Cerebral glucose metabolism in patients with AD and different *APOE* genotypes

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Abstract—*Objective:* To examine the influence of the *APOE* ϵ4 allele on cerebral glucose metabolism in a large series of patients with Alzheimer disease (AD). *Methods:* Eighty-three patients (41 *APOE* ϵ4 positive and 42 ϵ4 negative) were selected from a pre-existing databank of patients with AD ($n > 1,000$). The patients were carefully matched for age, age at onset, approximate disease duration, educational level, and overall degree of cognitive impairment. Cerebral [^{18}F]fluorodeoxyglucose PET imaging was performed in all patients by a standardized protocol. Statistical comparison of patient PET data vs a healthy control population was performed as well as an analysis of differences between groups (SPM99; Wellcome Department of Cognitive Imaging, London, UK). *Results:* A similar pattern of cerebral hypometabolism was detected in the ϵ4-positive and -negative patient groups vs healthy volunteers in regions typically affected by AD (bilateral temporal, parietal, posterior cingulate, and prefrontal cortical areas). The comparison between ϵ4-positive and -negative patients additionally revealed stronger abnormalities in ϵ4 carriers in parietal, temporal, and posterior cingulate cortical regions. *Conclusions:* A generally similar pattern of cerebral hypometabolism was detected in *APOE* ϵ4-positive and -negative patients with Alzheimer disease. However, in direct comparison of the two matched groups, the abnormalities in the ϵ4-positive group were demonstrated to be more pronounced.

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Homozygous and heterozygous carriers of the ϵ4 allele have an increased risk to develop Alzheimer disease (AD), yet the mechanism leading to the increased susceptibility for AD in ϵ4-positive subjects is not known. Effects on neurofibrillary tangle formation, amyloid precursor protein processing, β-amyloid clearance, as well as impaired regenerative capabilities are possible contributing factors.[1-4]

With use of [^{18}F]fluorodeoxyglucose (FDG) PET, characteristic abnormalities of cerebral glucose metabolic rate (CMRglc) have been found in patients with AD.[5] Interestingly, even cognitively normal ϵ4-positive subjects had cerebral metabolic reductions in areas typically affected by AD.[6] These abnormalities may identify early preclinical AD. Furthermore, a stronger decrease of metabolic activity over time was demonstrated in otherwise healthy carriers of the ϵ4 allele.[7]

Although there is general consensus on the involvement of *APOE* in the pathogenesis of AD, a possible association with the disease progression is still controversial. Several recent publications indicate an involvement of the *APOE* genotype on disease course measures such as neuropsychological performance, reaction to treatment, and survival.[8-10] Correspondingly, current neuroimaging studies suggest a possible influence of the *APOE* genotype on cerebral perfusion deficits, progression of atrophy, and decline of cerebral glucose metabolism in patients with AD.[11,12] In contrast, others dispute an influence of the *APOE* genotype on disease course measures and on the cerebral glucose metabolism in patients with AD.[13-19]

FDG PET imaging is a reliable tool for early diagnosis, follow-up, and therapeutic monitoring of AD.[7] Therefore, we sought to examine possible effects of the *APOE* genotype on the cerebral metabolic pattern in a sufficiently large population of patients with AD after elimination of possible confounding covariates.

Materials and methods. *Patient characteristics.* Patients were selected using a pre-existing database established in cooperation of the Departments of Psychiatry and Nuclear Medicine at the local university hospital (Technische Universität München, Munich, Germany). The database contains >1,000 patients with clinically diagnosed AD who underwent a standardized examination protocol including extensive neuropsychiatric evaluation and neuroimaging procedures. Patients had been recruited at the memory clinic of the local dementia research unit. All patients underwent a diagnostic work-up, routinely applied in the outpatient clinic for clinical evaluation of patients with memory impairment.

