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Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism

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Having a parent affected with late-onset Alzheimer's disease (AD) is a risk factor for developing AD among cognitively normal subjects. We examined whether cognitively normal subjects with a parental family history of AD show cerebral metabolic rate of glucose (CMRglc) reductions consistent with AD as compared with those without a family history and whether there are parent gender effects. Forty-nine 50- to 80-year-old normal subjects were examined who received clinical, neuropsychological, and 2-[^{18}F]fluoro-2-deoxy-D-glucose–positron emission tomography examinations, including 16 subjects with a maternal (FHm) and eight with a paternal (FHp) family history of AD and 25 with no family history (FH$^-$). FH groups were comparable for demographic and neuropsychological measures. As compared with both FH$^-$ and FHp groups, FHm subjects showed CMRglc reductions in the same regions as clinically affected AD patients, involving the posterior cingulate cortex/precuneus, parietotemporal and frontal cortices, and medial temporal lobes ($P < 0.05$, corrected for multiple comparisons). These effects remained significant after accounting for possible risk factors for AD, including age, gender, education, apolipoprotein E genotype, and subjective memory complaints. No CMRglc differences were found between FHp and FH$^-$ subjects. This study shows a relationship between reduced CMRglc in AD-vulnerable brain regions and a maternal family history of AD in cognitively normal individuals.

After advanced age, the most significant risk factor for late-onset Alzheimer's disease (AD) is a family history of AD (1). Normal individuals with a first-degree relative affected by AD, especially a parent, are at a 4- to 10-fold higher risk for developing AD as compared with individuals with a negative family history (2–4). Apart from the rare early-onset form of familial AD related to autosomal dominant genetic mutations, genes with a clear Mendelian pattern of transmission for late-onset familial AD have not been identified. To date, the ε4 allele of the apolipoprotein E (ApoE) gene is the only established genetic risk factor for late-onset AD and is found in ≈40% of late-onset AD cases with a positive family history (1). The ApoE-4 genotype has, however, no clear familial pattern of transmission and appears to act as a risk modifier by lowering the age at onset of clinical symptoms, rather than as a genetic determinant (see ref. 5 for review), indicating that other factors contribute to the etiology and phenotypic expression of disease. The biological mechanisms through which family history of AD confers increased susceptibility to late-onset AD are not known.

A consistent feature of AD is the marked reduction of the cerebral metabolic rate of glucose (CMRglc) as measured by using positron emission tomography (PET) imaging with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) as the tracer (FDG-PET). FDG-PET studies demonstrate a specific pattern of CMRglc impairment in AD, involving the parietotemporal, posterior cingulate, and to a lesser extent frontal cortices and medial temporal lobes (MTL) (6). CMRglc reductions within these regions occur years before symptom onset and predict clinical decline in individuals from families with early-onset familial AD (7, 8), as well as in patients with mild cognitive impairment (MCI) (9–12), often a prodrome to late-onset AD (13). Our recent FDG-PET studies showed that reduced CMRglc in the MTL, a specific early target for AD pathology (14), predicts decline to MCI and AD among normal elderly (15, 16).

The present FDG-PET study in cognitively normal elderly examines the associations between parental family history of late-onset AD and CMRglc. Moreover, we compared the effects of having a maternal family history as compared with a paternal family history. Because the risk for AD in individuals with a family history of AD is further increased when an ApoE-4 allele is present (3), and the ApoE-4 genotype affects CMRglc (17–19), we also examined the data for interactions between family history and ApoE genotype.

Results

Clinical and Cognitive Measures. A total of 78 clinically and cognitively normal elderly had complete FDG-PET and family history evaluations. From this cohort, 49 subjects were selected that fulfilled the study criteria, including 25 subjects who did not have a family history of any dementia (FH$^-$) and 24 subjects with a single-parent family history of AD (FH$^+$). The FH$^+$ group included eight subjects with only the father affected with AD (FHp) and 16 subjects with only the mother affected with AD (FHm).

Of the 29 subjects that were not included in the analysis, seven were FH$^-$ but were excluded because of technical reasons related to the PET scans (i.e., artifacts or incomplete head coverage that precluded image size normalization; see below), three subjects had parents that died before the age of risk for AD, three had both parents affected with AD, seven had only siblings affected with AD, and nine reported a family history of an unspecified dementia and were conservatively excluded.

Demographic characteristics and neuropsychological test scores of the subjects under study are shown in Table 1. There were no significant differences between groups for age, years of education, prevalence of the ApoE-4 genotype, prevalence of subjective memory complaints, Mini Mental State Examination scores, and neuropsychological test performances. Gender distribution differed across groups; the percentage of females was lower in the FHp group (25%) as compared with both FH$^-$ and FHm groups (76% and 69%, respectively; $\chi^2_{(2)} = 7.1$; $P = 0.03$).

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Abbreviations: MTL, medial temporal lobe; PCC, posterior cingulate cortex; CMRglc, cerebral metabolic rate of glucose; FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; PET, positron emission tomography; GLM, general linear model; AD, Alzheimer's disease; SVC, small-volume random field correction; BA, Brodmann area; ApoE, apolipoprotein E; MCI, mild cognitive impairment.

