

Baseline Microglial Activation Correlates With Brain Amyloidosis and Longitudinal Cognitive Decline in Alzheimer Disease

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Abstract

Background and Objectives

This study aims to quantify microglial activation in individuals with Alzheimer disease (AD) using the 18-kDa translocator protein (TSPO) PET imaging in the hippocampus and precuneus, the 2 AD-vulnerable regions, and to evaluate the association of baseline neuroinflammation with amyloidosis, tau, and longitudinal cognitive decline.

Methods

Twenty-four participants from the Knight Alzheimer Disease Research Center (Knight ADRC) were enrolled and classified into stable cognitively normal, progressor, and symptomatic AD groups based on clinical dementia rating (CDR) at 2 or more clinical assessments. The baseline TSPO radiotracer [¹¹C]PK11195 was used to image microglial activation. Baseline CSF concentrations of A β 42, A β 42/A β 40 ratio, tau phosphorylated at position 181 (p-tau181), and total tau (t-tau) were measured. Clinical and cognitive decline were examined with longitudinal CDR and cognitive composite scores (Global and Knight ADRC-Preclinical Alzheimer Cognitive Composite [Knight ADRC-PACC] Score).


Results

Participants in the progressor and symptomatic AD groups had significantly elevated [¹¹C]PK11195 standard uptake value ratios (SUVRs) in the hippocampus but not in the precuneus region. In the subcohort with CSF biomarkers (16 of the 24), significant negative correlations between CSF A β 42 or A β 42/A β 40 and [¹¹C]PK11195 SUVR were observed in the hippocampus and precuneus. No correlations were observed between [¹¹C]PK11195 SUVR and CSF p-tau181 or t-tau at baseline in those regions. Higher baseline [¹¹C]PK11195 SUVR averaged in the whole cortical regions predicted longitudinal decline on cognitive tests.

Discussion

Microglial activation is increased in individuals with brain amyloidosis and predicts worsening cognition in AD.

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 **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
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Glossary

AD = Alzheimer disease; A β = β -amyloid; CDR = clinical dementia rating; CDR-SB = CDR Sum of Boxes; Knight ADRC-PACC = Knight Alzheimer Disease Research Center Preclinical Alzheimer Composite Score; MMSE = Mini-Mental State Examination; MPRAGE = magnetization-prepared rapid acquisition gradient echo; PET = positron emission tomography; SB = sum of boxes; SUVR = standard uptake value ratio; TSPO = 18 kDa translocator protein.

Classification of Evidence

This study provides Class II evidence that in patients with AD, higher baseline [11C]PK11195 SUVR averaged in the whole cortical regions was associated with longitudinal decline on cognitive tests.

The characteristic pathology of Alzheimer disease (AD) is the deposition of extracellular β -amyloid (A β) plaques and intracellular tau fibrils. Amyloid plaques and tau tangles are believed to initiate a cascade of pathology that includes neuroinflammation,¹ synaptic dysfunction, and neuronal death, resulting in dementia. There is extensive literature documenting a microglial-mediated inflammatory response in AD.² Multiple longitudinal studies demonstrate that inflammation and microglial activation begin early in AD, many years before dementia onset.^{3,4} It is also notable that microglia play a key role in neuroinflammatory response not only to amyloid deposition but also to tau accumulation in AD brains.⁵

Despite the association of neuroinflammation with AD, the exact role of inflammation in AD remains unclear. It has been suggested that in the early stages of AD, the initial microglial activation may serve a protective role trying to clear amyloid.⁶ In the later stages of AD, when clearance fails, microglia could play a detrimental role by producing proinflammatory cytokines, leading to progressive neurodegeneration.⁷ Furthermore, the relationship between neuroinflammation, amyloidosis, and cognitive decline is still unclear and warrants further investigation. The hippocampus and precuneus are involved in the earliest neuropathologic changes in AD and are sensitive to AD pathologies of amyloid and tau.⁸⁻¹¹ Focusing analyses on those regions would shed light on the relationships among the neuroinflammation, amyloid, tau, and cognition.

