ORIGINAL ARTICLE

Influence of Cognitive Status, Age, and *APOE-4* Genetic Risk on Brain FDDNP Positron-Emission Tomography Imaging in Persons Without Dementia

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Context: Amyloid senile plaques and tau neurofibrillary tangles are neuropathological hallmarks of Alzheimer disease that accumulate in the brains of people without dementia years before they develop dementia. Positron emission tomography (PET) scans after intravenous injections of 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP), which binds to plaques and tangles in vitro, demonstrate increased cerebral binding in patients with Alzheimer disease compared with cognitively intact controls. Here we investigated whether known risk factors for Alzheimer disease and dementia are associated with FDDNP-PET binding.

Objective: To determine if impaired cognitive status, older age, apolipoprotein E-4 (*APOE-4*) genetic risk for Alzheimer disease, family history of dementia, and less education are associated with increased regional cerebral FDDNP-PET binding.

Design: Cross-sectional clinical study.

Setting: A university research institute.

Participants: Volunteer sample of 76 middle-aged and older persons without dementia (mean age, 67 years) including 36 with mild cognitive impairment. Of the 72 subjects with genetic data, 34 were *APOE-4* carriers.

Main Outcome Measures: The FDDNP-PET signal in brain regions of interest, including medial and lateral temporal, posterior cingulate, parietal, and frontal.

Results: For all regions studied, cognitive status was associated with increased FDDNP binding ($P < .02$ to .005). Older age was associated with increased lateral temporal FDDNP binding. Carriers of *APOE-4* demonstrated higher frontal FDDNP binding than noncarriers. In the mild cognitive impairment group, age was associated with increased medial and lateral temporal FDDNP binding, and *APOE-4* carriers had higher medial temporal binding than noncarriers.

Conclusions: Impaired cognitive status, older age, and *APOE-4* carrier status are associated with increased brain FDDNP-PET binding in persons without dementia, consistent with previous clinical and postmortem studies associating these risk factors with amyloid plaque and tau tangle accumulation. Stratifying subject groups according to *APOE-4* carrier status, age, and cognitive status may therefore be an informative strategy in future clinical trials using FDDNP-PET.

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NEURODEGENERATION associated with aging progresses along a continuum,[1] but it has been categorized according to the degree of cognitive impairment. In normal aging, mild memory concerns with minimal objective cognitive deficits have been observed in nearly half of people by 50 years of age.[2] Such awareness of memory changes is usually stable and not a risk factor for future cognitive decline.[3] Mild cognitive impairment (MCI) is a more advanced form of age-related cognitive decline in which people notice memory changes and neuropsychological tests often confirm problems with delayed recall, although non–memory-related cognitive domains may also be impaired.[4] People experiencing this transitional state between normal aging and dementia are still able to live independently, but they have an increased risk for developing dementia. A recent study that followed patients with MCI for 30 months reported conversion rates to Alzheimer disease (AD) ranging from 27% to 49%, depending on the subtype of MCI.[5] The prevalence of MCI may be as high as 19% in people older than 65 years and 29% in those older than 85 years.[6] When cognitive decline interferes with daily functioning and impairs not just memory but other mental abilities, dementia is often diagnosed.[7] Alzheimer disease, which accounts for most cases, is insidious in its onset and pro-

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gressive in its course.[8] The prevalence of AD in individuals aged 71 years and older approaches 10%,[9] and by 85 years has been reported to be as high as 50%.[10]

Age is the strongest known risk factor for AD. The estimated annual incidence of AD in a community-based sample ranged from 0.6% for people aged 65 to 69 years to 8.4% for those 85 years and older.[11] In a meta-analysis of 23 studies,[12] the incidence of AD increased exponentially with age until 90 years.