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Table 1. Subject characteristics by family history groups

Characteristics	FH−	FHp	FHm
N	25	8	16
Age, years [range]	69 (8) [48–80]	67 (8) [52–78]	63 (8) [46–75]
Gender, F/M [% F]	19/6 [76]	2/6 [25]*†	11/5 [69]
Education, years	16 (2)	17 (1)	16 (2)
ApoE-4, yes/no [% ApoE-4]	9/16 [36]	3/5 [38]	6/10 [38]
SMC, yes/no [% SMC]	20/5 [80]	6/2 [75]	9/7 [56]
MMSE	29.4 (0.9)	29.7 (0.7)	29.7 (0.5)
Designs	6.7 (2.3)	6.0 (3.3)	6.5 (1.8)
Digit symbol substitution	57 (8)	52 (12)	58 (10)
Object naming	57 (3)	57 (2)	57 (2)
Paired associates	8.2 (3.8)	7.7 (4.7)	7.8 (4.2)
Paragraph delayed recall	6.4 (2.7)	5.8 (4.2)	6.4 (2.6)
WAIS vocabulary	68 (10)	67 (8)	69 (9)

Values are mean (SD). ApoE-4, apolipoprotein E-4 genotype; FH, parental family history of AD; FH−, negative FH; FHm, maternal FH; FHp, paternal FH; MMSE, Mini Mental-State Examination; SMC, subjective memory complaints.
*Lower than FH− ($P < 0.05$).
†Lower than FH− and FHm ($P < 0.05$).

At the time of the FDG-PET, six of 49 (12%) participants were taking medications. In the FHm group, one subject was on estrogen replacement therapy. In the FHp group, one subject was taking antihypertensive drugs. In the FH− group, two subjects were taking cholesterol-lowering drugs, one was taking antihypertensives, and one was on estrogen replacement therapy.

FDG-PET Measures. As compared with FH−, FH+ subjects showed CMRglc reductions bilaterally in the inferior parietal lobe and the posterior cingulate cortex (PCC), superior temporal gyrus, inferior and superior frontal cortex, and MTL, including the hippocampus and parahippocampal gyrus, of the left hemisphere [$P < 0.05$, small-volume random field corrections (SVC)] (Table 2). Results remained significant after controlling for age, gender, education, ApoE genotype, and the presence of subjective memory complaints. At $P < 0.001$ (uncorrected) two additional clusters in the left hemisphere reached significance in the anterior cingulate cortex [Brodmann area (BA) 24, 311 voxels, $x = -5, y = 34, z = 20, Z = 2.36$] and the inferior frontal gyrus (BA 46, 298 voxels, $x = -45, y = 31, z = 25, Z = 2.86$).

Comparison of the three groups (FH− vs. FHp vs. FHm) revealed that the CMRglc reductions observed in the FH+ as compared with the FH− subjects were driven by the FHm group, which showed reduced CMRglc in the above as well as in additional regions as compared with both FH− and FHp groups.

With and without controlling for age, gender, education, ApoE genotype, and the presence of subjective memory complaints, as compared with FH−, FHm subjects showed CMRglc reductions bilaterally in the inferior parietal lobe and middle temporal gyrus, and in the PCC/precuneus, superior frontal gyrus, and MTL of the left hemisphere ($P < 0.05$, SVC) (Table 3 and Fig. 1). CMRglc reductions ranged from 8% in the left superior frontal gyrus to 22% in the left PCC (Table 4 and Fig. 2). At $P < 0.001$ (uncorrected) two additional clusters reached significance, in the inferior frontal cortex in the left hemisphere (BA 46, 367 voxels, $x = -46, y = 29, z = 20, Z = 3.18$) and right hemisphere (BA 46, 219 voxels, $x = 48, y = 27, z = 20, Z = 2.89$).

With and without controlling for the above confounds, as compared with the FHp group, the FHm group showed reduced CMRglc bilaterally in the middle and superior temporal gyrus, and in the left PCC/precuneus and MTL ($P < 0.05$, SVC) (Table 3 and Fig. 1). CMRglc reductions ranged from 5% in the right middle temporal gyrus [general linear model (GLM), $P = 0.05$; Mann–Whitney, $P = 0.044$] to 27% in the PCC/precuneus (GLM, $P = 0.001$; Mann–Whitney, $P = 0.001$) (Table 4 and Fig. 2). No additional clusters reached significance at $P < 0.001$ (uncorrected).

Analysis of the three demographically matched and size-matched FH groups confirmed the CMRglc effects in the right inferior parietal lobe ($F_{(2,21)} = 3.79, P = 0.041$), in the left PCC/precuneus ($F_{(2,21)} = 4.31, P = 0.029$), and in the bilateral temporal gyri ($F_{(2,21)} = 3.53$, $F_{(2,21)} = 3.49$, $P < 0.05$). The FHm group had reduced CMRglc as compared with FH− in all these regions, ranging from 8% in the right middle temporal gyrus to 31% in the PCC/precuneus ($P < 0.05$), and reduced CMRglc in the left middle temporal gyrus (17%, $P = 0.036$) and the PCC/precuneus (23%, $P = 0.017$) as compared with the FHp group.

Among the eight FHp subjects, three were ApoE-4 carriers. Therefore, there were not enough FHp subjects to examine FH by ApoE interactions across all groups simultaneously. We examined FH by ApoE status interactions in the FH− and FHm groups and did not find ApoE effects or FH by ApoE interactions ($P \geq 0.57$). On nonparametric analysis, there were no differences between ApoE-4 carriers and non-carriers within the FHp group ($P \geq 0.88$).