To compare regional glucose metabolism between patients and a population of healthy control subjects, a pre-existing FDG PET dataset of 16 healthy control subjects was used that had been collected in the dementia research unit previously for clinical and scientific purposes.[20] The PET data of these volunteers had been

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acquired following the identical criteria as for the patients, and the population was age matched to the patient group (seven men, nine women; mean age 65 ± 8 years). The scans for all normal control subjects were acquired on the same scanner using the same acquisition protocol, reconstruction software, and image-processing procedures. All normal subjects had undergone MRI of the brain and neuropsychological evaluation without detection of abnormalities. The study protocol was approved by the Ethics Committee of the Technische Universität München and the radiation protection authorities.

Diagnostic work-up. The diagnostic work-up included medical, psychiatric, and neurologic examinations, neuropsychological testing, routine blood screening, and an interview with the patient and an informant. Cranial MRI was performed for assessing morphologic pathologies, and cranial FDG PET imaging was used to determine cerebral metabolism. The Clinical Dementia Rating Scale (CDR) was used for definition of clinically manifest dementia.[21] The Mini-Mental State Examination (MMSE) was used to assess the overall severity of cognitive decline, and classification of probable Alzheimer type of dementia was performed using criteria for probable AD.[22] In addition to age and gender, the onset at the disease was assessed in interview with an informant, and disease duration was calculated. Educational levels were assessed as years of education, defined as years attending school plus years of apprenticeship, technical school, college, and university.

For determination of *APOE* genotype, DNA was extracted according to standardized procedures, and genotyping was performed as previously described.[23]

For exclusion of anatomic abnormalities or vascular lesions and detection of atrophy, cranial MRI was performed in all patients on a 0.5 T Siemens Magnetom Open (Munich/Erlangen, Germany) at the time of evaluation, using a standardized imaging protocol. Axial T1-weighted (repetition time [TR] 22 milliseconds, echo time [TE] 8 milliseconds) fluid-attenuated inversion recovery images in a three-dimensional gradient echo technique (slice thickness 3 mm, voxel dimensions 1.3 × 0.9 × 3 mm) and coronal T1-weighted (TR 6,570 milliseconds, TE 48 milliseconds, T1 250 milliseconds) turbo inverse recovery sequences (slice thickness 1.5 mm, voxel dimensions 0.9 × 0.9 × 1.5 mm) were performed.

FDG PET imaging was performed in all patients. An IV bolus of 370 MBq of FDG was injected at rest with the eyes closed, and PET imaging was started 30 minutes post injection. Scans were performed under standard resting conditions (eyes closed in dimmed ambient light) using a Siemens 951 R/31 PET scanner (CTI, Knoxville, TN). A sequence of three frames, each of 10-minute duration, was started and later combined into a single frame. Acquisitions were in two-dimensional mode with a total axial field of view of 10.5 cm and no interplane dead space. To obtain transaxial images approximately parallel to the intercommissural line (anterior–posterior commissural line), subjects were positioned with the canthomeatal line parallel to the detector rings. Attenuation correction was performed using a transmission scan acquired at the end of the PET session. After data acquisition, corrections for random, dead time, and scatter were performed, and images were reconstructed by filtered back-projection with a Hamm filter (cut-off frequency 0.5 cycle/projection element), resulting in 47 slices in a 128 × 128 pixel matrix (pixel size 2.0 mm) and interplane separation of 3.447 mm. For comparison of patient baseline PET data with a normal group, the pre-existing PET database of healthy volunteers was used.

Inclusion/exclusion criteria. From the patient database, subjects were selected according to the following criteria. Patients were included in the study if they met National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria of AD, International Classification of Diseases-10 (ICD-10) diagnostic criteria for dementia, with a CDR score of ≥1.[22] Furthermore, patients were included in the study only if the *APOE* genotype had been assessed and cranial FDG PET and MRI had been performed without complications.

Patients were excluded from the study if they showed symptoms of any functional psychiatric disorder other than AD, including depressive episodes, normal-pressure hydrocephalus, Parkinson disease, progressive supranuclear palsy, corticobasal atrophy, Lewy body dementia, and frontotemporal lobe degeneration. The National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria were used to exclude relevant ischemic processes causing cognitive impairment.[24] Patients were also excluded if they showed any major structural abnormalities or signs of major vascular pathology such as status post infarction, extensive leukoencephalopathy, intracerebral aneurysm, or arteriovenous malformation on MRI. Furthermore, other extracerebral causes possibly influencing neuropsychological function, such as psychotropic medication (e.g., antidepressants, neuroleptics) or substance abuse, were excluded. These criteria resulted in groups of 42 *APOE* ε4-positive and 41 ε4-negative subjects.