In addition to cognitive status and age, many genetic and nongenetic[13] factors contribute to the risk for developing AD. For the common forms of late-onset AD, the major genetic risk is associated with the apolipoprotein E (*APOE*) gene on chromosome 19, which has 3 allelic variants (2, 3, and 4) and 5 common genotypes (2/3, 3/3, 2/4, 3/4, and 4/4). The *APOE-4* allele increases risk and decreases the average age of dementia onset in a dose-related fashion (ie, AD risk is lowest for the 3/3 genotype, higher for the 3/4 genotype, and highest for the 4/4 genotype),[14] while *APOE-2* lowers the risk.[15]

Because *APOE-4* accounts for only part of the genetic risk for AD, family history of dementia, regardless of whether an individual is an *APOE-4* carrier, may increase the risk for developing AD. People with a first-degree relative with dementia have a 10% to 30% increased risk of developing the disorder,[16] although a recent investigation reported that family history of dementia was associated with increased risk of dementia and AD only in *APOE-4* carriers.[17]

Less education also appears to increase the risk for AD.[18] Although this association suggests that the cognitive stimulation resulting from higher education protects the brain,[19] other factors may explain the higher risk of dementia in people with less education including unhealthy lifestyles, lower cognitive reserve,[20] and higher prevalence of small vascular lesions.[21]

In patients with AD, 2 proteins, β-amyloid (in senile plaques) and tau (in neurofibrillary tangles), accumulate abnormally in the brain in a predictable spatial pattern; however, these proteins also appear to accumulate before people develop dementia and increase gradually with age.[22,23] For a definitive diagnosis of AD, high cerebral concentrations of amyloid senile plaques and tau neurofibrillary tangles must be present in the brain at autopsy.[8]

Newly developed small molecule tracers used in conjunction with positron emission tomography (PET) have made it possible to obtain measures of these abnormal protein deposits in living people.[24-26] For example, the amyloid-binding radiotracer Pittsburgh Compound B has been used with PET imaging to demonstrate significantly greater cortical Pittsburgh Compound B retention in patients with AD vs controls.[24]

Our group has developed a small molecule, 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP), for use as an in vivo chemical marker of cerebral amyloid and tau proteins.[26] This molecule and its parent compound, DDNP, are both fluorescent and may be used with confocal fluorescence microscopy to clearly visualize plaques and tangles in vitro in brain specimens of patients with AD.[27] Initial studies have found that global FDDNP-PET binding (average of temporal, parietal, posterior cingulate, and frontal regions) in MCI is intermediate between controls with normal cognition and patients with AD, and that subjects who progress clinically over time show corresponding increases in FDDNP signal.[28] Moreover, 3-dimensional cortical surface projection images of FDDNP-PET show patterns remarkably similar to those expected from autopsy studies demonstrating regional brain accumulation patterns of plaques and tangles.[1,22,28]

In this study, we determined whether previously reported risk factors for developing a clinical diagnosis of AD were also associated with plaque and tangle accumulation as measured with FDDNP-PET binding in volunteers without dementia. We hypothesized that several established risk factors, including impaired cognitive status, older age, *APOE-4* genetic risk for AD, family history of dementia, and lower educational achievement would be associated with increased regional cerebral FDDNP-PET binding.

METHODS

SUBJECTS AND CLINICAL ASSESSMENTS

We performed neuropsychiatric evaluations, cognitive assessments, and PET scanning on 63 volunteers without dementia from a larger longitudinal study.[28] Subjects were recruited through study advertisements regarding mild memory concerns, media coverage, and referrals from physicians and families. Although all subjects had mild memory concerns, patients with any form of dementia were excluded. Also excluded were individuals taking medications that might affect cognition, such as sedatives, or those taking nonsteroidal antiinflammatory drugs, which bind to amyloid plaques and may affect FDDNP binding values.[27]

Subjects had screening laboratory tests and structural imaging scans (3-dimensional magnetic resonance imaging [MRI] or computed tomography [CT]) to rule out other causes of cognitive impairment (eg, stroke, tumor)[8] and for coregistration with PET scans for region-of-interest image analyses. Computed tomography scans instead of MRI were performed on 4 subjects because they could not tolerate MRI (eg, owing to claustrophobia, metal in body). Subjects with vascular lesions on the MRI or CT scan were excluded from the study. In addition to the Mini-Mental State Examination[29] and Hamilton Rating Scale for Depression,[30] a neuropsychological test battery[31] was administered to assess 5 cognitive domains: (1) memory, including logical memory, selective reminding, and complex figure recall; (2) language, including Boston naming and letter and category fluency; (3) attention and information-processing speed, including Trail Making A, Stroop Color (Kaplan version), and Digit Symbol; (4) executive functioning, including Trail Making B, Stroop Interference (Kaplan version), Wisconsin card sort, and perseverative errors; and (5) visuospatial, including block design, complex figure copy, and visual retention.

