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Hypometabolism and Altered Cerebrospinal Fluid Markers in Normal Apolipoprotein E E4 Carriers with Subjective Memory Complaints

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Abstract

Background—We examined whether cerebral metabolic rates for glucose (CMRglc) on 2-[¹⁸F] fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) and cerebrospinal fluid (CSF) markers of Alzheimer's disease (AD) are altered in cognitively normal apolipoprotein E (ApoE) E4 carriers with subjective memory complaints (SMC).

Methods—Twenty-eight middle-aged normal subjects (NL) were examined, including 13E4 carriers (E4+; 6 with SMC [SMC+] and 7 without SMC [SMC−]) and 15 noncarriers (E4−; 7 SMC+ and 8 SMC−). Subjects received an FDG-PET scan and a lumbar puncture to measure CSF total (T-Tau) and hyperphosphorylated tau₂₃₁ (P-Tau), 40 and 42 amino acid forms of β-amyloid (Aβ40 and Aβ42), and F₂-isoprostane (IP).

Results—As compared with E4−, E4+ subjects showed decreased CMRglc in AD-related brain regions and associated higher CSF IP, P-Tau, T-Tau, and P-Tau/Aβ42 levels (p 's < .05). As compared with SMC−, SMC+ subjects showed reduced parietotemporal and parahippocampal gyrus (PHG) CMRglc. A significant ApoE by SMC status interaction was found, with the E4+/SMC+ showing the lowest PHG CMRglc and the highest CSF IP, P-Tau, and P-Tau/Aβ42 levels as compared with all other subgroups (p 's ≤ .05). The combination of CSF and CMRglc measures significantly improved the accuracy of either measures alone in discriminating ApoE groups (86% accuracy, odds ratio [OR] = 4.1, p < .001) and E4+/SMC+ from all other subgroups (86% accuracy, OR = 3.7, p = .005). Parahippocampal gyrus CMRglc was the most accurate discriminator of SMC groups (75% accuracy, OR = 2.4, p < .001).

Conclusions—Normal E4 carriers with SMC show altered AD-related CSF and FDG-PET measures. Longitudinal studies are needed to assess whether these brain abnormalities foreshadow clinical decline.

Keywords

Alzheimer's disease; amyloid beta; ApoE; CSF; FDG-PET; isoprostane; normal aging; subjective memory complaints; tau

The E4 allele of the apolipoprotein E (ApoE) gene is a well-recognized genetic risk factor for late-onset Alzheimer's disease (AD) (1,2). The mechanisms through which the ApoE E4 genotype confers increased susceptibility to age-related memory problems and AD are not fully understood.

There is recent evidence that normal individual E4 carriers show abnormal cerebral metabolic rates for glucose (CMRglc), as measured with positron emission tomography (PET) imaging with 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG). As compared with E4 noncarriers, asymptomatic E4 carriers have severe CMRglc reductions in the same brain regions as clinically affected AD patients, mainly parieto-temporal, posterior cingulate, and frontal cortices (3,4). Such CMRglc reductions were found in individuals as young as 20 to 30 years and are considered the earliest brain abnormalities yet found in living persons at risk for AD (5). A recent study showed that the extent of hypometabolism in the E4 carriers correlates with perceived loss of memory ability (6). However, it remains to be determined whether the CMRglc abnormalities in normal E4 carriers foreshadow the decline to AD.

Cerebral metabolic rates of glucose reductions are a risk factor for developing AD in patients with mild cognitive impairment (MCI) (7), the extent of the CMRglc reductions being exacerbated in MCI E4 carriers (8,9). Moreover, CMRglc reductions in the medial temporal lobes accurately predict decline from normal aging to MCI and dementia (10,11). Cerebral metabolic rates of glucose reductions reflect synapse dysfunction and are considered sensitive indicators of neuronal damage. However, these measures do not provide information on the hallmark lesions of AD, which may confer disease specificity and increase preclinical diagnostic accuracy.

Several cerebrospinal fluid (CSF) biomarkers of AD pathology have been developed. The most widely utilized CSF analytes in AD include markers for neurofibrillary tau (i.e., total tau [T-Tau] and hyperphosphorylated tau [P-Tau] proteins) and amyloid beta (A β) pathology (i.e., peptide fragments of the 40 amino acid form of β -amyloid [A β 40] and 42 amino acid form of β -amyloid [A β 42] amino-acid residues), and lipid membrane oxidative damage (F₂-isoprostane [IP]). These CSF markers have value in discriminating AD and MCI from control subjects and other dementias (12–14) and in predicting the transition from MCI to AD (15), although more replication studies are needed. A recent study showed that the ratio P-Tau/A β 42 predicts decline from normal cognition to dementia (16). There is also evidence that CSF A β 42 levels are decreased in normal elderly ApoE E4 carriers as compared with noncarriers (17,18), presumably reflecting increased brain A β deposition.

There are no studies that have examined the association of FDG-PET and CSF measures in normal subjects. Only two studies have examined such a relationship in AD or MCI and they provided controversial results (19,20).

The present study examines the association between CMRglc and several CSF analytes, including T-Tau, P-Tau, A β 40 and A β 42, and IP, in normal middle-aged ApoE E4 carriers and noncarriers and whether the association is modified in the presence of subjective memory complaints.

