD**, and **Dr. Eric M. Reiman, MD**

Banner Alzheimer's Institute and Arizona Alzheimer's Consortium (Drs Protas, Chen, Langbaum, Fleisher, and Reiman, Ms Lee, and Mr Bandy) and Division of Neurogenomics, Translational Genomics Research Institute (Dr Reiman), Phoenix, Department of Mathematics and Statistics, Arizona State University, Tempe (Dr Chen), Departments of Psychology (Dr Alexander) and Psychiatry (Dr Reiman) and Evelyn F. McKnight Brain Institute (Dr Alexander), University of Arizona, Tucson, and Department of Neurology, Mayo Clinic Arizona, Scottsdale (Dr Caselli); New York University School of Medicine, New York (Drs de Leon and Mosconi); Department of Neurosciences, University of California, San Diego (Dr Fleisher), and Department of Veterans

Correspondence: Hillary D. Protas, PhD, Banner Alzheimer's Institute, 901 E Willetta St, Phoenix, AZ 85006 (hillary.protas@bannerhealth.com).

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Affairs Medical Center and Department of Radiology, University of California, San Francisco (Mss Buckley and Truran-Sacrey and Drs Schuff and Weiner)

Abstract

Objective—To characterize and compare measurements of the posterior cingulate glucose metabolism, the hippocampal glucose metabolism, and hippocampal volume so as to distinguish cognitively normal, late-middle-aged persons with 2, 1, or 0 copies of the apolipoprotein E (*APOE*) ε^4 allele, reflecting 3 levels of risk for late-onset Alzheimer disease.

Design—Cross-sectional comparison of measurements of cerebral glucose metabolism using ^{18}F-fluorodeoxy-glucose positron emission tomography and measurements of brain volume using magnetic resonance imaging in cognitively normal ε^4 homozygotes, ε^4 heterozygotes, and noncarriers.

Setting—Academic medical center.

Participants—A total of 31 ε^4 homozygotes, 42 ε^4 heterozygotes, and 76 noncarriers, 49 to 67 years old, matched for sex, age, and educational level.

Main Outcome Measures—The measurements of posterior cingulate and hippocampal glucose metabolism were characterized using automated region-of-interest algorithms and normalized for whole-brain measurements. The hippocampal volume measurements were characterized using a semiautomated algorithm and normalized for total intracranial volume.

Results—Although there were no significant differences among the 3 groups of participants in their clinical ratings, neuropsychological test scores, hippocampal volumes (P=.60), or hippocampal glucose metabolism measurements (P = .12), there were significant group differences in their posterior cingulate glucose metabolism measurements (P=.001). The *APOE* ε^4 gene dose was significantly associated with posterior cingulate glucose metabolism (r=0.29, P=.0003), and this association was significantly greater than those with hippocampal volume or hippocampal glucose metabolism (P<.05, determined by use of pairwise Fisher z tests).

Conclusions—Although our findings may depend in part on the analysis algorithms used, they suggest that a reduction in posterior cingulate glucose metabolism precedes a reduction in hippocampal volume or metabolism in cognitively normal persons at increased genetic risk for Alzheimer disease.

We and others have been using positron emission tomography (PET) measurements of the cerebral metabolic rate for glucose (CMRgl) in the posterior cingulate cortex and other brain regions that are known to be preferentially affected by Alzheimer disease (AD), magnetic resonance imaging (MRI) measurements of hippocampal and other brain tissue volumes, and other biomarker measurements to detect and track some of the brain changes that precede the clinical onset of AD.[1–12] These findings have led our group and others to consider how these biomarkers could be used for people at increased risk for AD in the accelerated evaluation of presymptomatic AD treatments.[8,12–14] They have also led researchers to propose models that characterize the trajectory of different biomarker changes associated with the pre-clinical stages of the disorder.[15,16] For instance, ^{18}F-fluorodeoxyglucose (FDG)–PET studies[17–24] reveal characteristic and progressive CMRgl reductions in the posterior cingulate, precuneus, and parietal, temporal, and prefrontal brain regions beginning years before the clinical onset of AD. In other studies, we have reported evidence of CMRgl reductions in an automatically characterized hippocampal region of interest; these reductions were associated with apparent normal aging and predicted future cognitive decline.[5] Magnetic resonance imaging studies reveal progressively reduced hippocampal volumes, which tend to parallel the earliest memory changes that herald the clinical onset of AD.[25]