To diagnose MCI, we used standard diagnostic criteria for amnestic MCI (ie, memory impairment without other cognitive impairments), which include (1) patient awareness of a memory problem, preferably confirmed by another person; (2) memory impairment detected with standard assessment tests; and (3) ability to perform normal daily activities.[4] For a broad definition of MCI, we also used guidelines to identify subjects with other MCI subtypes, including those with memory impairment and additional cognitive deficits.[32] The

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diagnosis was corroborated by clinical judgment[4] and included subjects with MCI who scored 1 SD or more less than age-corrected norms, as this threshold for impairment yields high sensitivity for predicting dementia.[33] To balance increased sensitivity with specificity, we required impairment on at least 2 neuropsychological tests within 1 of the 5 cognitive domains.[34] Subjects in the MCI group did not meet diagnostic criteria for AD,[7,8] and the presence of memory concerns was documented using a standardized subjective memory instrument (Memory Functioning Questionnaire)[35] and clinical interview.

Volunteers with 1 or more first-degree relatives (ie, sibling or parent) with AD or dementia were classified as having a positive family history of dementia. Prior educational achievement was quantified according to years and months completed, beginning with elementary school (ie, first grade).

All clinical assessments were performed within 4 weeks of scanning procedures, and clinicians were blinded to the results of FDDNP-PET scans. Written informed consent was obtained in accordance with the University of California, Los Angeles Human Subjects Protection Committee procedures. Cumulative radiation dosimetry for all scans was below the mandated maximum annual dose and in compliance with state and federal regulations. Two minor adverse events occurred during PET scanning: one subject developed minor bruises at venipuncture sites, and another subject experienced a transient headache.

GENETIC ANALYSIS

All DNA was obtained from blood samples. The *APOE* genotypes were determined using standard techniques as previously described.[14] Genetic data were available for 72 subjects.

SCANNING AND IMAGE ANALYSIS PROCEDURES

As previously described, FDDNP was prepared at very high specific activities (>37 gigabecquerel [GBq]/μmol).[26,28] All scans were performed with the ECAT HR or EXACT HR+ tomograph (Siemens-CTI, Knoxville, Tennessee) with subjects supine and with the imaging plane parallel to the orbitomeatal line. A bolus of FDDNP (320-550 megabecquerel [MBq]) was injected via an indwelling venous catheter, and consecutive dynamic PET scans were performed for 2 hours. Scans were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5 mm full-width at half-maximum) with scatter and measured attenuation correction. The resulting images contained 47 contiguous slices with plane separation of 3.37 mm (ECAT HR) or 63 contiguous slices with plane separation of 2.42 mm (EXACT HR+). Results did not differ significantly according to the scanner used.

The FDDNP binding data were quantified using Logan graphical analysis with the cerebellum as the reference region for time points between 60 and 125 minutes.[28,36] The slope of the linear portion of the Logan plot is the relative distribution volume, which is equal to the distribution volume of the tracer in a region of interest divided by that in the reference region. The relative distribution volume parametric images were generated and analyzed using regions of interest traced on the coregistered MRI or CT scans for left and right parietal, medial temporal (limbic regions including hippocampus, parahippocampal areas, and entorhinal cortex), lateral temporal, posterior cingulate, and frontal regions, as previously described.[28] Each regional relative distribution volume or binding value was expressed as an average of left and right regions. Rules for region-of-interest drawing were based on the identification of gyral and sulcal landmarks with respect to the atlas of Talairach and Tournoux.[37] All PET scans were read and regions of interest drawn by individuals who were blinded to clinical assessments and genotype. Repeat scans performed on the same 2 subjects within several weeks indicated stability of these measures (≤3% SD of regional values).