Methods and Materials

Subjects

Among a large pool of clinically and cognitively normal (NL) individuals recruited at the Center for Brain Health at New York University (NYU), 28 middle-aged NL volunteers that completed an FDG-PET and a lumbar puncture (LP) examination were studied. Study subjects were derived from multiple community sources, including individuals interested in research

participation, memory evaluation, and risk consultation; self-referred individuals with cognitive complaints; and family members and caregivers of impaired patients participating in other studies.

Subjects were 45 to 70 years of age, had education ≥ 12 years, and had Mini Mental State Examination (MMSE) scores of 28 to 30. All subjects received a standard diagnostic evaluation that included medical (history, physical, and laboratory), neuropsychological, and magnetic resonance imaging (MRI) examinations. Individuals with medical conditions or history of conditions that may affect brain structure or function, i.e. stroke; diabetes; head trauma; any neurodegenerative diseases; depression; MRI evidence of hydrocephalus, intracranial mass, and infarcts (see below); or the use of psychoactive medications were excluded. All subjects had normal fasting plasma glucose, cholesterol, and high-density lipoprotein levels; normal blood pressure; and Modified Hachinski Ischemia Scale < 4 (21). None of the subjects had any acute or chronic inflammatory syndromes/diseases, were smokers, or were taking high doses of antioxidant vitamins. All subjects gave their informed consent to this NYU Institutional Review Board (IRB) approved study.

Subjective reports of late life memory and other cognitive changes were evaluated during a structured informant-corroborated interview with the study physician. Subjects had Clinical Dementia Rating (CDR) scores = 0 (22); Global Deterioration Scale (GDS) scores = 1 or 2 (23), as based on the Brief Clinical Rating Scale (BCRS) (24), which indicate NL functioning subjects differentiated only by the absence (GDS = 1) or presence (GDS = 2) of subjective memory complaints (i.e., occasional forgetting names or forgetting where one placed objects), in the absence of clinically recognizable impairment.

The neuropsychological testing battery included the MMSE, immediate and delayed recall of a paragraph and verbal paired associates, the digit-symbol substitution test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the designs, and the object-naming tests. All subjects had normal cognitive test performance relative to appropriate normative values (10, 11).

Apolipoprotein E genotype was determined using standard polymerase chain reaction (PCR) procedures (10).

CSF Acquisition and Evaluation Protocol

After an overnight fast, 15 mL of clear CSF was collected using fluoroscopy to guide a 24-gauge beveled LP needle. Samples were centrifuged for 10 minutes at 1500 rpm at 4°C, aliquoted to .25 mL polypropylene tubes, and stored at -80°C. Assays were blinded to clinical data and were batch processed.

Amyloid Beta 40 and 42—Amyloid beta levels were measured using a monoclonal antibody 6E10 (specific to an epitope present on A β -16 and to rabbit antisera to A β 1-40 and A β 1-42, respectively) in a double antibody sandwich enzyme-linked immunosorbent assay (ELISA) (detection limit = 10 pg/mL, 8% to 14% intra-assay and 10% to 18% interassay reproducibility) (25).

F₂-Isoprostane—Cerebrospinal fluid samples were spiked with a fixed amount of internal standard (d₄-iPF₂ α -VI) and extracted on a C18 cartridge column. The eluate was purified by thin layer chromatography and assayed by negative ion chemical ionization gas chromatography/mass spectrometry (detection limit = 1 pg/mL, 4% to 7% intra-assay and 4.5% to 6.5% interassay reproducibility) (13).

Hyperphosphorylated Tau₂₃₁—A sandwich ELISA assay was used to detect CSF tau phosphorylated at threonine 231 by capturing tau with two backbone-directed antibodies, tau-1 and CP-27. The captured tau is then detected by CP9, which is specific for P-Tau₂₃₁ (detection limit = 9 pg/mL, 6.0% to 10.3% intra-assay and 11.6% to 14.4% interassay reproducibility) (26). In what follows, P-Tau₂₃₁ will be referred to as P-Tau.

Total Tau—Cerebrospinal fluid T-Tau measurements were determined using the commercially available INNOTEST hTAU Antigen kit from Innogenetics (Ghent, Belgium) (detection limit = 60 pg/mL, 5.5% intra-assay and 11.6% interassay reproducibility) (15).

Brain Imaging

Subjects received a standardized whole-brain MRI protocol on a 1.5 T GE Signa imager (General Electric, Milwaukee, Wisconsin), including a 3-mm, axial T2-weighted scan and a 124-slice, 1.2 mm thick T1-weighted fast gradient-echo image (field of view [FOV] = 25 cm; number of excitations = 1; 256 × 128 matrix; 35 msec relaxation time; 9 msec excitation time; and 60° flip angle). These scans were used to rule out hydrocephalus, intracranial mass, strokes, subcortical gray matter lacunes, moderate-to-severe nonspecific white matter disease, and focal white matter hyperintensities (27).