When the analysis was restricted to the ApoE-4 non-carriers, the FHm group still showed CMRglc reductions in the same regions as above as compared with the FH− group ($P \leq 0.05$) and, as compared with the FHp group, showed CMRglc reductions in the left PCC (25%; GLM, $P = 0.005$; Mann–Whitney, $P = 0.002$), left MTL (17%; GLM, $P = 0.041$; Mann–Whitney, $P = 0.027$), left and

Table 2. Brain regions showing significant CMRglc reductions in FH+ subjects as compared with FH− subjects

Cluster extent	Coordinates*	*Z* value†	Functional area	BA
940	−60, −37, 35	3.07	Inferior parietal lobe	40
799	62, −48, 28	3.33	Inferior parietal lobe	40
664	−48, 53, 8	2.95	Superior frontal gyrus	10
392	−28, −23, −8	2.76	Hippocampus	
	−20, −21, −12	2.54	Parahippocampal gyrus	35
220	−16, −63, 16	2.88	PCC	31
208	−62, −49, −4	2.62	Superior temporal gyrus	21

*Coordinates (*x*, *y*, *z*) from the atlas of Talairach and Tournoux (46). *x* is the distance in millimeters 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.
†*Z* values at the peak of maximum statistical significance at $P < 0.05$, SVC (47). On post hoc examination, these regional effects were driven by the FHm group, which showed reduced CMRglc as compared to both FH− and FHp groups, whereas no differences were found between FH− and FHp groups (see Table 3 and Fig. 2).

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Table 3. Brain regions showing significant CMRglc reductions in subjects with maternal family history of AD as compared with the other groups

Cluster extent	Coordinates*	*Z* values†	Functional area	BA
	CMRglc reductions in FHm subjects as compared with FH⁻ subjects			
1,056	−4, −70, 24	2.86	Precuneus	7
	−3, −67, 20	2.75	PCC	31
710	−43, −35, 39	2.69	Inferior parietal lobe	40
	−39, −56, 30	2.63	Inferior parietal lobe	40
	−61, −48, −4	2.60	Superior temporal gyrus	21
569	−28, −23, −8	2.70	Hippocampus	
	−20, −21, −12	2.65	Parahippocampal gyrus	35
	−21, −24, −8	2.35	Parahippocampal gyrus	28
357	52, −52, 32	3.23	Inferior parietal lobe	40
300	−23, 54, 4	2.75	Superior frontal gyrus	10
237	62, −43, −8	2.55	Superior temporal gyrus	21/37
	63, −46, −4	2.52	Middle temporal gyrus	21
171	−55, 2, −8	2.97	Middle temporal gyrus	21
	CMRglc reductions in FHm subjects as compared with FHp subjects			
231	−25, −29, −8	3.08	Hippocampus	
	−19, −28, −8	2.39	Parahippocampal gyrus	28/35
676	−65, −16, 8	4.09	Middle temporal gyrus	22
	−64, −32, −4	3.38	Superior temporal gyrus	21
873	7, −61, 8	3.63	Cingulate gyrus	23/30
	4, −58, 12	3.49	Cingulate gyrus	23
510	64, −26, −8	3.40	Middle temporal gyrus	21
410	−4, −71, 24	2.69	Precuneus	7
	−3, −65, 21	2.55	PCC	31

*See legend to Table 2.

†*Z* values at the peak of maximum statistical significance at $P < 0.05$, SVC (47).

right middle temporal gyrus (11% and 16%, respectively; GLM, $P = 0.049$ and $P = 0.004$; Mann–Whitney, $P = 0.027$ and $P = 0.002$).

Discussion

The present results show that cognitively normal FHm individuals have reduced CMRglc in the MTL, parietotemporal, posterior cingulate, and frontal cortices as compared with FHp and FH⁻ subjects. These CMRglc reductions showed the same topography as the typical pattern of hypometabolism detected in clinical AD patients as compared with age-matched controls [supporting information (SI) Fig. 3] and remained significant after accounting for potential risk factors for late-onset AD such as age, female gender, education, ApoE-4 genotype, and the presence of subjective memory complaints.

CMRglc reductions within the MTL, parietotemporal, and posterior cingulate cortices are known to precede the onset of AD by many years (6). FDG-PET studies of presymptomatic individuals carrying autosomal dominant mutations responsible for early-onset familial AD also show consistent hypometabolism in these regions, as long as 15 years before symptoms onset (7, 8). Studies in MCI, considered by many as a transitional state between healthy aging and dementia (13), have shown severe hypometabolism in these same brain regions among MCI patients before converting to AD as compared with those who remained stable over time (9–11, 20). We recently showed that reduced MTL CMRglc in normal elderly is a risk factor for declining to MCI and AD (15, 16). Our normal FHm individuals showed reduced CMRglc in the MTL as compared with the other groups. The MTL region contained the hippocampus and the anterior portion of the entorhinal cortex, two key brain regions for memory functions and early targets of AD pathology (14). Longitudinal examination of our subjects are needed to establish whether the observed CMRglc reductions predispose FHm individuals to develop clinical symptoms of AD.