Table. Demographic and Clinical Characteristics

Characteristic	Mean (SD)	
	MCI (n = 36)	No MCI (n = 40)
Mini-Mental State Examination	27.7 (1.6)	29.5 (0.7)
Age, y	66.8 (12.1)	66.8 (9.4)
Education, y	16.6 (2.8)	17.8 (2.7)
Female, No. (%)	19 (52.7)	20 (50.0)
Family history of dementia, No. (%)	17 (47.2)	27 (67.5)
Hamilton Depression Scale score	1.8 (2.4)	1.9 (2.1)
APOE-4 carriers, No. (%)	14 (43.7)	20 (50.0)

Abbreviation: MCI, mild cognitive impairment.

STATISTICAL ANALYSIS

Data were screened for outliers and normality assumptions. Descriptive statistics were computed for the entire sample and for the MCI and control subjects separately. The *t* test was used to compare the continuous variables of cognitive groups and χ^2 tests were used for categorical variables. General linear models were used to determine which variables— age, *APOE-4* status, family history, education, and cognitive status (MCI vs normal)—were associated with regional FDDNP binding in the entire sample. We first included all of these risk factors as predictors in the general linear model. We then computed the final model by deleting the risk factors that did not contribute significantly. All tests were 2-tailed, and a significance level of $P = .05$ was used for all inferences.

RESULTS

Subjects were middle-aged or older (range, 47-87 years; mean [SD] age, 66.8 [10.7] years) and educated (mean [SD] education, 17.0 [2.9] years). They showed minimal impairment on cognitive testing (mean [SD] Mini-Mental State Exam scores, 28.7 [1.5]), and 44 (59%) had a family history of dementia in at least 1 first-degree relative. Of the 36 patients with MCI, 17 showed memory impairment consistent with amnestic MCI and 19 had amnestic MCI plus deficits in other cognitive areas. The memory symptoms of all other subjects were normal for their age. Of the 72 subjects with genetic data, 34 (47%) were *APOE-4* carriers (**Table**). Of these, 4 subjects were homozygotes (4/4 genotype).

For all regions of interest studied, cognitive status (ie, diagnosis of MCI vs normal aging) was associated with increased FDDNP binding (medial temporal $F_{1,67} = 6.04$, $P < .02$; lateral temporal $F_{1,68} = 8.34$, $P < .005$; parietal $F_{1,70} = 7.46$, $P < .008$; posterior cingulate $F_{1,70} = 3.83$, $P < .05$; and frontal $F_{1,68} = 9.27$, $P < .003$). Older age was associated with increased lateral temporal FDDNP binding ($F_{1,68} = 5.41$, $P < .02$). Subjects' *APOE-4* status was associated with higher frontal FDDNP binding; *APOE-4* carriers showed more binding than noncarriers ($F_{1,68} = 3.93$, $P < .05$).

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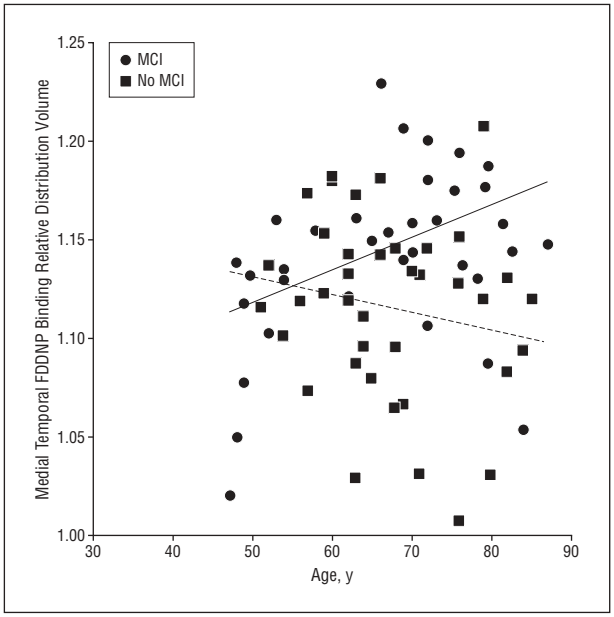