The FDG-PET scans were acquired at Brookhaven National Laboratory on an ECAT EXACT HR+ scanner (Siemens, Knoxville, Tennessee) (3.6 mm in-plane full width at half maximum [FWHM], 2.46 mm slice thickness, 155 mm axial FOV) (10,28,29). Subjects received 3 to 5 mCi of FDG intravenously while laying supine in a dimly lit room. Positron emission tomography images were obtained 35 minutes after injection and acquired over 20 minutes. Arterial blood samples were drawn at standard intervals throughout the study and CMRglc measures (μmol/100 g/min) calculated using Sokoloff's model with standard kinetic constants (30,31). Data were reconstructed using filtered back-projection (Fourier rebinning/two-dimensional [2-D] back-projection, Hanning filter with .5 cycles/pixel frequency cutoff) and corrected for attenuation using ⁶⁸Ga/⁶⁸Ge transmission scans, scatter, and radioactive decay.

Image Analysis

Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, United Kingdom) (32) was used for image analysis. The FDG-PET images were spatially normalized to a standard FDG-PET brain template in the Montreal Neurological Institute (MNI) space, which approximates the Talairach and Tournoux space (33) by estimating the optimum least-squares 12-parameter affine transformation, followed by 7 × 8 × 7 discrete cosine functions (32,34). The spatially normalized PET images were resampled on a 105 × 126 × 91 matrix with 1.5 × 1.5 × 1.5 mm voxels and smoothed with a 12-mm FWHM Gaussian filter (32). Only voxels with values greater than 80% of the whole-brain mean CMRglc and only clusters exceeding an extent threshold of 30 voxels were considered significant. Anatomical location of brain regions showing significant effects was described after coordinates conversion from the MNI to the Talairach space (<http://www.mrc-cbu.cam.ac.uk/Imaging/>). Cerebral metabolic rates for glucose were extracted from the clusters showing significant group effects using Marsbar (<http://www.mrc-cbu.cam.ac.uk/Imaging/marsbar.html>).

Statistical Analysis

Analyses were done with SPSS 12.0 (SPSS Inc., Chicago, Illinois) and SPM2 (32).

Differences in demographic and neuropsychological measures between groups were examined with χ^2 tests, Fisher exact test, and analysis of covariance. Because of prior evidence for their diagnostic utility, ratios were created between A β 42/A β 40 (15) and P-Tau/A β 42 (16). The

general linear model (GLM), univariate analysis, was used to examine ApoE status (E4 carriers [E4+] vs. noncarriers [E4-]), the presence of subjective memory complaints (SMC+ vs. SMC-), and the interaction between ApoE and SMC status as predictors of CSF and CMRglc measures. The effects of age and gender were also examined, and if showing significant group or interaction effects with the dependent variables, these variables were set as covariates. All FDG-PET analyses were performed accounting for the global CMRglc, as done by previous PET studies in similar subject groups to highlight regional CMRglc abnormalities (3–5,8), using SPM2 global normalization routine. Whole-brain CMRglc measures showed no ApoE (E4+: 38.0 ± 5.9 vs. E4-: 38.1 ± 3.8 $\mu\text{mol/g/min}$), SMC (SMC+: 38.0 ± 5.5 vs. SMC-: 38.1 ± 4.5 $\mu\text{mol/g/min}$), or ApoE by SMC effects (p 's $> .1$).

For CSF data, measures showing significant effects on GLM/univariate analysis were reexamined with a GLM/multivariate analysis and post hoc Scheffe tests at $p < .05$. For CMRglc data, results were examined using F contrasts with post hoc t contrasts after a correction for family-wise error (FWE) multiple comparisons at $p < .05$. Results from the ApoE by SMC interaction analysis were confirmed with nonparametric Kruskal-Wallis tests with post hoc Mann-Whitney rank sum tests ($\alpha = .05$, exact significance, two-tailed).

Linear regressions were used to examine correlations between CSF and CMRglc measures at $p < .05$, and when significant, an index of CSF-CMRglc associations was created by residualizing CMRglc by CSF measures across subjects. For example, in the case of an inverse relationship between CSF and CMRglc, a negative CSF-CMRglc index indicates high CSF levels and low CMRglc, while a positive index indicates low CSF levels and high CMRglc. Cerebrospinal fluid-CMRglc measures were examined for group effects using the same statistical models as above.

Multiple logistic regression analyses were used to examine whether group membership can be predicted by CSF, CMRglc, and CSF-CMRglc measures. First, measures showing significant group differences were included separately in the logistic regression model with age and gender as confounds. The variables that were significant in the first step were then simultaneously placed into a stepwise forward regression model to identify the most significant predictor for each category of biomarkers. Third, the incremental values of the best predictors for each category were examined as forward conditional effects. Finally, we examined whether the combination of CSF and CMRglc measures added to the accuracy of the CSF and CMRglc measures alone in classifying groups. Results were considered significant at $p < .05$.

Results

Clinical Measures

Subjects' characteristics are found in Table 1. Of the 28 subjects examined, 13 were E4+, including 6 SMC+ and 7 SMC-, and 15 were E4-, including 8 SMC+ and 7 SMC-. The frequency of SMC+ subjects was not significantly different between ApoE groups (E4+: 46% vs. E4-: 53%; $\chi^2_{(1)} = .14$, ns; Fisher exact $p = .78$, ns). Among the E4+, there were four E4 homozygotes (E4/E4) and nine E4 heterozygotes (E3/E4) (Table 1). A family history of AD was found in 13 (46%) of the 28 subjects. Neither ApoE nor SMC group status nor their interactions were associated with age, educational level, MMSE, and neuropsychological measures. There was a trend toward higher percentage of female subjects for the E4+ (85%) than for the E4- (60%) (Fisher exact $p = .10$). Gender was therefore accounted for in subsequent ApoE analyses.