After activation, microglia proliferate and express a series of genes for proinflammatory cytokines and certain receptors on their surface, including the 18-kDa translocator protein (TSPO). The advent of PET radioligands that bind the microglial protein, TSPO, including [11C]PK11195, allows assessment of activated microglia in many neurologic disorders, including AD.¹² The aim of this study was to measure microglial activation with [11C]PK11195 PET imaging in cognitively normal and symptomatic AD participants and evaluate its association with CSF biomarkers of AD pathology and performance on cognitive tests. We hypothesized that microglial activation would be associated with amyloidosis and tau and would predict cognitive decline. These primary research questions have been addressed in this study.

Methods

Study Participants

Study participants were enrolled in ongoing studies at the Knight Alzheimer Disease Research Center (Knight ADRC) at Washington University School of Medicine (St. Louis, MO). The Human Research Protection Office at Washington University approved all studies, and written informed consent was obtained from all participants. Both cognitively normal and symptomatic AD participants with an age range from 55 to 90 years who underwent [11C] PK11195 PET scans were included in this study. The cognitively normal and the symptomatic AD participants were evaluated by the Clinical Core of the Knight ADRC. Detailed clinical assessments of the participants were performed in accordance with the Uniform Data Set protocol of the National Alzheimer's Coordinating Center.¹³ A clinical diagnosis of symptomatic AD, where appropriate, was made in accordance with criteria developed by working groups from the National Institute on Aging and the Alzheimer's Association.¹⁴ The severity of dementia was measured with the global clinical dementia rating (CDR),¹⁵ whereby CDR 0 is cognitively unimpaired, 0.5 is very mild dementia, 1 is mild dementia, 2 is moderate dementia, and 3 is severe dementia. The CDR sum of boxes (CDR-SB) was used as a more granular measure of clinical impairment.¹⁶ The Mini-Mental State Examination (MMSE) was also administered.¹⁷

Participants were categorized into 3 groups. Participants with normal cognition (CDR = 0) at the time of the PET scan who remained cognitively normal over 15 years were categorized as stable cognitively normal. Participants who were cognitively normal (CDR = 0) at the time of the PET scan and developed symptomatic AD (encompassing both mild cognitive impairment due to AD and AD dementia [CDR > 0]) over an average of 7 years of follow-up were categorized as progressors. Participants with symptomatic AD dementia at the time of PET scan (CDR > 0) were categorized as symptomatic AD.

Standard Protocol Approvals, Registrations, and Patient Consents

The local ethics committee of the Washington University School of Medicine approved the study, and all participants provided written informed consent before entering the study.

Cognitive Measures

As a measure of cognitive performance, we used the Knight ADRC Preclinical Alzheimer Cognitive Composite (Knight ADRC-PACC) score and a global composite score for each individual from the Knight ADRC cognitive battery. Consistent with previously published methods, the Knight ADRC-PACC score was calculated by averaging the *z* score across 5 cognitive tests measuring memory, attention, and processing speed.¹⁸ The cognitive tests were performed annually for each individual. Specifically, the included tests were MMSE, the Digit Symbol subtask of the Wechsler Adult Intelligence Scale, the animal naming test, the associate learning summary score from the Wechsler memory scale, and the free and cued selective reminding test. The global score was derived by averaging the *z* score for each individual across all common tasks collected by the neuropsychologic battery of the Knight ADRC. In addition to the tasks described earlier, the global score also included the Trail A and Trail B subtasks of the trail making test, the Boston naming test, the summary score of the crossing-off task, the mental control subtask of the Wechsler Memory Scale, the summary score for the S & P word fluency task, the digit span forward and backward subtasks of the revised Wechsler Memory Scale, and the information and block subtasks of the Wechsler Adult Intelligence Scale. The resulting Knight ADRC-PACC and global scores were used as measures of specific and overall cognitive performance in subsequent analyses, respectively. The baseline cognitive scores used the cognitive assessment closest to the TSPO PET scan (all were within 1 year).