The apolipoprotein E (*APOE*) ε^4 allele is the major genetic risk factor for late-onset AD.[26] Each additional ε^4 allele in a person's *APOE* genotype is associated with a greater risk of AD and a younger average age at clinical onset.[26] We and others have found that cognitively normal, late-middle-aged and young adult *APOE* ε^4 carriers exhibit CMRgl reductions in these AD-affected regions[7–9,27,28] and that these reductions in late middle age are correlated with *APOE* ε^4 gene dose (the number of ε^4 alleles in a person's *APOE* genotype, reflecting 3 levels of genetic risk for AD).[10] In a preliminary study of cognitively normal, late-middle-aged ε4 homozygotes and noncarriers, we were able to detect CMRgl reductions in the posterior cingulate cortex and other brain regions preferentially affected by AD, prior to detectable evidence of hippocampal volumes; CMRgl reductions in the location with maximal posterior cingulate CMRgl reductions were still apparent after controlling for hippocampal volume differences, and smaller hippocampal volumes were associated with poorer long-term memory scores.[25] Together, these and other findings led us to propose that posterior cingulate CMRgl reductions were apparent prior to hippocampal atrophy and that hippocampal atrophy may correspond to the earliest memory declines associated with the clinical onset of AD.[25] In the present study, we sought to extend our previous findings to a much larger group of cognitively normal, late-middle-aged persons with 2 copies, 1 copy, and no copies of the *APOE* ε^4 allele and to compare posterior cingulate CMRgl measurements, hippocampal CMRgl measurements, and hippocampal volumes in automatically selected regions of interest.

METHODS

PARTICIPANTS

Cognitively normal volunteers 47 to 68 years of age were recruited using newspaper advertisements and were enrolled into a longitudinal cohort study as previously described.[7,10,29] Participants provided informed consent, agreed not to receive any information about their *APOE* genotype, and were studied under guidelines approved by the human subjects committees at Banner Good Samaritan Medical Center in Phoenix, Arizona, and the Mayo Clinic in Scottsdale, Arizona. Venous blood samples were obtained, and *APOE* genotypes were characterized with analysis by restriction fragment-length polymorphisms.[30] *APOE* ε^4 heterozygotes and noncarriers were individually matched to each *APOE* ε^4 homozygotes for their sex, age (within 3 years), and educational level (within 2 years). Individuals who were enrolled reported a first-degree family history of probable AD and denied any cognitive symptoms. Additional inclusion criteria for participation consisted of a Folstein Mini-Mental State Examination score of at least 28, a Hamilton Depression Rating Scale score of less than 10, the absence of a current psychiatric disorder based on a structured psychiatric interview,[31] and normal neurological examination results. Participants with a reported history of coronary artery disease, diabetes mellitus, or cerebrovascular accidents were excluded. Participants with clinically significant abnormalities, including but not limited to the presence of lacunar infarcts on their T1-weighted MRI scans, were also excluded. Note that, at the time these MRI scans were acquired, a complete clinical MRI examination, including T2-weighted images, was not performed; hence, the evaluation of more subtle evidence of cerebrovascular disease was not possible. For the present study, cross-sectional MRI and FDG-PET data from 160 participants were available for analysis. Data from 11 participants were excluded owing to technical MRI failures that resulted in the inability to segment the hippocampus. The remaining 149 participants included 31 *APOE* ε^4 homozygotes, 42 ε^4 heterozygotes, and 76 noncarriers, all 49 to 67 years of age.

BRAIN IMAGING

^{18}F-fluorodeoxyglucose PET and volumetric T1-weighted MRI were performed as previously described.[7,9,10,25,32] ^{18}F-fluorodeoxyglucose PET was performed with a 951/31 ECAT scanner (Siemens), a 20-minute transmission scan, the intravenous injection of 10 mCi of FDG, and a 60-minute dynamic sequence of emission scans as the participants, who had fasted for at least 4 hours, lay quietly in the darkened room with their eyes closed and directed forward. The PET images were reconstructed using the filtered back-projection with Hanning filter of 0.40 cycles per pixel and measured attenuation correction, resulting in 31 slices with an in-plane resolution of about 8.5 mm, full-width at half-maximum, an axial resolution of 5.0-to 7.1-mm full-width at half-maximum, a 3.375-slice thickness, and a 10.4-cm axial field of view. Magnetic resonance imaging was performed using a 1.5-T Signa system (General Electric) and a T1-weighted, 3-dimensional pulse sequence (radio-frequency–spoiled gradient recall acquisition in the steady state; repetition time, 33 ms; echo time, 5 ms; α =30°; number of excitations, 1; field of view, 24 cm; 256×192 imaging matrix; slice thickness, 1.5 mm; scan time, 13:36 minutes). The MRI data set consisted of 124 contiguous horizontal slices with an in-plane voxel dimension of 0.94 by 1.25 mm.