CSF Measures

Cerebrospinal fluid measures are found in Table 1. On univariate analysis, the E4+ had higher IP (58%, $p = .006$), P-Tau (90%, $p = .01$), T-Tau (68%, $p = .01$), and P-Tau/A β 42 (61%, $p = .035$) levels than the E4-. No ApoE group differences were found for A β 40, A β 42, and A β 42/A β 40 measures. Multivariate analysis of these measures confirmed these ApoE effects [$F(4, 22) = 2.59$, $p = .05$], with the E4+ having significantly higher IP, P-Tau, and P-Tau/A β 42 as compared with E4- (p 's $\leq .045$).

No SMC effects were found for any of the CSF measures.

Although the ApoE by SMC status interaction was not significant as main effect, on post hoc examination, the E4+/SMC+ had higher IP and P-Tau levels as compared with E4-/SMC- (64% and 82%, respectively, p 's $< .05$) and higher P-Tau/A β 42 as compared with E4-/SMC- and E4-/SMC+ groups (43% and 100%, respectively, p 's $< .05$). There was a trend toward higher IP and P-Tau in E4+/SMC+ as compared with E4+/SMC-, which did not reach statistical significance. On multivariate analysis, ApoE by SMC effects were restricted to IP [$F(3,23) = 3.50$, $p = .032$], which on post hoc examination were driven by the E4+/SMC+ showing higher IP than E4-/SMC- ($p = .043$; Mann-Whitney $p = .020$). There was a trend toward P-Tau effects [$F(3,23) = 2.53$, $p = .08$], also driven by E4+/SMC+ having higher P-Tau levels than E4-/SMC- (Mann-Whitney $p = .071$).

FDG-PET Measures

Anatomical location and description of brain regions showing significant statistical effects are found in Table 2. As compared with E4-, the E4+ group showed CMRglc reductions in the inferior parietal lobe (IPL), inferior temporal gyri (ITG) and middle temporal gyri (MiTG), middle occipital gyrus (MiOG), fusiform gyrus (FuG), and thalamus in the left hemisphere and bilateral CMRglc reductions in the superior frontal gyri (SFG) (Figure 1A). The CMRglc reductions ranged from 5% (SFG) to 17% (MiOG). The E4- group did not show CMRglc reductions as compared with the E4+ group.

As compared with SMC-, SMC+ subjects showed CMRglc reductions in the parahippocampal gyrus (PHG) and MiTG, bilaterally; in the IPL, inferior frontal gyrus (IFG), FuG, and thalamus in the left hemisphere; and in the right putamen (Figure 1B). The PHG showed the most severe CMRglc reduction (18%).

Apolipoprotein E by SMC status interactions were found bilaterally in the PHG; in the left ITG, MiTG, inferior occipital gyrus (IOG), and thalamus; and in the right IFG (Figure 1C). On post hoc examinations, these effects were driven by the E4+/SMC+, who had lower CMRglc measures as compared with E4-/SMC-, E4-/SMC+, and E4+/SMC- subgroups in all regions (Figure 1D). The most severe CMRglc reductions in the E4+/SMC+ with respect to the average of the other subgroups were in the PHG (18%). Nonparametric analysis of these data showed significant effects for all regions (Kruskal-Wallis p 's $< .05$, ranging from $p = .013$ for PHG to $p = .027$ for ITG), which were driven by the E4+/SMC+ having lower CMRglc as compared with all other subgroups (Mann-Whitney p 's $< .05$).

CSF and FDG-PET Measures

Negative relationships were found between CSF IP and P-Tau, and CMRglc in several brain regions, leading to the following CSF-CMRglc associations: IP-IPL ($r = -.35$), IP-MiOG ($r = -.54$), IP-PHG ($r = -.35$), IP-thalamus ($r = -.45$); P-Tau-MiOG ($r = -.33$), P-Tau-PHG ($r = -.41$), P-Tau-SFG ($r = -.41$), P-Tau-thalamus ($r = -.39$); P-Tau/A β 42-PHG ($r = -.35$) and P-Tau/A β 42-MiOG ($r = -.32$) (p 's $< .05$). No significant relationships were found between A β 40, A β 42, or A β 42/A β 40 and CMRglc in any regions.

Cerebrospinal fluid-CMRglc measures are shown in Figure 2. As compared with the E4−, the E4+ showed lower negative CSF-CMRglc indexes, reflecting higher CSF values and lower CMRglc for the following combinations: IP-MiOG, IP-PHG, P-Tau-MiOG, P-Tau-PHG, P-Tau-SFG, P-Tau/Aβ42-MiOG, and P-Tau/Aβ42-PHG (p 's $\leq .04$). All effects remained significant on multivariate analysis (p 's $\leq .05$).

As compared with the SMC−, the SMC+ showed lower CSF-CMRglc indexes for IP-IPL, IP-PHG, IP-thalamus, P-Tau-PHG, P-Tau-thalamus, and P-Tau/Aβ42-PHG ($p \leq .05$). All effects remained significant on multivariate analysis (p 's $\leq .05$).