APOE Genotyping

DNA was extracted from peripheral blood samples by standard procedures. *APOE* genotyping was performed as previously described.¹⁹ Individuals carrying at least 1 *APOE* $\epsilon 4$ allele were classified as *APOE* $\epsilon 4$ positive (*APOE* $\epsilon 4+$).

CSF Collection and Analysis

CSF was collected under a standard protocol. Participants underwent a lumbar puncture at approximately 8 AM after overnight fasting. Twenty to 30 mL of CSF was collected in a 50-mL polypropylene tube through gravity drip using an atraumatic Sprotte 22-gauge spinal needle. CSF was kept on ice and centrifuged (2,000 g, 10 minutes) within 2 hours of collection to pellet any cellular debris and then transferred to another 50 mL tube. CSF was aliquoted in 500- μ L volumes into polypropylene tubes and stored at -80°C , as previously described.²⁰

Before analysis, samples were brought to room temperature. Samples were vortexed and transferred to provided cuvettes for analysis. Concentrations of A β 40, A β 42, tau phosphorylated at position 181 (p-tau181), and total tau (t-tau) were measured by chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE G1200, Fujirebio, Malvern, PA) according to manufacturer's specifications. A single lot of reagents was used for all samples.

MRI Acquisition

Anatomic MRI was obtained on each participant with T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequences using a Siemens Vision 1.5T scanner or a Siemens Avanto 1.5T scanner (Siemens, Erlangen, Germany). The acquisition parameters for MPRAGE were the following: TR, 9.7 ms; TE, 4.0 ms; inversion time, 20 ms; imaging resolution, $1 \times 1 \times 1.25 \text{ mm}^3$. The T1-weighted MRI was used for FreeSurfer parcellation²¹ (freesurfer.net/).

PET Acquisition and Processing

TSPO PET imaging was performed on a Siemens 962 HR + PET scanner using the radiotracer [11C]PK11195 [1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide]. A 6th-minute dynamic PET scan in 3-dimensional mode (septa retracted) was acquired (24 \times 5-second frames; 9 \times 20-second frames; 10 \times 1-minute frames; 9 \times 5-minute frames). PET scans were processed, as previously described, using the 10- to 60-minute motion-corrected frames for partial volume-corrected standard uptake value ratio (SUVR).^{22,23} The visual check on the registration between the [11C]PK11195 SUVR maps and MPRAGE images has been performed for each individual. Cerebellar cortex has the lowest density of microglia²⁴ and was used as the reference region. Partial volume-corrected SUVRs²³ were calculated for each [11C]PK11195 scan, using the 10- to 60-minute frames with the FreeSurfer regions and the calculated reference region of nonspecific binding in the cerebellar cortex. As the global index to reflect neuroinflammation, a mean cortical SUVR was calculated based on the cortical regions defined by FreeSurfer.

Regions of Interest

The hippocampus and precuneus are the 2 regions of interests selected based on previous work finding those 2 cerebral regions as sensitive to AD pathologies of amyloid and tau.^{9,23} Both regions are from FreeSurfer parcellation. [11C]PK11195 SUVRs were calculated for these regions and the whole cortex regions.