Table 1 *Patient characteristics*

Characteristic	Genotype		*p* Value
	APOE ε4 positive	*APOE* ε4 negative	
n	42	41	—
Sex, male/female	18:24	21:20	χ^2 = 0.582
Age, y	67.5 ± 9.9	64.9 ± 12.1	0.29
MMSE	22.8 ± 5.0	23.8 ± 3.6	0.34
Approximate age at onset, y	65.0 ± 10.8	62.6 ± 12.3	0.34
Approximate duration of disease, y	2.5 ± 2.1	3.1 ± 2.2	0.26
Years of education	12.1 ± 2.6	12.3 ± 2.9	0.80

Data are means ± SD.

MMSE = Mini-Mental State Examination.

FDG PET image analysis. Image analysis was performed on an SGI O2 workstation (Silicon Graphics, Mountain View, CA). A fully automated software (Neurostat, University of Michigan, Ann Arbor, MI) was used for stereotactic normalization of the FDG PET images.[25,26] This routine has been extensively validated in previous publications.[27-29] Following realignment, in this program, spatial adjustment to the proportional grid system, proposed by Talairach and Tournoux, is performed, resulting in a standardized image set of 60 slices with a uniform voxel size of 2.25 × 2.25 × 2.25 mm in a matrix size of 128 × 128 voxels.[25,26,30] This procedure was preferred to the normalization procedure integrated in the SPM99 routine (Wellcome Department of Cognitive Imaging, London, UK), because previous studies showed less susceptibility to cortical atrophy, which may be present in Alzheimer patients.[31]

Statistical analysis. Further statistical analysis of the data was performed using SPM99 software on MATLAB 5.3 (Mathworks, Newton, MA). FDG PET image sets were smoothed with an isotropic Gaussian filter (12-mm full width at half-maximum), and individual global counts were normalized by proportional scaling to a mean value of 50 mg/100 mL/min. Then, between-group differences in regional cerebral glucose metabolism were assessed on a voxel-by-voxel basis using a two-sample *t* test (*t* values were converted to *Z* scores). A statistical group comparison has been performed between the two AD patient groups (ε4 carriers and noncarriers); additionally, each patient group was compared with the healthy control population.[12,31] To avoid false-positive results, generally a significance level of $p < 0.001$ (uncorrected) was applied, which is consistent with other studies using comparable approaches.[20,31] Based on previous FDG PET studies in AD, we defined the temporoparietal, frontal, and posterior cingulate cortex as predominant candidate areas for possible reduction in glucose metabolism in patients with AD.[28,32] For metabolic differences between groups, voxels exceeding the *p* value threshold within this set of predefined cortical areas were regarded as significant. All statistical approaches have been selected in correspondence with previously published studies on similar questions.[20,31]

Results. Eighty-three individuals were selected from the database and included in this study (table 1). For further

Table 2 *Differences of cerebral metabolic patterns in* APOE *ε4-positive and ε4-negative patients with AD*

AD ε4 positive < healthy controls				AD ε4 negative < healthy controls				AD ε4 positive < AD ε4 negative			
Talairach coordinates *x y z*, mm	Brodmann area	Region, cluster maximum	*Z* score	Talairach coordinates *x y z*, mm	Brodmann area	Region, cluster maximum	*Z* score	Talairach coordinates *x y z*, mm	Brodmann area	Region, cluster maximum	*Z* score
Left hemisphere											
−52 −56 27	39–40	STG/SMG	6.6	−38 14 29	44	IFG	6.1	−43 −36 54	40	IPL	3.9
−16 −34 2	27	HG	3.1	−52 −52 29	39–40	STG/SMG	5.6	−47 −79 4	37	MTG	3.5
				−58 −43 −4	21	MTG	4.8	−50 −72 −2	19	ITG	3.4
				−34 −16 −25	36	HG	3.1	−63 −29 7	42–22	STG	3.3
Right hemisphere											
54 −47 32	40	IPL	7.2	56 −43 38	40	IPL	5.7	36 −43 56	40	IPL	3.5
2 −29 34	24–31	PCC	6.5	0 −29 32	23–31	PCC	5.2	65 −52 20	22	STG	3.3
38 29 2	45	IFG	3.2	32 −4 −34	20–36	U	3.5	54 −25 47	2–40	PCG/IPL	3.2
				36 29 2	45	IFG	3.5	0 −32 27	23–31	PCC	3.2
				38 −14 −22	20	ITG	3.2	38 −32 38	40	IPL	3.2