Apolipoprotein E by SMC effects were found for IP-PHG [GLM multivariate analysis $F(3, 24) = 4.62, p = .011$; Kruskal-Wallis $p = .017$], P-Tau-PHG [$F(3, 24) = 4.27, p = .015$; Kruskal-Wallis $p = .014$], P-Tau-SFG [$F(3, 24) = 4.27, p = .015$; Kruskal-Wallis $p = .014$], and P-Tau/Aβ42-PHG [$F(3, 24) = 4.33, p = .014$; Kruskal-Wallis $p = .027$]. On post hoc examination, these effects were driven by the E4+/SMC+ having lower CSF-CMRglc indexes than all other subgroups (GLM p 's $< .05$; Mann-Whitney p 's $\leq .05$) (Figure 2).

Group Separation

Results from logistic regressions are summarized in Table 3.

ApoE Status

Cerebrospinal fluid IP and P-Tau/Aβ42 predicted ApoE status, with 57% accuracy for IP [$\chi^2_{(1)} = 3.84, p = .05$, odds ratio (OR) = .9, 95% confidence interval (CI) = .8–1.0] and 68% accuracy for P-Tau/Aβ42 [$\chi^2_{(1)} = 4.37, p = .037$, OR = 1.5, 95% CI = .7–5.6].

Among the FDG-PET measures, MiOG CMRglc was the strongest predictor with 68% accuracy [$\chi^2_{(1)} = 12.6, p < .001$, OR = 2.3, 95% CI = 1.2–4.3].

Adding the CSF to the CMRglc measures improved the accuracy of the CMRglc measures alone for P-Tau-MiOG [$\chi^2_{\text{increment}(1)} = 8.15, p = .004$] and IP-PHG [$\chi^2_{\text{increment}(1)} = 3.56, p = .05$]. Cerebrospinal fluid-CMRglc P-Tau-MiOG and IP-PHG indexes were the strongest predictors of ApoE status, with 68% accuracy for P-Tau-MiOG [$\chi^2_{(1)} = 10.9, p = .001$, OR = 2.3, 95% CI = 1.2–4.5] and 57% accuracy for IP-PHG [$\chi^2_{(1)} = 5.9, p = .015$, OR = 1.7, 95% CI = 1.1–2.6]. Adding IP-PHG to P-Tau-MiOG increased the accuracy of P-Tau-MiOG [$\chi^2_{\text{increment}(1)} = 4.97, p = .026$], for a combined model with 86% accuracy [$\chi^2_{(2)} = 15.9, p < .001$, OR = 4.1, 95% CI = 1.1–5.3] (Figure 3A).

SMC Status

None of the CSF measures predicted SMC status.

Among the FDG-PET measures, PHG was the most significant predictor of SMC status with 75% accuracy [$\chi^2_{(1)} = 17.1, p = .001$, OR = 2.4, 95% CI = 1.3–4.8] (Figure 3B).

Adding CSF to CMRglc measures did not improve the accuracy of the PET measures alone. Among CSF-CMRglc indexes examined, IP-IPL was the strongest predictor of SMC status with 75% accuracy [$\chi^2_{(1)} = 23.7, p < .001$, OR = 2.7, 95% CI = 1.2–5.9]. Adding IP-IPL to PHG CMRglc increased the accuracy of the PHG [$\chi^2_{\text{increment}(1)} = 14.8, p < .001$], for a combined model with 93% accuracy [$\chi^2_{(2)} = 31.8, p < .001$, OR = 5.6, 95% CI = 1.5–50] (Figure 3B).

ApoE E4 Carriers with Subjective Memory Complaints

None of the CSF measures reached significance in discriminating the E4+/SMC+ from the other three subgroups.

Among FDG-PET measures, PHG and ITG CMRglc were both predictors of membership with 82% accuracy [PHG: $\chi^2_{(1)} = 11.8$, $p = .001$, OR = 3.5, 95% CI = 1.1–11.0; ITG: $\chi^2_{(1)} = 11.6$, $p = .001$, OR = 2.3, 95% CI = 1.1–5.9].

Adding IP and P-Tau/A β 42 to CMRglc measures increased the accuracy of the PHG CMRglc (p 's < .05). Among CSF-CMRglc indexes, IP-PHG was the best predictor of group membership with 79% accuracy [$\chi^2_{(1)} = 10.6$, $p = .001$, OR = 3.1, 95% CI = 1.4–9.1], while the combination of IP-PHG and P-Tau/A β 42-PHG yielded the highest odds ratio (OR = 3.7, 95% CI = 1.7–15.2, $p = .005$) (Figure 3C).

Discussion

This study examined four principal classes of biomarkers for AD in normal middle-aged subjects, including reduced FDG-PET CMRglc, amyloid beta, and tau pathology and cellular oxidative damage and their associations in relationship to the ApoE genotype and the presence of SMC. The ApoE E4 allele is known to increase the risk for AD in cognitively normal individuals, possibly because of less effective neural protection and repair mechanisms as compared with the other allelic variants (1,2). Subjective memory complaints are very common in the elderly, with prevalence estimates of 25% to 50%, and may represent preclinical signs of incipient dementia (35), although their predictive value remains to be validated (35,36). Our data show that the relationship between AD-related CSF and CMRglc measures differs in normal subjects as a function of the ApoE genotype and is further modulated by the presence of SMC.