IMAGE ANALYSES

SPM99 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/) was used by investigators at the Banner Alzheimer's Institute in Phoenix, Arizona, to linearly and nonlinearly deform (normalize) each participant's PET image into the coordinates of a standard brain atlas. The Automated Anatomical Labeling toolbox[33] was used to extract the PET data from the bilateral posterior cingulate. An automated algorithm developed at New York University was used by these investigators to characterize bilateral hippocampal regions of interest and extract CMRgl measurements from each person's FDG-PET image.[23,34] Posterior cingulate and hippocampal CMRgl measurements were normalized for the individual variation in whole-brain measurements using proportionate scaling. A semiautomated algorithm (Surface Navigator Technologies; Medtronic) was used by investigators at the University of California, San Francisco, to characterize bilateral hippocampal volumes (Medtronic Surgical Navigation Technologies) as previously described.[35,36] Hippocampal volumes were normalized for the individual variation in total intracranial volumes[37] using proportionate scaling.

A 1-way analysis of variance with a linear trend was used to examine the ability of posterior cingulate CMRgl measurements, hippocampal CMRgl measurements, and hippocampal volume measurements to distinguish among the 3 levels of risk for AD. Two-tailed *t* tests were subsequently performed to characterize and compare between-group measurements in the ε^4 homozygotes, ε^4 heterozygote, and noncarrier groups. An analysis of covariance with a linear trend was used to examine *APOE* ε^4 dose effects on posterior cingulate and hippocampal CMRgl measurements, covarying for hippocampal volume. Using the Fisher *z* test, we directly compared the correlation coefficients relating *APOE* ε^4 gene dose to posterior cingulate CMRgl, hippocampal CMRgl, and hippocampal volume.[38] Lastly, the area under the curve of the receiver operating characteristic for the posterior cingulate CMRgl, hippocampal CMRgl, and hippocampal volume was computed using *U* statistics[39] in order to characterize and compare the ability of the 3 measurements to distinguish among the 3 levels of genetic risk for AD.

RESULTS

The *APOE* ε^4 homozygote, ε^4 heterozygote, and non-carrier group characteristics are reported in Table 1. There were no significant differences in age, sex, educational levels, clinical ratings, or neuropsychological test scores.

Brain imaging measurements are reported in Table 2 and in our Figure. The 3 groups of participants differed from each other in posterior cingulate CMRgl measurements (analysis of variance: $P = .001$; pairwise comparisons: $P < .05$) but not in bilateral hippocampal CMRgl measurements (analysis of variance: $P = .12$) or left, right, or bilateral hippocampal volume measurements (analysis of variance: $P = .23$, .89, and .60, respectively). The posterior cingulate and hippocampal CMRgl findings remained unchanged after controlling for hippocampal volumes (analysis of covariance: $P = .002$ and .11, respectively).

Supporting the between-group differences, the *APOE* $\varepsilon 4$ gene dose was more closely correlated with posterior cingulate hypometabolism ($r = 0.29$, $P = .0003$) than with hippocampal hypometabolism or hippocampal volumes ($r = 0.07$ and 0.013, respectively, determined using pairwise Fisher z tests; $P < .05$). Indeed, posterior cingulate CMRgl measurements were significantly better than hippocampal CMRgl or hippocampal volume measurements in distinguishing between the $\varepsilon 4$ homozygote and noncarrier groups (area under the receiver operating characteristic curve: 0.71, 0.52, and 0.54, respectively, using pairwise comparisons: $P = .04$), whereas the hippocampal CMRgl and hippocampal volume measurements did not differ significantly in their ability to distinguish between the groups of participants.

A quadratic model was used post hoc to further explore the relationship between *APOE* $\varepsilon 4$ gene dose and each of the imaging measurements following the exploratory finding of lower mean hippocampal CMRgl measurements in the *APOE* $\varepsilon 4$ heterozygotes than in $\varepsilon 4$ homozygotes or noncarriers (Table 2). Although the finding of a significant quadratic relationship between *APOE* $\varepsilon 4$ gene dose and baseline measurements of hippocampal CMRgl ($P = .04$) may or may not be consistent with greater hippocampal activation in functional MRI studies of cognitively normal older adult *APOE* $\varepsilon 4$ carriers during learning and memory tasks,[40] this observation must be considered exploratory. We failed to detect a significant difference between carriers and noncarriers using either hippocampal CMRgl ($P = .30$) or hippocampal volume ($P = .32$).