ε4 positive = carrier of *APOE* ε4 allele; ε4 negative = noncarrier of *APOE* ε4 allele; AD = Alzheimer disease; STG = superior temporal gyrus; SMG = supramarginal gyrus; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; HG = hippocampal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; PCC = posterior cingulate cortex; PCG = postcentral gyrus; U = uncus.

analysis, subjects were divided into *APOE* ϵ4 allele carriers and noncarriers; all ϵ4 allele–positive subjects were pooled together, as done in previous studies.[33] Forty-two patients were carriers of the ϵ4 allele (5 homozygous, 37 heterozygous). Of the heterozygous subjects, one subject carried a complementary ϵ2 allele, and 36 carried an ϵ3 allele. The remaining ϵ4-negative group contained 41 subjects: 36 homozygous ϵ3 allele carriers and 5 heterozygous subjects who carried one ϵ2 allele and one ϵ3 allele. The two groups were age matched; a χ^2 test revealed no difference in the gender ratios, and no differences were found in *t* tests comparing MMSE, approximate age at onset, duration of the disease, and educational level (at a significance level of $p < 0.05$).

PET. Comparison with healthy control population. Both *APOE* ϵ4 carriers and noncarriers were compared with the group of age-matched volunteers to assess the extent and localization of cerebral metabolic abnormalities. In this group comparison, significant relative hypometabolic abnormalities in regions typically affected by AD were identified in both patient groups, including bilateral temporal, parietal, frontal, and posterior cingulate cortex. The pattern of abnormalities was generally similar in both groups regarding localization and configuration. However, the hypometabolic lesions appeared markedly more extended and confluent in the *APOE* ϵ4-positive group. Correspondingly, the number of single dividable clusters that could be distinguished by the SPM routine based on the predefined significance threshold of $p < 0.001$ was smaller than in the *APOE* ϵ4-negative group (table 2; figure, A and B). To examine if these visually apparent differences between the groups fulfilled the criteria of significance, a direct statistical comparison between the two patient groups was performed.

Between-group comparison. The direct voxel-based comparison between the cerebral glucose metabolism in the *APOE* ϵ4-negative and ϵ4-positive group revealed the following results. No significantly stronger abnormalities were observed in the ϵ4-negative group as compared with the ϵ4-positive group. However, a significantly lower relative CMRglc was detected in bilateral temporal and parietal cortex and posterior cingulate in the ϵ4-positive subjects. These differences were observed between the two matched groups who, apart from genotype, showed no significant differences regarding mean age, cognitive performance, educational level, or approximate duration and onset of disease (see table 2 and the figure, C).

Discussion. In this study, the relative cerebral glucose metabolic deficits in an *APOE* ϵ4-positive group of patients with AD were significantly more pronounced than in a ϵ4-negative group, in spite of the careful matching of the two groups. This finding may imply that the presence of the *APOE* ϵ4 allele not only favors a higher susceptibility for AD but also exerts clear functional effects on the metabolic pattern. The role of the ϵ4-positive genotype is generally recognized as a major risk factor for the development of AD. Consequently, relatively broad consent can be found regarding early abnormalities in neuroimaging studies on cerebral resting metabolism (FDG PET) and brain activation (fMRI), even in cognitively still unimpaired *APOE* ϵ4-positive subjects, decades before onset of dementia.[6,7,12,34-36] All of these findings have been interpreted as a consequence of early cerebral functional abnormalities with a predictive value for subsequent memory impairment and development of AD.