There are no prior reports of an association between FDG-PET and CSF measures in normal subjects. Of the two published FDG-PET and CSF studies, one reported an association between reduced CMRglc and increased P-Tau levels in MCI (20) and the other a relationship between CMRglc and CSF A β 42 levels, but no relationship with T-Tau, in a group of patients with AD and other dementing disorders (19). However, an [123 I]iodoamphetamine (123 IMP) single photon emission computed tomography (SPECT) study by the same authors showed an association between cerebral perfusion and CSF T-Tau, which predicted decline from MCI to AD (37).

Our E4 carriers showed significantly higher levels of CSF IP, P-Tau, T-Tau, and P-Tau/A β 42 as compared with the noncarriers. The groups were comparable for clinical and demographic characteristics and showed a similar performance on neuropsychological testing. These findings are consistent with previous reports of significantly higher CSF IP levels in AD patients carrying the E4 allele as compared with noncarriers (13). There are no previous studies of P-Tau and P-Tau/A β 42 measures in E4 carriers.

Although CSF measures were not different between SMC groups, there was a significant interaction between ApoE and SMC status, which was driven by the E4 carriers with SMC who had significantly higher IP, P-Tau, and P-Tau/A β 42 as compared with the noncarriers. Previous studies showed that CSF IP and P-Tau are increased in AD and MCI patients (38–41), and P-Tau₁₈₁/A β 42 measures increase in nondemented adults prior to developing dementia (16). Our study shows that P-Tau₂₃₁/A β 42 measures are significantly higher in NL E4 carriers and even more in those with SMC. Among different possible P-Tau epitopes, P-Tau₂₃₁ levels are thought to be specific for AD (12,42,43). Although oxidative stress is

common in most neurodegenerative diseases, there is also evidence that IP levels distinguish AD from other dementias (44,45).

No differences were found for CSF A β 40 and A β 42 between ApoE and SMC groups. A previous study showed that A β 42 levels are decreased in NL elderly E4 carriers as compared with noncarriers in an E4 allele dose-dependent fashion (17). Although limited by the small number of subjects, we also found progressively reduced A β 42 levels: noncarriers (1305 ± 504 pg/mL) > E4 heterozygotes (1191 ± 450 pg/mL) > E4 homozygotes (883 ± 272 pg/mL). The 40 amino acid form of β -amyloid (A β 40) showed a similar trend. Since A β effects were reported in normal E4 carriers (17), MCI, and AD (46–48), the present lack of group differences may depend on the small sample size. Alternatively, P-Tau and IP levels were significantly different between groups, suggesting that alterations in these biomarkers may be detectable in the CSF of normal E4 carriers prior to A β changes. Longitudinal examination of our study subjects as well as other studies with larger samples are needed to replicate these findings and to address questions related to potential pathophysiological models of AD (49).

Our E4 carriers showed CMRglc reductions in the parieto-temporal, occipital, and frontal cortices; fusiform gyrus; and thalamus as compared with the noncarriers. These results are consistent with previous FDG-PET studies showing that CMRglc abnormalities in middle-aged and young normal E4 carriers involve brain regions typically affected in AD (e.g., parieto-temporal cortices) and also extend to other regions that decline metabolically with aging, like the frontal and occipital regions and thalamus (3–5). Although the functional significance of progressive CMRglc reductions in aging-related regions remains to be established, they may reflect an interaction between the E4 allele and aging rather than a static trait (3–5). On the other hand, we did not find CMRglc deficits in the posterior cingulate cortex (PCC) of our E4 carriers, which was found in some FDG-PET ApoE studies (3,5) but not in others (6,10). Since PCC hypometabolism appears to be an early sign of AD (7), possibly associated with the onset of episodic memory deficits (10), it remains to be established whether our subjects will also develop PCC CMRglc abnormalities.

Subjects with SMC showed hypometabolism in the PHG, parieto-temporal, and frontal cortices as compared with subjects without SMC. There are no previous FDG-PET studies directly comparing NL subjects with and without SMC. Our data are in agreement with MRI studies showing that SMC in subjects without cognitive impairment is associated with greater medial temporal lobes (MTL) atrophy, including the PHG, and neocortical regions (50,51). Parahippocampal gyrus CMRglc abnormalities in subjects with SMC may have an impact on subjects' awareness of memory decline.

Moreover, CMRglc reductions in the E4 carriers with SMC were exacerbated in the PHG and its functionally associated temporal and occipital regions and thalamus (52). The PHG region mainly included the entorhinal cortex, an MTL key brain region for memory (53). The E4 carriers with SMC had three to four times greater risk of having reduced PHG CMRglc and increased IP and P-Tau/A β 42 levels as compared with all other subgroups. These findings suggest that the E4 genotype and the presence of SMC may confer risk for cognitive impairment in an incremental fashion, as reflected not only in more severe and extended CMRglc reductions but also elevated CSF markers for AD pathology.

Amyloid and neurofibrillary tangles (NFT) PET imaging (54,55) may provide more regionally specific information about the underlying distribution of AD pathology. Nonetheless, the association between PHG hypometabolism and increased CSF IP and P-Tau is consistent with the expected effects of progressive AD pathology resulting in MTL NFT, neuronal loss, and volume reductions (56–58). Consistently with our findings, MTL CMRglc and perfusion were shown to correlate with regional densities of NFT but not senile plaques (59,60).