Statistical Analysis

Nonparametric Kruskal-Wallis and the χ^2 tests were used for comparing continuous and categorical variables of the participants' demographics, respectively. One-way ANOVA was used to test the group differences in [11C]PK11195 binding, CSF biomarkers, and cognition. The Tukey honest significant differences were computed to perform multiple pairwise comparison between the mean values of groups. Spearman correlations were used to measure the strength of the associations between [11C]PK11195 SUVR and CSF biomarkers while adjusting for effects of age and sex.²⁵ A random coefficient model²⁶ was used to examine whether the baseline [11C]PK11195 SUVR was associated with the longitudinal cognitive change for all participants. This statistical method allows us to accommodate heterogeneous numbers of visits and intervals between visits for our included participants. The cognitive measure within 1 year of the [11C]PK11195 scan

and all available follow-up cognitive measures for each individual were included in our statistical model. Age and sex were included in this model as the covariates. Of importance, time is considered a continuous variable (measured in years) in this model, representing the interval between the baseline cognitive assessment and each subsequent visit. Within this model, time is treated as both a fixed and random effect. The statistical model is the following:

$$\text{Cognition} = \beta_1 \times \text{time} + \beta_2 \times \text{baseline PK} + \beta_3 \times \text{time} \times \text{baseline PK} + \beta_4 \times \text{age} + \beta_5 \times \text{sex} \quad (1)$$

The estimate (β by type 3 sum of squares) and corresponding p values from the interaction term, $\text{time} \times \text{baseline PK}$, were reported to investigate whether the baseline [11C]PK11195 SUVR predicts cognitive decline. The random coefficient model approach allows for different intercepts and slopes for each individual across variables of interest. This approach is particularly useful because it accommodates the heterogeneous number of visits and intervals between visits. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC) or R (R Core Team [2020]), and $p <$

0.05 was regarded as statistically significant after Bonferroni correction.

Data Availability

All data associated with this study are present in the article or the supplementary material. Deidentified data will be shared on reasonable request from a qualified investigator.

Results

Participant Demographics

Demographic data are summarized in Table 1. Individuals were categorized into the following groups: 9 stable cognitively normal (CDR = 0 at the PET scan and follow-up 13.2 ± 3.9 years later), 9 progressors (CDR = 0 at the PET scan and CDR > 0 at follow-up 7.4 ± 4.8 years later), and 6 symptomatic AD (3 with CDR = 0.5 and 3 with CDR = 1 at the PET scan). Individuals in the progressor and AD dementia groups were significantly older than individuals in the stable cognitively normal group (79.7 ± 6.2, 78.2 ± 7.5, and 67.9 ± 9.8 years [mean ± SD], respectively, $p = 0.04$). There were no significant group differences in sex, years of education, APOE ε4 status, or race. CDR and CDR-SB at

Table 1 Demographic and Clinic Characteristics of the Participants

	Nonconverter	Converter	AD		<i>p</i> Value
No.	9	9	3	3	
CDR	0	0	0.5	1	<0.001
CDR-SB	0.1 (0.2)	0.1 (0.2)	3.0 (2.2)		0.004
MMSE	28.3 (1.9)	29.0 (0.7)	23.5 (5.8)		0.30
Age, y	67.9 (9.8)	79.7 (6.2)	78.2 (7.5)		0.04
Female	5 (56%)	5 (56%)	4 (67%)		0.89
Education, y	14.3 (2.6)	16.0 (3.0)	13.8 (3.9)		0.32
APOE ε4 carriers	4 (44%)	1 (11%)	4 (67%)		0.09
Non-Hispanic Whites	8 (89%)	9 (100%)	4 (67%)		0.17
Averaged duration of follow-ups, y	13.2 (3.9)	7.4 (4.8)	4.1 (2.9)		<0.001
Global composite score	0.11 (0.34)	0.10 (0.44)	-0.61 (0.86)		0.08
Rate of change in global composite score	-0.03 (0.02)	-0.13 (0.12)	-0.32 (0.23)		0.004
Knight ADRC-PACC score	0.05 (0.51)	0.01 (0.70)	-0.74 (0.94)		0.19
Rate of change in Knight ADRC-PACC score	-0.04 (0.04)	-0.10 (0.28)	-0.39 (0.49)		0.11
CSF measures (no.)	6	6	4		
CSF Aβ42 (pg/mL)	971 (286)	672 (380)	505 (125)		0.06
CSF Aβ42/Aβ40	0.08 (0.02)	0.05 (0.02)	0.04 (0.00)		0.008
CSF p-tau181 (pg/mL)	44.1 (11.6)	74.5 (30.7)	151.1 (85.5)		0.008
CSF t-tau (pg/mL)	354 (120)	549 (198)	1,004 (573)		0.02