The clinical data about the influence of the *APOE* genotype on manifestation and course of the disease are more controversial. Some former studies on neuropsychology denied an influence of the *APOE* genotype on the progression of AD, whereas others concluded that the ϵ4 allele leads to a faster rate of

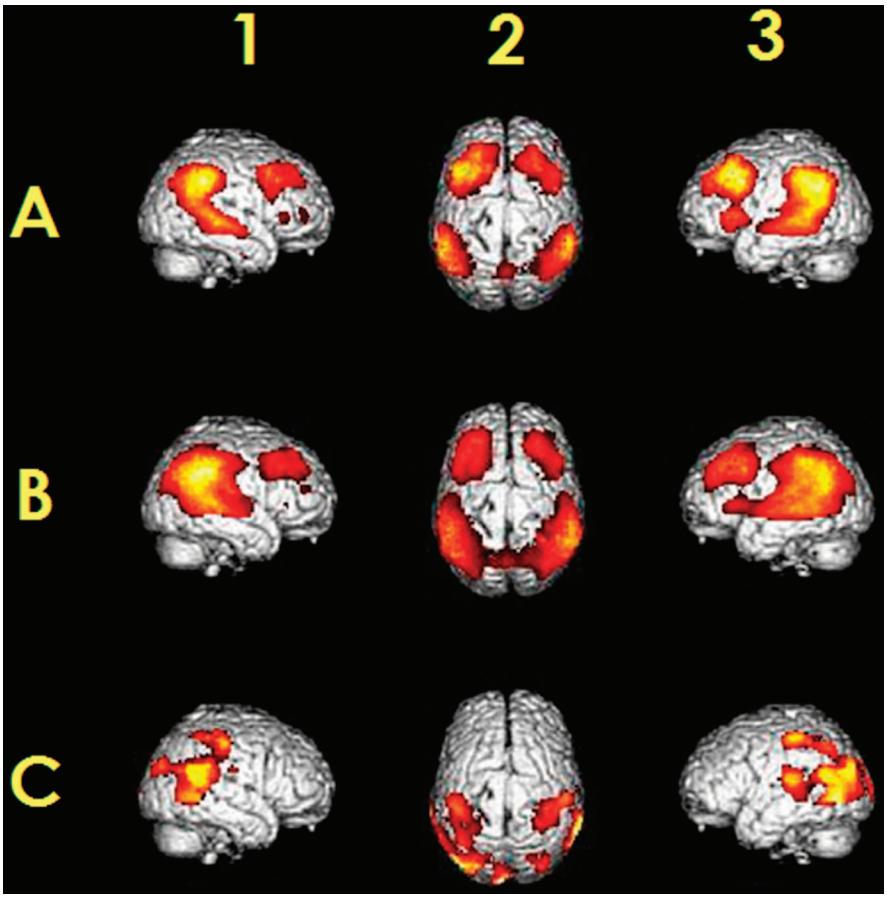

Figure. Cerebral metabolic abnormalities in APOE *ϵ4-positive and -negative patients with Alzheimer disease (AD). Images 1 to 3 show results superimposed on a standard MRI surface: 1 = right lateral aspect; 2 = cranial aspect; 3 = left lateral aspect. (A) Cerebral metabolic deficits in* APOE *ϵ4-negative patients with AD as compared with healthy volunteers. (B) Cerebral metabolic deficits in* APOE *ϵ4-positive patients with AD as compared with healthy volunteers. (C) Stronger cerebral metabolic deficits in* APOE *ϵ4-positive patients as compared with* APOE *ϵ4-negative patients.*

decline.[9,10,13,14] In our study, no significant difference in the MMSE was found between the groups of *APOE* ϵ4-positive and -negative patients with AD. However, it may be generally difficult to objectively assess the rate of actual neurodegeneration using neuropsychological tests. Compared to neuropsychological measures, the time of survival may be more reliable to assess disease progression. However, studies on survival in patients with different *APOE* genotypes also reveal contradictory results.[10,15,16]

Neuroimaging studies may offer a way to assess some of the effects of AD pathology in vivo. In contrast to the results of our study, other groups did not detect a difference in cerebral metabolism in patients with AD and differing *APOE* genotypes, and any correlation of the ϵ4 dose with regional deficits of brain metabolism has been denied.[18,19] However, the results detected in our study may have been missed in other studies owing to limited patient numbers and methodologic restrictions resulting in limited statistical power. In contrast to these studies, a large number of subjects (n = 83) were systematically selected out of a large database (>1,000 subjects) in the current study, a strategy that has been recently advocated.[37] This may have rendered our findings possible, in spite of the high interindividual variation of cerebral metabolic abnormalities in patients with AD in general and the potentially subtle differences between ϵ4-positive and -negative individuals.