Our determination of SMC is vulnerable to error. There are no established criteria for SMC, SMC do not presently constitute a universally accepted clinical entity, and the association between SMC and AD remains to be established (35,36). To reduce potential for misclassification, all our subjects were carefully screened for conditions potentially related to reporting memory complaints, such as depression, and uniform structured procedures were used in all clinical exams. Nonetheless, our SMC cohort may have included subjects with a tendency to underestimate their level of cognitive functioning, and some of the subjects without SMC may be denying perceived deficits. In either case, this would lead to erroneous distribution of subjects across groups, with the effect of conservatively reducing group differences. Our results suggest that individuals with SMC possess some insight into their level of functioning, which may be related to CMRglc changes in memory-related brain regions.

The E4 genotype is also a risk factor for vascular disease (61). None of the subjects in the present study had significant cerebrovascular disease or showed evidence for cortical or lacunar infarcts or extensive white matter disease. It is unlikely that small vessel disease, which usually is a subcortical phenomenon, may have impacted the FDG-PET results.

The present cross-sectional results need to be replicated with larger samples and longitudinal follow-ups to assess whether the CMRglc and CSF abnormalities are predictive of cognitive decline.

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Figure 1.

Statistical parametric maps showing CMRglc reductions in (A) ApoE E4 carriers (E4+) as compared with noncarriers (E4-), (B) subjects with subjective memory complaints (SMC+) as compared with those without (SMC-), and (C) ApoE by SMC interaction effects. (D) Posthoc analyses for the ApoE by SMC interactions showing the size of effect in the brain regions identified in (C), plotted for E4-/SMC- (white), E4-/SMC+ (light gray), E4+/SMC- (dark gray), and E4+/SMC+ (black). Anatomical location and description of brain regions are found in Table 2. Areas of hypometabolism are represented on a red to yellow color-coded scale, reflecting progressively higher Z scores, and displayed (from left to right) onto the inferior, left lateral, left medial, anterior, and posterior views of a volume-rendered spatially normalized MRI. ApoE, apolipoprotein E; CMRglc, cerebral metabolic rate of glucose; E4, allele of the apolipoprotein E gene; ITG, inferior temporal gyrus; MiOG, middle occipital gyrus; MRI, magnetic resonance imaging; PHG, parahippocampal gyrus; SMC, subjective memory complaints; Thal, thalamus.

Figure 2.

CSF-CMRglc indexes: group differences as a function of ApoE by SMC effects. Legend: E4+ = E4 carriers, E4- = noncarriers, SMC- = subject with no SMC, SMC+ = subjects with SMC. Error bars are SEM. ApoE, apolipoprotein E; CSF, cerebrospinal fluid; CMRglc, cerebral metabolic rate of glucose; E4, allele of the apolipoprotein E gene; SMC, subjective memory complaints.

Figure 3.

Combinations of CSF-CMRglc (unitless) and CMRglc ($\mu\text{mol/g/min}$) measures in discriminating (A) E4+ from E4-, (B) SMC- from SMC+, and (C) E4+/SMC+ from the other subgroups. Lines show the best group separation, as determined from logistic regressions. CSF, cerebrospinal fluid; CMRglc, cerebral metabolic rate of glucose; E4, allele of the apolipoprotein E gene; SMC, subjective memory complaints.

Table 1
Subject Characteristics by ApoE and SMC Group

	E4-		E4+	
	SMC-	SMC+	SMC-	SMC+
<i>N</i>	7	8	7	6
Age (years)	63 (5), 46–70	60 (9), 42–70	54 (9), 40–69	59 (7), 48–70
Gender (M/F)	3/4	3/5	2/5	1/5
Education (years)	17(2)	16(2)	17(2)	17(1)
E4 Heterozygotes/Homozygotes	NA	NA	4/3	5/1
Neuropsychological Measures				
MMSE	29.0 (.9), 28–30	29.5 (.8), 28–30	29.8 (.4), 29–30	29.3 (.8), 28–30
Designs	8(2)	9(2)	7(2)	7(2)
Digit Symbol Substitution	66(8)	63(12)	68(7)	60(10)
Object naming	57(2)	53(10)	59(2)	56(5)
Paired Associates Delayed Recall	10(4)	9(2)	10(4)	10(1)
Paragraph Delayed Recall	8(3)	6(4)	6(3)	6(3)
Perceptual Speed	78(5)	82(10)	79(3)	85(10)
CSF Measures (pg/mL)				
Aβ40	9513(2284)	8185(2967)	7552(2778)	9302(2916)
Aβ42	1264(456)	1338(572)	942(377)	1276(420)
Isoprostane	30(7)	25(9)	30(10) ^a	41(14), ^{ab}
T-Tau ₂₃₁	8(4)	6(4)	9(8) ^a	12(5), ^{ab}
T-Tau	323(139)	204(113)	384(226) ^a	372(163) ^a
Aβ42/Aβ40 (unitless)	.13(.03)	.16(.03)	.13(.03)	.14(.03)
P-Tau ₂₃₁ /Aβ42 × 100 (unitless)	.71(.38)	.52(.32)	.84(.59) ^a	1.01(.51), ^{ab}

Values are mean (SD), range.

CSF measures are adjusted for demographic variables.