Figure. Medial temporal 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) binding correlated with age in persons with mild cognitive impairment (MCI) (r=0.35, P<.03; solid line) but not in those without (dotted line). The interaction between cognitive status and age was significant ($F_{1,65}$=4.74, P<.03).

In the MCI group, older age was associated with increased medial temporal ($F_{1,29}$=4.08, P<.05)(**Figure**) and lateral temporal ($F_{1,34}$=6.73, P<.01) FDDNP binding, and *APOE-4* carriers had more medial temporal FDDNP binding than noncarriers ($F_{1,29}$=5.22, P<.03). In the group without MCI, *APOE-4* carriers had more frontal FDDNP binding than noncarriers ($F_{1,37}$=4.40, P<.04).

Family history of dementia and years of educational achievement were not associated with increased FDDNP binding values. No associations between Hamilton Depression Scale scores and FDDNP binding were found.

COMMENT

These findings indicate that impaired cognitive performance, older age, and *APOE-4* genetic risk for AD are associated with increased brain FDDNP-PET binding in persons without dementia. Moreover, the degree of cognitive impairment (ie, normal aging vs MCI) appears to influence the interactions among risk factors. For example, in the MCI group, *APOE-4* carriers show higher medial temporal FDDNP binding, whereas in normal aging, *APOE-4* carriers demonstrate higher frontal binding. Overall, the results are consistent with our hypotheses and with previous clinical and postmortem studies demonstrating a relationship between such risk factors and amyloid plaque and tau tangle formation in the brain. By contrast, the other risk factors we tested, family history of dementia and prior years of education, were not found to be associated with higher FDDNP binding values.

Brain deposition of plaques and tangles follows a pattern in which tau tangles accumulate initially in the entorhinal cortex in normal aging and then spread to medial temporal regions as MCI develops; concentrations of medial temporal tangles become intermediate between those of normal aging and AD.[22,23,38] The finding in our study that *APOE-4* status was associated with FDDNP binding in the medial temporal region of patients with MCI is interesting in light of autopsy studies showing that this region is among the earliest to demonstrate increased plaque and tangle accumulation.[22,23,38] Also, neuritic and diffuse plaques and tangles in patients with MCI are widely distributed throughout the neocortex and limbic structures.[38] This spatial pattern and progression of abnormal protein accumulation may be consistent with an interaction between plaque and tangle accumulation. At some critical point in neurodegeneration, β-amyloid peptides may accelerate age-related tangle accumulation, which would otherwise progress relatively slowly with age.[23] Tangle load has been associated with cognitive decline in older individuals, but plaque load has not consistently demonstrated such an association.[38] The findings that FDDNP binds both plaques and tangles, particularly in the medial temporal lobe, may explain, in part, the association between higher FDDNP binding values and impaired cognitive function. Moreover, the regional pattern of FDDNP binding appears consistent with plaque and tangle accumulation patterns observed in autopsy studies.[22,23,28,38]

This is the first study to explore and demonstrate that a genetic risk for AD is associated with increased FDDNP-PET binding in persons without dementia. These results are consistent with previous neuropathological studies demonstrating increased plaque and tangle formation in middle-aged and older *APOE-4* carriers without dementia.[39,40] For example, in a study of persons without dementia who died between the ages of 50 and 93 years, *APOE-4* carriers showed a premature appearance of β-amyloid and neurofibrillary tangles.[40] By contrast, autopsy studies of patients with AD find that *APOE-4* heterozygotes do not show increased plaque and tangle accumulation, whereas *APOE-4* homozygotes do show increased accumulation.[41] Thus, the effect of the *APOE-4* allele on cerebral plaque and tangle formation may only occur early in the course of neurodegeneration.