Several recent neuroimaging studies indicate a clear influence of the ϵ4 allele on expression of neuropathology and thus support the findings of our study. In an MRI study, accelerated hippocampal atrophy has been found in ϵ4-positive patients with AD as compared with ϵ4-negative subjects.[38] In the current study, no atrophy correction was performed; thus, atrophy may also have contributed in part to our results. In addition to morphologic imaging, some former studies also demonstrated an effect of *APOE* genotype on functional neuroimaging findings in AD patients. It has been demonstrated that severity of dementia and ϵ4 status were independent predictors of the cerebral metabolic pattern in AD.[33] In SPECT studies, stronger cortical hypoperfusion in *APOE* ϵ4-positive patients with AD at baseline has been demonstrated, as well as a stronger reduction of regional cerebral perfusion over time.[11,39] Stronger longitudinal reduction of CMRglc in the temporal neocortex has been observed in healthy elderly ϵ4-positive subjects who developed mild cognitive impairment over time as compared with ϵ4-negative subjects, in spite of comparable cognitive decline.[36]

From PET findings alone, the causality of the differences detected in our study cannot be judged con-

clusively. The extent of detected hypometabolic lesions does not necessarily represent the extent of the underlying neuropathology, and the results may be partially based on remote functional changes. However, in several studies, a correlation of the reductions in resting state regional brain metabolism in AD with the distribution of neuropathology and cell loss post mortem has been described.[40-42] Regarding this, the more extended hypometabolic lesions detected in our study in *APOE* ϵ4-positive patients with AD could possibly reflect a more extended neuropathology, based on an advanced disease progression. This raises the question of why *APOE* ϵ4-positive patients did not show essentially more severe neuropsychological deficits in our population. As educational levels of the two groups were entirely comparable, better compensation strategies or better cognitive reserve cannot be assumed. Thus, it appears more plausible that the low sensitivity of the MMSE evaluation was not able to properly register the presumably slightly advanced stage of neurodegeneration in the ϵ4-positive group. This hypothesis is supported by the trend to lower MMSE scores detected in these patients in spite of the somewhat shorter mean duration of disease as compared with the ϵ4-negative group. Generally, the imprecision of the estimate of clinical duration has to be taken into account; thus, an unnoticed longer disease duration/earlier onset in the ϵ4-positive patients cannot be completely excluded.

As in many former studies, homozygote and heterozygote carriers of the ϵ4 allele have been pooled together in the current study. All subjects have been selected from a large pre-existing databank of AD patients. This led to a ratio of heterozygote and homozygote *APOE* ϵ4 carriers that was comparable with distributions found in AD populations in previous epidemiologic studies.[43] Thus, the proportion of homozygote and heterozygote ϵ4 carriers in the current study can be assumed to be fairly representative for AD patients in the general population. However, potential differences between homo- and heterozygote carriers of the ϵ4 allele have not been assessed, and it remains unclear to what extent the small number of ϵ4 homozygotes influenced the results. This could be evaluated in further studies.

From a pathomechanistic point of view, a gene that favors susceptibility for AD and the formation of AD pathology may have an influence on disease expression as well. Correspondingly, in brain autopsy studies, the ϵ4 allele appears to be closely linked with the clinical manifestations of AD such as amyloid plaque deposition and neurofibrillary change formation.[44,45] It appears therefore probable that some of these effects may be mirrored in the cerebral metabolic pattern, as indicated in our study. The results of this study underline the need for long-term follow-up studies to further evaluate the influence of the *APOE* genotype on clinical measures and the course of AD.

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