COMMENT

Our study directly compared posterior cingulate CMRgl, hippocampal CMRgl, and hippocampal volume measurements using preselected, automatically or semiautomatically generated regions of interest in a large number of well-matched, late-middle-aged, cognitively normal persons at 3 levels of genetic risk for AD. As expected, a higher *APOE* $\varepsilon 4$ gene dose was associated with a lower posterior cingulate CMRgl. These findings were apparent in the absence of detectable hippocampal CMRgl or hippocampal volume differences. Together, these findings confirm and extend our observation that posterior cingulate CMRgl reductions can be detected before hippocampal CMRgl or hippocampal volume alterations in the pre-clinical stages of late-onset AD, and they support similar findings in early-onset AD-causing mutation carriers.[41]

As previously noted, posterior cingulate CMRgl reductions could reflect a reduction in the density activity or metabolism of terminal neuronal fields or perisynaptic astroglial cells[7]; as previously shown, these reductions are unlikely to reflect the combined effects of brain atrophy and partial-volume averaging.[9,10] Posterior cingulate hypometabolism was also found in young adult carriers several decades before possible dementia[9]; indeed, young adult carriers who died were found to have reduced cytochrome oxidase activity, even before they showed evidence of soluble or fibrillar amyloid-β pathology.[42]

In comparison with our previous report,[25] the present study compared FDG and volumetric MRI measurements in a much larger number of research participants and compared measurements in persons at 3 levels of genetic risk for AD. It compared posterior cingulate

and hippocampal measurements in automatically or semiautomatically generated regions of interest, free from the inflated type I error associated with multiple regional comparisons in our previous FDG-PET analysis. It included the additional comparison of hippocampal CMRgl measurements, which had been implicated in the early detection and tracking of AD, and found that the posterior cingulate measurements were more sensitive to detecting this preclinical stage of the disorder. We previously demonstrated reduced posterior cingulate CMRgl measurements in cognitively normal young adult *APOE* ε^4 heterozygotes, more than 4 decades before their estimated age at clinical onset.[9] Based on other comparisons,[8,9,43] we found that the reduction in the posterior cingulate CMRgl does not progress between young adulthood and late middle age but that it anticipates progressive CMRgl declines, with some of the earliest fibrillar Aβ deposition starting in late-middle-aged ε^4 carriers.

Additional analyses will be needed to compare CMRgl measurements with regional gray matter volume or cortical thickness measurements using other voxel-based or region-of-interest–based methods because the sensitivity to detect a change using any biomarker method may be at least partly related to technical factors, such as the data analysis technique used, and not solely attributable to the underlying biological process. Although we found that the posterior cingulate CMRgl was more sensitive than the hippocampal CMRgl or the hippocampal volume in its ability to discriminate among cognitively normal, late-middle-aged persons at 3 levels of genetic risk for AD, the differential sensitivity could be related to actual differences in the underlying processes, the image acquisition, the region of interest, the analysis techniques used, or a combination of these factors. It is possible that future technical developments could further improve the sensitivity of these biomarker measurements for the preclinical detection of AD.

Additional analyses will also be needed to compare CMRgl measurements with fibrillar amyloid-β measurements using PET; we have acquired these measurements in a smaller number of participants. As we have stated in the past, these and other biomarker measurements are not yet recommended to predict a cognitively normal person's clinical course or his or her response to suggested but unproven risk-reducing treatments. Additional studies are needed to characterize and compare the trajectory of these and other biomarker changes during the preclinical stages of AD[16,44] because these bio-marker changes continue to set the stage for the accelerated evaluation of presymptomatic AD treatments.[13]

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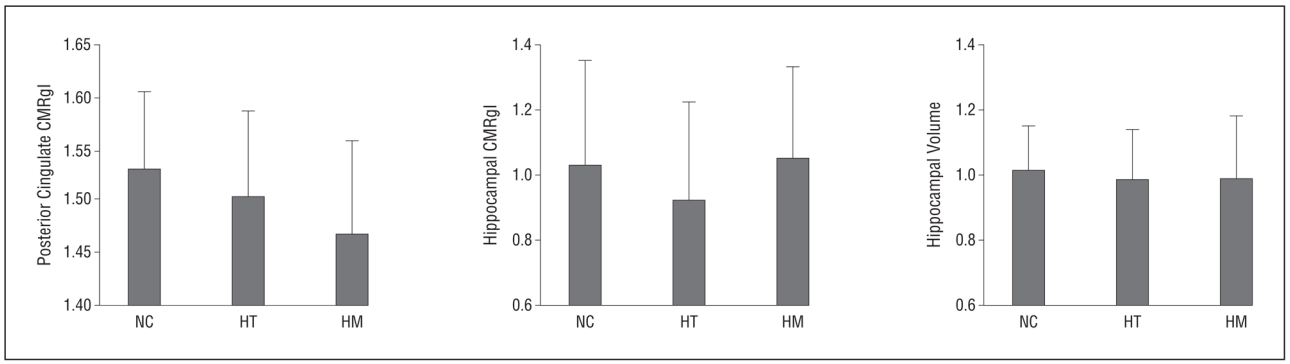

Figure.