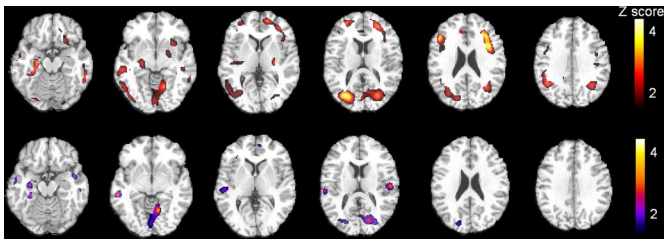

Fig. 1. Statistical parametric maps showing CMRglc reductions in normal FHm subjects as compared with FH⁻ (*Upper*) and FHp (*Lower*) subjects. Anatomical location and description of brain regions are in Table 2. Areas of hypometabolism are represented on red-to-yellow and purple-to-yellow color-coded scales for the two contrasts, reflecting *Z* scores between 2 and 4, and displayed on a standardized spatially normalized MRI.

There are no previous imaging studies that compared subjects with maternal and paternal family history of AD. A functional MRI study of normal individuals showed that subjects with a family history of AD failed to activate the MTL during an encoding task as compared with subjects with a negative family history (21). An FDG-PET study compared persons with age-related memory impairment with and without first-degree relatives with AD and did not report CMRglc differences between groups (22). Our FDG-PET data in normal subjects shows that, by combining FHm and FHp subjects into a single positive family history group, there are significant cortical and MTL CMRglc reductions in FH⁺ as compared with FH⁻ subjects. However, post hoc examinations demonstrated that these effects were driven by the CMRglc reductions in the FHm as compared with both FHp and FH⁻ groups. This observation suggests that the previously reported absence of CMRglc differences between memory-impaired patients with and without a family history of AD (22) might be due to the confounding effects of disease on CMRglc and inclusion of individuals with maternal and paternal family history, as well as other first-degree relatives, in the same group.

Epidemiological studies have provided evidence for both maternal and paternal transmission of AD (23, 24), but none of these studies used biological measures to characterize the phenotypes. There is, however, evidence for parent-of-origin effects in late-onset AD families. AD affects more women than men, with a relative of risk of 1.5 across different ethnic groups (3). Among AD patients with one affected parent the ratio mother:father affected is 3:1, whereas with one affected parent and two or more affected siblings the parent gender ratio goes up to 9:1 (23). A recent genetic study has identified new possible regions of linkage on chromosomes 10 and 12 only among families with maternal disease transmission (25).

Although our data do not offer insights into genetic mechanisms, they intuitively suggest either chromosome X transmission or inheritance of mtDNA. Chromosome X-linked inherited diseases are typically transmitted from the mother to the sons, whereas daughters can become carriers but typically do not develop disease unless a very rare X-linked dominant pattern is present. On the other hand, mtDNA is inherited solely from the mother in humans and is transmitted equally to siblings (see ref. 26 for review). Reexamination of our data for gender effects showed that, among FHm individuals, men did not show more severe CMRglc reductions as compared with women ($P \geq 0.57$, not significant). There were no significant CMRglc interactions between family history and gender across the three family history groups in any brain regions ($P \geq 0.20$, not significant). The absence of child gender effects appears to be more consistent with a mtDNA inheritance pattern. Moreover, although our CMRglc data need to be confirmed with a larger data set and X-linked mechanisms cannot be excluded, with all that is known about the molecular processes involved in glucose metabolism, the hypometabolism in FHm individuals is more likely due to possible mitochondrial deficits (26). mtDNA deficits were suggested to be involved in neurodegenerative diseases like AD and

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Table 4. FDG-PET CMRglc measures by family history groups

ROI CMRglc	FH⁻	FH⁺		Pairwise *P* values*	
		FHp	FHm	FH⁻ vs. FHm	FHp vs. FHm
Inferior parietal lobe, left	33.1 ± 4.2	30.6 ± 3.9	29.2 ± 5.3	0.012	
	(33.2 ± 3.4)	(30.9 ± 3.8)	(29.1 ± 3.5)	0.016	
Inferior parietal lobe, right	34.0 ± 6.0	33.1 ± 4.7	28.2 ± 5.7	0.003	0.054
	(34.2 ± 4.6)	(33.7 ± 3.8)	(27.5 ± 3.5)	0.002	0.025
Medial temporal lobe, left	30.0 ± 4.0	31.1 ± 3.8	25.6 ± 3.3	0.001	
	(30.5 ± 2.8)	(30.2 ± 2.4)	(25.5 ± 3.4)	0.003	
Middle temporal gyrus, left	34.9 ± 3.7	32.5 ± 3.7	28.4 ± 4.6	0.001	0.003
	(34.7 ± 3.6)	(32.3 ± 3.5)	(28.7 ± 2.8)	0.002	0.014
Middle temporal gyrus, right	33.2 ± 4.1	31.3 ± 2.3	29.6 ± 4.5	0.012	0.053
	(32.9 ± 3.5)	(31.6 ± 2.7)	(29.2 ± 2.9)	0.01	0.05
Superior frontal gyrus, left	43.0 ± 2.7	40.5 ± 2.5	39.1 ± 5.2	0.004	
	(42.9 ± 1.8)	(40.1 ± 2.4)	(39.5 ± 1.9)	0.009	
PCC/precuneus, left	34.1 ± 6.3	36.4 ± 3.9	26.5 ± 5.7	0.001	0.001
	(34.2 ± 5.1)	(35.7 ± 3.0)	(26.3 ± 3.3)	0.001	0.001
Whole brain	25.5 ± 4.7	24.6 ± 4.1	25.3 ± 4.2		

Values are mean CMRglc values ± SD adjusted for global CMRglc. Data in parentheses are adjusted for age, gender, ApoE, and the presence of subjective memory complaints. Anatomical localization of the above brain regions is in Table 2.