Aβ40, 40 amino acid form of β-amyloid; Aβ42, 42 amino acid form of β-amyloid; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; E4-, ApoE E4 noncarriers; E4+, ApoE E4 carriers; F, female; M, male; MMSE, Mini Mental State Examination; NA, not applicable; P-Tau, hyperphosphorylated tau; SMC-, no subjective memory complaints; SMC+, subjective memory complainers; T-Tau, total tau.

^a E4+ higher than E4-, $p < .05$.

^b E4+/SMC+ higher than E4-/SMC- and E4-/SMC+, $p < .05$.

Table 2

Brain Regions Showing Significant CMRglc Effects from Two-Way GLM Analysis of ApoE and SMC Status and Their Interaction

Ke	Coordinates ^a	Z ^b	Functional Area	BA
ApoE E4 carriers < Noncarriers				
350	-33 -94 -5	3.79	Middle occipital gyrus	18
	-38 -77 8	3.06	Middle occipital gyrus	19
244	-58 -53 -12	3.04	Inferior temporal gyrus	37
	-58 -54 -8	3.26	Middle temporal gyrus	37/21
	-52 -5 -23	2.85	Fusiform gyrus	20
117	17 17 -16	3.16	Inferior frontal gyrus	47
110	-63 -37 28	4.02	Inferior parietal lobe	40
68	-15 -21 1	3.10	Thalamus	
40	-40 42 33	2.91	Superior frontal gyrus	9
35	24 55 -1	2.82	Superior frontal gyrus	10
SMC+ < SMC-				
1747	63 -12 -12	4.60	Middle temporal gyrus	21
	-26 -24 -20	3.91	Parahippocampal gyrus	35
	29 -21 -24	3.87	Parahippocampal gyrus	36
468	-63 -37 28	4.02	Inferior parietal lobe	40
	-62 -39 32	2.86	Inferior parietal lobe	40
314	-14 22 -20	4.02	Inferior frontal gyrus	47
68	-37 -56 -12	3.65	Fusiform gyrus	37
113	66 -37 -1	3.34	Middle temporal gyrus	21
126	22 1 8	3.34	Putamen	
273	-58 -23 -20	3.33	Inferior temporal gyrus	20
60	-11 -18 4	3.19	Thalamus	
ApoE by SMC Interactions				
510	27 -3 -16	3.84	Parahippocampal gyrus/amygdala	
	-18 -5 -24	3.49	Parahippocampal gyrus	28
	19 17 -16	3.23	Inferior frontal gyrus	47
151	-11 -18 4	3.47	Thalamus	
284	-33 -8 -32	3.40	Inferior temporal gyrus	20
90	-48 -83 -4	3.09	Middle temporal gyrus	19
51	-62 -52 -4	2.97	Middle temporal gyrus	21

ApoE, apolipoprotein E; BA, Brodmann area; CMRglc, cerebral metabolic rates for glucose; E4, allele of the ApoE gene; FEW, family-wise error; GLM, general linear model; Ke, cluster extent; SMC, subjective memory complaints.

^aCoordinates (x, y, z) from the atlas of Talairach and Tournoux (33): x is the distance in mm to the right (+) or left (-) of midline; y is the distance anterior (+) or posterior (-) to the anterior commissure, and z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

^bZ values at the peak of maximum statistical significance at $p < .05$, FWE corrected.

Table 3
Group Discrimination Accuracy of CSF, CMRglc and CSF-CMRglc Measures, and Their Combinations

	OR	95% CI	A	SS	SP	p
E4+vs. E4-						
IP	.9	.8-1.0	57	62	53	.05
P-Tau/A β 42	1.5	.7-5.6	68	62	73	.037
IP-PHG	1.7	1.1-2.6	57	62	53	.015
MIoG CMRglc	2.3	1.2-4.3	68	77	60	<.001
P-Tau-MiOG	2.3	1.2-4.5	68	62	73	.001
P-Tau-MiOG + IP-PHG	4.1	1.1-5.3	86	85	87	<.001
SMC+vs. SMC-						
PHG CMRglc	2.4	1.3-4.8	75	71	79	<.001
IP-IPL	2.7	1.2-5.9	75	71	79	<.001
PHG CMRglc + IP-IPL	5.6	1.5-50	93	93	93	<.001
E4+/SMC+ vs. Other Subgroups						
ITG CMRglc	2.3	1.1-5.9	82	83	82	.001
IP-PHG	3.1	1.4-9.1	79	83	77	.001
PHG CMRglc	3.5	1.1-11.0	82	100	77	.001
IP-PHG + P-Tau/A β 42	3.7	1.7-15.2	86	100	82	.005

A, accuracy; A β 42, 42 amino acid form of β -amyloid; ApoE, apolipoprotein E; CI, confidence interval; CMRglc, cerebral metabolic rate of glucose; CSF, cerebrospinal fluid; E4-, ApoE E4 allele carriers; E4+, ApoE E4 allele noncarriers; IP, isoprostane; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; MIoG, middle occipital gyrus; OR, odds ratio; *p*, *p* values from logistic regressions; PHG, parahippocampal gyrus; P-Tau, phosphorylated tau; SMC+, subjects with subjective memory complaints; SMC-, subjects without subjective memory complaints; SS, sensitivity; SP, specificity; Thal, thalamus.