Cerebral metabolic rate for glucose (CMRgl) in the posterior cingulate and the hippocampus, determined using positron emission tomography, and hippocampal volume, determined using magnetic resonance imaging, in *APOE* ε^4 homozygotes (HM), heterozygotes (HT), and noncarriers (NC). The CMRgl measurements are normalized to whole-brain measurement, whereas the hippocampal volumes are normalized for the variation in total intracranial volume. There is a significant decrease only with posterior cingulate CMRgl from noncarriers to homozygotes of the *APOE* ε^4 allele (analysis of variance: $P = .001$; linear trend: $P = .0003$). Error bars indicate standard deviation.

Table 1

Characteristics, Clinical Ratings, and Neuropsychological Test Scores of Participants

Variable	Mean (SD)			*P* Value[a]
	Noncarriers (n = 76)	*APOE* 34 Heterozygotes (n = 42)	*APOE* 34 Homozygotes (n = 31)	
Age, y	56.5 (4.7)	55.9 (4.0)	55.5 (5.1)	.60
Sex, No.				.90
Male	28	15	10	
Female	48	27	21	
Education, y	15.8 (1.5)	15.3 (1.5)	15.7 (1.4)	.17
MMSE score	29.8 (0.5)	29.8 (0.4)	29.8 (0.6)	.74
AVLT score				
Total	47.7 (8.0)	48.1 (9.6)	49.0 (10.2)	.81
STM	9.6 (2.5)	10.1 (2.4)	9.9 (3.3)	.51
LTM	8.9 (2.9)	9.7 (2.9)	9.5 (3.4)	.28
Complex Figure test score				
Copy	34.9 (1.6)	34.1 (2.7)	34.4 (1.9)	.09
Recall	18.7 (6.1)	19.0 (6.3)	17.1 (6.0)	.37
Boston Naming Test score	57.1 (3.1)	56.8 (3.0)	56.6 (3.5)	.80
WAIS-R score				
Information	12.0 (2.2)	12.3 (2.1)	11.3 (2.1)	.20
Digit span	11.3 (2.1)	11.8 (3.0)	11.1 (2.8)	.47
Block design	11.9 (2.6)	12.2 (2.6)	11.7 (2.6)	.78
Arithmetic	12 (2.4)	12.4 (2.2)	11.1 (2.8)	.09
Similarities	12.4 (2.2)	12.5 (2.0)	11.6 (1.9)	.18
COWAT score	44.0 (11.2)	44.3 (11.5)	48.3 (10.4)	.18
WMS-R orientation score	13.8 (0.5)	13.9 (0.3)	13.8 (0.4)	.41

Abbreviations: AVLT, Auditory Verbal Learning Test; COWAT, Controlled Oral Word Association Test; LTM, long-term memory; MMSE, Mini-Mental State Examination; STM, short-term memory; WAIS-R, Wechsler Adult Intelligence Scale–Revised; WMS-R, Wechsler Memory Scale–Revised.

[a]Significance at $\alpha = .05$.

Table 2

Imaging Measurements

Measurement	Mean (SD)			*P* Value	
	Noncarriers (n = 76)	*APOE*ε34 Heterozygotes (n = 42)	*APOE* 34 Homozygotes (n = 31)	ANOVA	Linear Trend
Hippocampal volume determined by MRI					
Left	0.519 (0.070)	0.498 (0.069)	0.496 (0.099)	.23	.11
Right	0.494 (0.075)	0.486 (0.094)	0.495 (0.100)	.89	.97
Total	1.012 (0.137)	0.985 (0.156)	0.991 (0.191)	.60	.41
CMRgl determined by PET					
Posterior cingulate	1.53 (0.07)	1.51 (0.08)	1.47 (0.09)	.001	.0003
Hippocampus	1.03 (0.32)	0.92 (0.30)	1.05 (0.28)	.12	.88

Abbreviations: ANOVA, analysis of variance; CMRgl, cerebral metabolic rate for glucose; MRI, magnetic resonance imaging; PET, positron emission tomography.