*There are no differences between FH⁻ and FHp, so no *P* values are presented.

Parkinson's disease (26). Studies of cytoplasmic hybrid (cybrid) cells provide direct evidence for mtDNA involvement in the metabolic abnormalities characteristic of AD. Cybrids are created by mixing mtDNA from patients' platelets with cell lines depleted of their own endogenous mtDNA, resulting in cell lines containing mtDNA from the patient (27). These cybrid cell lines grow under standard culture conditions, and assessment of their biochemical behavior allows evaluation of mitochondria activity and the mtDNA they carry. Cybrid data indicate that mtDNA at least partly accounts for impaired metabolism in AD, as reflected in increased reactive oxygen species production, mitochondrial respiratory enzymes defects, particularly affecting cytochrome oxidase complex IV (COX, i.e., the mitochondrial enzyme responsible for the activation of oxygen for aerobic energy metabolism critically tied to ATP production), decreased ATP production, enhanced amyloid-β toxicity, and a vastly increased percentage of morphologically abnormal mitochondria (28, 29).

A growing body of evidence indicates a deficient or altered energy metabolism that could change the overall oxidative microenvironment for neurons during the pathogenesis and progression of AD, rendering synapses more vulnerable to neurodegeneration (26). Oxidative stress is strongly associated with the known topographical distribution of neuronal loss and pathology observed in AD, mainly affecting the hippocampus, parietotemporal, and posterior cingulate cortices (30–33). Overall, our findings suggest that these CMRglc alterations may be in part maternally inherited in AD.

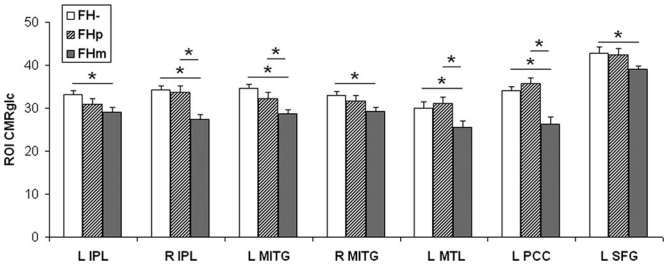

Fig. 2. Covariate-adjusted region of interest CMRglc by family history groups. Error bars are standard errors of the mean. Asterisks mark significant differences at $P < 0.05$.

Our determination of parental AD in the absence of neuropathological confirmation is vulnerable to error. We relied on a consensus diagnostic conference to review family history medical records, diagnoses were based on established clinical diagnostic criteria for AD (34, 35), and questionnaires used to elicit family history information are known to have good agreement with clinical and neuropathological findings (36), which reduce potential for misclassification. Nonetheless, our affected family history cohort may have included subjects whose parents did not have AD but had another dementia. This would lead to inclusion of subjects with decreased risk for AD in the affected family history group, with the effect of conservatively reducing power in detecting differences between groups. Moreover, our findings of hypometabolism in AD-vulnerable brain regions in FHm subjects as compared with the other groups indicate that our group assignment criteria were likely correct.

In our study group there were eight FHp subjects. The proportion of subjects per family history group in our study yields a ratio of affected mother:father of 2.3:1, which is consistent with prior estimates in the general population (23). Our FHp group did not show CMRglc deficits as compared with the FH⁻ and FHm groups, either in the whole data set or in the comparison of three demographically size-matched groups. However, there may be phenotypic differences associated with a paternal family history of AD that were not detected in the present analysis because of the small sample and conservative statistical procedures. Replication studies with larger samples are warranted to specifically examine this question.

Although the present CMRglc findings were independent of the ApoE-4 genotype, a relatively high proportion of subjects in our study (37%) were ApoE-4 carriers. This is likely because of the fact that the prevalence of ApoE-4 carriers is often higher in familial late-onset AD (3) and that subjects with a family history of AD, particularly with first-degree relatives affected, are more likely to worry about their cognitive status and seek clinical attention. Therefore, the ApoE-4 genotype is often overrepresented in the "worried-well" subjects who self-refer to memory clinics and associated research settings, such as ours. Future studies are needed to replicate these research findings in community-based samples.

The factors that confer risk for AD through family history of late-onset AD are poorly understood, and several co-occurring risk factors may be involved, including, but not limited to, gene–gene interactions, lifestyle, and environmental variables (5). Our data

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add to previous reports demonstrating an association between risk factors for AD and brain hypometabolism showing that cognitively normal healthy FHm individuals show CMRglc reductions in the same brain regions as affected AD patients. The present findings may motivate further research on parent-of-origin effects at the preclinical stages of AD. Continued follow-up examination of our subjects is necessary to determine whether the observed CMRglc reductions are related to ongoing AD rather than a trait feature with no clinical consequences. If these metabolic abnormalities predispose individuals to develop AD, FDG-PET studies of normal FHm individuals could provide a homogenous group to direct investigation of potential susceptibility genes for AD, to examine brain changes predisposing to AD, and to select participants for prevention studies. We caution that our observations were made with small numbers of subjects under controlled clinical conditions, and clinical application is not justified.