Abbreviations: AD = Alzheimer disease; ADRC = Alzheimer Disease Research Center; CDR = clinical dementia rating; MMSE = Mini-Mental State Examination; PACC = preclinical Alzheimer cognitive composite. The mean (SD) values are provided for continuous variables; number (%) for dichotomous variables.

baseline were higher (worse) in the symptomatic AD group compared with the progressor and stable cognitively normal groups ($p < 0.001$ and 0.004 , respectively). However, there were no significant group differences in the MMSE, global composite scores, or Knight ADRC-PACC scores.

[11C] PK11195 PET SUVR Maps

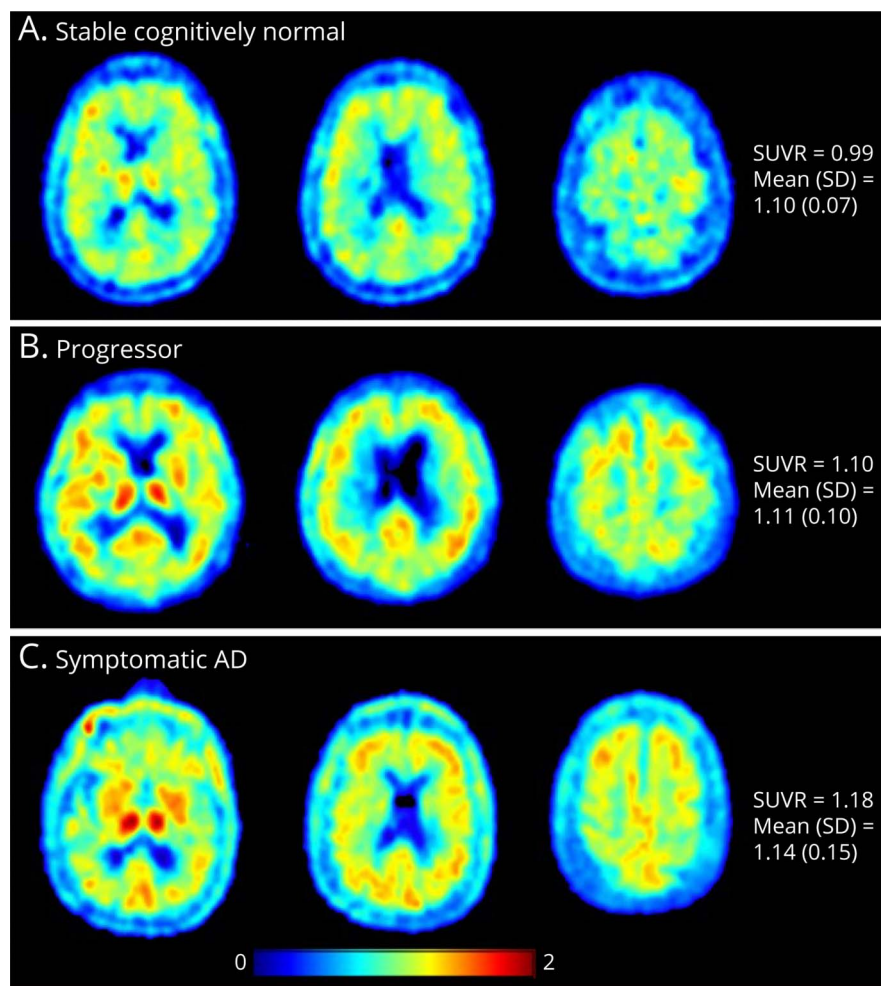
Representative [11C]PK11195 PET SUVR images from 1 representative individual for each group are shown in Figure 1. Panel A is an individual from the stable cognitively normal group (mean cortical SUVR of 0.99), panel B is from the progressor group (SUVR 1.10), and panel C is from the symptomatic AD group (SUVR 1.18). The mean cortical SUVRs for the groups were as follows: stable cognitively normal, 1.10 ± 0.07 (mean \pm SD); progressor, 1.11 ± 0.10 ; symptomatic AD, 1.14 ± 0.15 . Although there were no significant group differences in mean cortical SUVR, there were significant regional elevations of [11C]PK11195 SUVR in the hippocampus (Figure 2A) in the progressor and symptomatic AD groups compared with those in the stable cognitively normal group. No group differences were found in the precuneus (Figure 2B).