Clearly *APOE-4* lowers the age of clinical dementia onset, but surprisingly, several studies do not demonstrate acceleration of clinical progression of the disease in *APOE-4* carriers.[42-46] Consistent with such findings, *APOE-4* has been reported to accelerate transitions from normal aging to MCI, but not from MCI to dementia.[46-49] While controversial, these results suggest that *APOE-4* may have a larger effect on a central precipitating event like amyloid plaque deposition, arguably a poor correlate of clinical progression or initial pathology in medial temporal regions, as observed in this study with FDDNP.

Previous autopsy studies of individuals without dementia ranging from young adults to elderly persons also have demonstrated that plaque and tangle formation is age-related.[22,50] Other research has demonstrated interactions among these various risk factors. For example, *APOE-4* carrier status may lead to increased tangle accumulation in relatively young age groups. In an autopsy study of asymptomatic younger adults (mean age, 38 years), tangle formation was significantly greater in *APOE-4* carriers compared with controls.[51] Sex may also modify the effect of *APOE-4* on the deposition of AD brain pathology; in a study of 729 brains examined by routine autopsy, an association between the *APOE-4* allele and

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plaques was found only for women aged between 60 and 79 years, whereas the association was found for men in all age groups.[52] In the present study, we did not find sex to be associated with greater FDDNP binding.

Subjective memory concerns and minimal decline in memory ability compared with young adults are expected with normal aging.[2] Although cognitive impairment is a risk factor for dementia, it is also a consequence of the brain lesions causing AD. The results of this study suggest that in vivo measures of plaques and tangles are associated with increased cognitive impairment, but other factors besides plaques and tangles can contribute to cognitive impairment including cerebrovascular disease and head trauma.[53,54]

Revised research criteria for the diagnosis of AD have been proposed.[55] These criteria include the presence of early episodic memory impairment along with 1 or more abnormal biomarker such as molecular neuroimaging with PET or cerebrospinal fluid analysis of β-amyloid or tau proteins. Our findings that FDDNP binding patterns differ according to the degree of cognitive impairment (ie, normal aging vs MCI) suggest that FDDNP-PET might be a useful tool in applying such revised research diagnostic criteria. Additional studies clarifying the patterns of FDDNP binding and other molecular imaging techniques in AD, MCI, and normal aging will likely have an effect on the use of such diagnostic criteria.

Family history of dementia was not associated with higher FDDNP binding values. Previous studies have found that family history of dementia increases the risk for neurodegeneration[56] and is associated with subsequent cognitive decline[57] and lower scores on neuropsychological testing.[58] Family history of dementia is an established risk factor for AD,[59] but not all studies have confirmed such a risk.[60,61] Moreover, the effect of family history on risk for dementia may be age-dependent—some studies have found the effect in persons older than 75 years,[62] while other reports suggest that the effect of familial or genetic factors on dementia risk diminishes with increasing age.[17] Misclassification in the assessment of dementia history and cohort effects (ie, relatives may be more likely to report dementia in siblings than in parents) may also diminish the accuracy of family history estimates. The relatively small sample size also may explain why family history was not associated with increased FDDNP binding values.

This small sample also may explain why we did not find prior educational achievement to influence our results. In addition, the lack of variance in years of education in these subjects may have minimized any effect of education in the present analysis. Other methodological issues could have influenced these results as well, including partial volume effects[63] and use of a relatively educated sample who may not be representative of the general population.

Despite such limitations, these results, that FDDNP-PET may be an informative biological marker for people at risk for dementia, are encouraging. An important potential application of emerging technologies such as FDDNP-PET is in early detection of neurodegeneration. Our finding that greater FDDNP binding is associated with increased cognitive impairment in individuals without dementia suggests that this approach might be useful in detecting people at risk for dementia, which would also be useful for identifying candidates for clinical trials of prevention treatments. These results suggest that in future clinical trials using FDDNP-PET, stratifying subject groups according to *APOE-4* carrier status, age, and cognitive status may be an informative strategy.

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