Materials and Methods

Subjects. This study retrospectively examined clinically and cognitively normal elderly who received an FDG-PET scan and completed thorough family history evaluations. Subjects were recruited at the Center for Brain Health and the Alzheimer's Disease Center at the New York University School of Medicine to participate as volunteers for FDG-PET studies of the aging brain. They came from multiple community sources, including individuals interested in research participation and risk consultation; self-referred individuals with cognitive complaints; and spouses, family members, and caregivers of impaired patients participating in other studies. Informed consent was obtained from all subjects. The study was approved by the New York University School of Medicine and Brookhaven National Laboratory (Upton, NY) institutional review boards.

All subjects received a standard diagnostic evaluation that included medical (history, physical, and laboratory), psychiatric, neuropsychological, and clinical MRI examinations completed within a 2-month window. Individuals with medical conditions or history of significant 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 including lacunes (see below), as well as use of psychoactive medications, were excluded. All subjects had normal fasting plasma glucose levels, blood pressure, cholesterol and high-density lipoprotein levels, and modified Hachinski ischemia scale scores of <4 (37).

Subjects were 46–80 years of age at baseline, had education ≥ 12 years, clinical dementia rating scores of 0 (38), global deterioration scale scores of ≤ 2 (39), and Mini Mental State Examination scores of 28–30. The neuropsychological testing battery included evaluation of verbal declarative memory (immediate and delayed recall of paired associates and delayed recall of a paragraph), attention/psychomotor speed (the Digit-Symbol Substitution Test of the WAIS-R), and the designs, object naming, and WAIS vocabulary tests. All subjects had normal cognitive test performance relative to appropriate normative values (15, 16).

A family history of dementia that included at least one first-degree relative whose dementia onset was between the ages of 65 and 80 years (4) was elicited by using the New York University School of Medicine Brain Aging Family History form, a 35-item questionnaire assessing 11 diseases (i.e., AD, Parkinson's disease, diabetes, etc.) over three generations of family members (grandparents, parents, and children). Participants were asked to fill in names, dates of birth, age at death, cause of death, and clinical information of affected family members. The information was confirmed with other family members in the interview with the examining neurologist. Subjects were not included if their parents had not lived to the age at risk of late-onset AD (i.e., 65 years). Only subjects with a positive family history with a single parent affected with AD (FH^+) were included in the present study. These subjects were divided into maternal (FHm; i.e., only the mother was affected with AD) and paternal (FHp; i.e., only the father was affected with AD) FH groups and compared with subjects without a family history of any dementia (FH^-).

ApoE genotype was determined by using standard PCR procedures (15). Subjects with one or two copies of the ApoE-4 allele were grouped as ApoE-4 carriers.

Brain Imaging. All participants completed the clinical, MRI, and FDG-PET exams within 2 months.

MRI. All subjects received a standardized whole-brain MRI scan protocol on a 1.5-T GE Signa imager (General Electric, Milwaukee, WI), including a contiguous 3-mm axial T2-weighted image and a T1-weighted fast gradient echo image (25-cm field of view, number of excitation = 1, 256 × 128 matrix, 35-ms relaxation time, 9-ms excitation time, 1.2-mm sections, and 60° flip angle). These scans were used to rule out MRI evidence of hydrocephalus, intracranial mass, strokes, subcortical gray matter lacunes, and moderate to severe nonspecific white matter disease (40).

FDG-PET. Each subject received a PET scan at Brookhaven National Laboratory using FDG as the tracer on an ECAT CTI-931 scanner (Siemens, Knoxville, TN; 10-cm axial and 20-cm transaxial field of view, 6.2-mm FWHM, 6.75-mm interslice distance). Subjects received 5–8 mCi of FDG intravenously while lying supine in a dimly lit room. Each subject's head was positioned by using two orthogonal laser beams and imaged with the scanner tilted 25° negative to the canthomeatal plane. PET images were obtained 35 min after injection and acquired as two interleaved 15-slice PET volumes that overlapped by a half-slice thickness (≈3.4 mm) over two 10-min frames to improve the counting statistics (41). Arterial blood samples were drawn at standard intervals throughout the study, and absolute CMRglc measures (micromoles per 100 g per minute) were calculated by using Sokoloff's model with standard kinetic constants (42, 43). Data were reconstructed by using filtered back-projection (Fourier rebinning/2D back-projection, Hanning filter with a frequency cutoff of 0.5 cycles per pixel) and corrected for attenuation by using $^{68}Ga/^{68}Ge$ transmission scans, scatter, and radioactive decay, yielding a 128 × 128 matrix with a pixel size of 1.56 mm.

Image Analysis. Statistical parametric mapping (SPM2; Wellcome Department of Neurology, London, U.K.) (44) was used for image analysis. FDG-PET images were spatially normalized to a standard FDG-PET brain template (45) in the Montreal Neurological Institute space, which approximates the Talairach and Tournoux space (46). The spatial normalization process involves estimating the optimum least-squares 12-parameter affine transformation, followed by an iterative estimate of local alignment based on a family of 7 × 8 × 7 discrete cosine functions (44). The spatially normalized PET images were then resampled with a voxel size of 1.5 × 1.5 × 1.5 mm and smoothed with a 12-mm FWHM Gaussian filter (44). Only voxels with values >80% of the whole mean CMRglc were included in the analysis, and only clusters exceeding an extent threshold of 30 voxels (i.e., more than two times the FWHM) were considered significant. Global calculation was obtained with respect to the mean voxel value while accounting for global CMRglc. Anatomical location of brain regions showing significant effects was described by using the Talairach and Tournoux coordinates using Talairach Daemon 12.0 (http://ric.uthscsa.edu/projects/talairachdaemon.html) after coordinates conversion from the Montreal Neurological Institute space to the Talairach space using linear transformations (www.mrc-cbu.cam.ac.uk/Imaging). CMRglc measures were extracted from the clusters of voxels showing significant group effects using the SPM-compatible Marsbar tool (www.mrc-cbu.cam.ac.uk/Imaging/marsbar.html) to be reexamined in further analyses (see below).

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Statistical Analysis. Analyses were done with SPSS 12.0 (SPSS, Chicago, IL) and SPM2 (44).

Differences in demographical and neuropsychological measures between the study groups were examined with χ^2 tests, Fisher's exact test, and analysis of covariance as appropriate. The GLM/univariate analysis of covariance was used to test for regional CMRglc differences between subjects with (FH^+) and without (FH^-) a family history of AD and to examine parent gender effects across FH groups (FH^- vs. FHp vs. FHm), controlling for the global CMRglc. Results were then reexamined controlling for other potential risk factors for late-onset AD, such as age, female gender, education, ApoE-4 genotype, and presence of subjective memory complaints.

For SPM analysis, main effects from the GLM were examined by using F contrasts to detect brain regions showing overall group effects, followed by post hoc t contrasts, which were used to perform pairwise (i.e., intergroup) comparisons within the brain regions that showed significant main effects. First, we examined whether there were CMRglc differences between FH^+ and FH^- groups. Second, we examined whether there were parent gender effects on CMRglc by comparing the three groups (FH^- vs. FHm vs. FHp). For all analyses, results were considered significant at $P < 0.05$ after correction for multiple comparisons according to the SVC (47). We used the MRIcro package (www.psychology.Nottingham.ac.uk/staff/cr1/mricro.html) to create a masking image from a set of predefined AD-related bilateral regions of interest, including the MTL (hippocampus and parahippocampal gyrus, BA 28/35), PCC/precuneus (BA 23/31/7), inferior parietal lobule (BA 40/39), superior and middle temporal gyrus (BA 21/22/37), and prefrontal cortex (BA 8/9/10) as candidate areas for CMRglc alterations (11). The mask was then applied to the full volume of data, and results were examined at $P < 0.05$ after correction for the number of comparisons in the searched volume defined by the masking image (234,566 mm^3 corresponding to 69,501 voxels, and 55.8 resolution elements) (47). SVC is a conservative procedure that reduces the potential for type 1 error without being overly conservative. However, this procedure does not allow assessment of significant results in the brain regions outside the masking image. Therefore, results were also examined at $P < 0.001$, uncorrected for multiple comparisons within the search volume.

Because of the small sample size of FHp subjects, all significant results from the above analyses were reexamined with the nonparametric Kruskal–Wallis test and post hoc Mann–Whitney rank sum tests to check for pairwise effects ($\alpha = 0.05$, exact significance, one-tailed). Moreover, we created three groups of eight subjects each, matched for age, gender, education, and ApoE genotype, and reexamined CMRglc for group effects by using the GLM with post hoc least significant difference tests to check for pairwise effects. Results were confirmed by using the nonparametric Kruskal–Wallis test with post hoc Mann–Whitney rank sum tests ($\alpha = 0.05$, exact significance, one-tailed).

Because the ApoE-4 genotype is associated with a positive family history of AD, the interaction between FH and ApoE genotype was also examined. Moreover, to examine whether a parental family history of AD affects CMRglc independent of ApoE genotype, the above analyses were repeated to examine FH status within the group of ApoE-4 non-carriers. Results were considered significant at $P < 0.05$.

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1. Farrer LA, Cuples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Rish N, Dujin CM (1997) *J Am Med Assoc* 278:1349–1356.
2. Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green (2004) *Genet Med* 6:192–196.
3. Green RC, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, Williams M, Hipps Y, Graff-Radford N, Bachman D, *et al.* (2002) *J Am Med Assoc* 287:329–336.
4. Silverman JM, Ciresi G, Smith CJ, Marin DB, Schnaider-Beeri M (2005) *Arch Gen Psychiatry* 62:565–573.
5. Tanzi RE, Bertram L (2001) *Neuron* 32:181–184.
6. Mosconi L (2005) *Eur J Nucl Med Mol Imaging* 32:486–510.
7. Kennedy AM, Newman SK, Frackowiak RS, Cunningham VJ, Roques P, Stevens J, Neary D, Bruton CJ, Warrington EK, Rossor MN (1995) *Brain* 118:185–205.
8. Mosconi L, Sorbi S, de Leon MJ, Li Y, Nacmias B, Bessi V, Tsui WH, Myoung PS, Fayyaz M, Caffarra P, *et al.* (2006) *J Nucl Med* 47:1778–1786.
9. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE (1997) *Ann Neurol* 42:85–94.
10. Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC (2003) *Neurology* 60:1374–1377.
11. Mosconi L, Perani D, Sorbi S, Herholz K, Nacmias B, Holthoff V, Salmon E, Baron JC, De Cristofaro MTR, Padovani A, *et al.* (2004) *Neurology* 63:2332–2340.
12. Drzezga A, Lautenschlager N, Siebner H, Riemenschneider M, Willoch F, Minoshima S, Schwaiger M, Kurz A (2003) *Eur J Nucl Med Mol Imaging* 30:1104–1113.
13. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Cummings J, *et al.* (2006) *Lancet* 367:1262–1270.
14. Ball MJ, Hachinski V, Fox A, Kirshen AJ, Fisman M, Blume W, Kral VA, Fox H (1985) *Lancet* 1:14–16.
15. de Leon MJ, Convit A, Wolf OT, Tarshish CY, De Santi S, Rusinek H, Tsui W, Kandil E, Scherer AJ, Roche A, *et al.* (2001) *Proc Natl Acad Sci USA* 98:10966–10971.
16. Mosconi L, De Santi S, Li J, Tsui WH, Li Y, Boppana M, Rusinek H, de Leon MJ (January 10, 2007) *Neurobiol Aging* 10.1016/j.neurobiolaging.
17. Small GW, Ercoli LM, Silverman DHS, Huang SC, Komo S, Bookheimer S, Lavretsky H, Miller K, Siddarth P, Rasgon NL, *et al.* (2000) *Proc Natl Acad Sci USA* 97:6037–6042.
18. Reiman EM, Caselli RJ, Chen K, Alexander GE, Bandy D, Frost J (2001) *Proc Natl Acad Sci USA* 98:3334–3339.
19. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J (2004) *Proc Natl Acad Sci USA* 101:284–289.
20. Drzezga A, Grimmer T, Riemenschneider M, Lautenschlager N, Siebner H, Alexopoulus P, Minoshima S, Schwaiger M, Kurz A (2005) *J Nucl Med* 46:1625–1632.
21. Johnson SC, Schmitz TW, Trivedi MA, Ries ML, Torgerson BM, Carlsson CM, Ashtana S, Hermann BP, Sager MA (2006) *J Neurosci* 26:6076–6069.
22. Small GW, Okonek A, Mandelkern MA, LaRue A, Chang L, Khonsary A, Ropchan JR, Blahd WH (1994) *Int Psychogeriatr* 6:23–44.
23. Edland SD, Silverman JM, Peskind ER, Tsuang D, Wijsman E, Morris JC (1996) *Neurology* 47:254–256.
24. Ehrenkrantz D, Silverman JM, Smith CJ, Birstein S, Marin D, Mohs RC, Davis KL (1999) *Am J Med Genet* 88:378–382.
25. Bassett SS, Avramopoulos D, Fallin D (2002) *Am J Med Genet* 114:679–686.
26. Lin MT, Beal MF (2006) *Nature* 443:787–795.
27. Lucas JJ, Kates JR (1976) *Cell* 7:397–405.
28. Trimmer PA, Swerdlow RH, Parks JK, Keeney PM, Bennett JP, Jr, Miller SW, Davies RE, Parker WD, Jr (2000) *Exp Neurol* 162:37–50.
29. Swerdlow RH, Parks JK, Cassarino DS, Maguire DJ, Maguire RS, Bennett JP, Jr, Davis RE, Parker WD, Jr (1997) *Neurology* 49:918–925.
30. Mutisya EM, Bowling AC, Beal MF (1994) *J Neurochem* 63:2179–2184.
31. Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Petersen RB, Perry G, *et al.* (2001) *J Neurosci* 21:3017–3023.
32. Valla J, Berndt JD, Gonzales-Lima F (2001) *J Neurosci* 21:4923–4930.
33. Simonian NA, Hyman BT (1994) *J Neuropathol Exp Neurol* 53:508–512.
34. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) *Neurology* 34:939–944.
35. American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (Am Psychiatr Assoc, Washington, DC), 4th Ed.
36. Kawas C, Segal J, Stewart WF, Corrada M, Thal LJ (1994) *Arch Neurol* 51:901–906.
37. Hachinski VC, Lassen NA, Marshall J (1974) *Lancet* 2:207–210.
38. Hanley JA, McNeil JS (1983) *Radiology* 148:839–843.
39. Reisberg B, Ferris SH, de Leon MJ, Crook T (1982) *Am J Psychiatry* 139:1136–1139.
40. George AE, de Leon MJ, Kalnin A, Rosner L, Goodgold A, Chase N (1986) *Am J Neuroradiol* 7:567–570.
41. Bendriem B, Dewey SL, Schlyer DJ, Wolf AP, Volkow ND (1991) *IEEE Trans Nucl Sci* 10:216–222.
42. Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M (1977) *J Neurochem* 28:897–916.
43. Reivich M, Alavi A, Wolf A, Fowler J, Russell J, Arnett C, MacGregor RR, Shiue CY, Atkins H, Anand A, *et al.* (1985) *J Cereb Blood Flow Metab* 5:179–192.
44. Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ (1995) *Hum Brain Mapp* 2:189–210.
45. Mosconi L, Tsui WH, De Santi S, Rusinek H, Li J, Convit A, Li Y, de Leon MJ (2005) *Neurology* 64:1860–1867.
46. Talairach J, Tournoux P (1988) *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme, Stuttgart, Germany).
47. Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996) *Hum Brain Mapp* 4:58–73.

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