CSF Biomarkers

Of the 24 participants, 16 had available data on CSF A β 42, A β 42/A β 40, p-tau181, and t-tau within 1 year of the PET scan. For CSF A β 42, which is less accurate than other analytes in detecting brain amyloidosis, there were no significant group differences in CSF A β 42 by omnibus testing (Figure 3A). Further data exploration revealed a trend toward lower CSF A β 42 in the symptomatic AD group compared with the stable cognitively normal group ($p = 0.06$) (Figure 3A). Significant group differences were observed in CSF A β 42/A β 40, p-tau181, and t-tau (Figures 3, B–D). The ratio of CSF A β 42/A β 40, which is more sensitive to amyloidosis than CSF A β 42,²⁷ was lower in the symptomatic AD group when compared with the stable cognitively normal group ($p = 0.009$) (Figure 3B). CSF p-tau181 and t-tau were higher in the symptomatic AD group when compared with those in the stable cognitively normal group (Figures 3, C and D, $p = 0.006$ and $p = 0.01$, respectively).

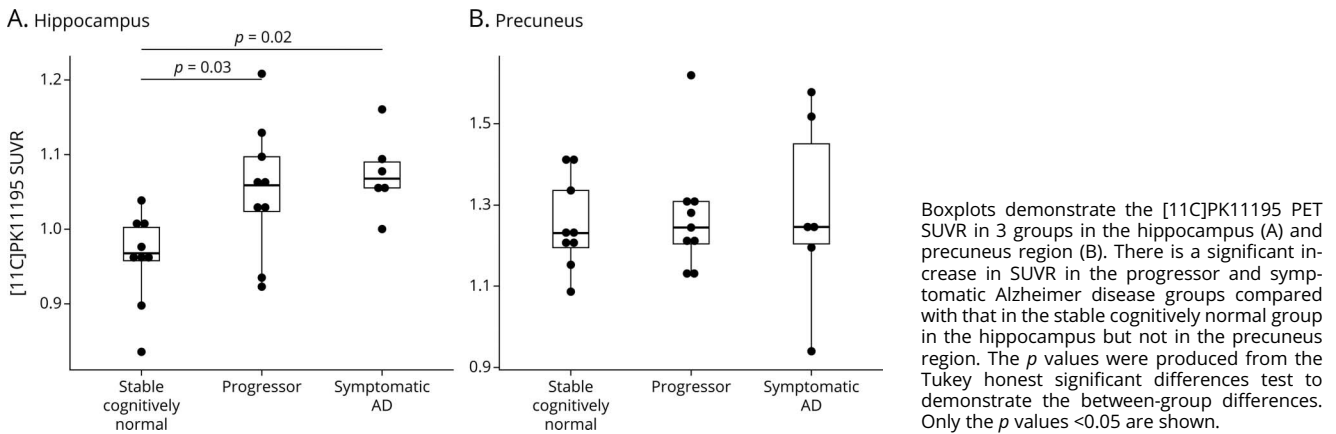
The relationship between CSF biomarkers and [11C] PK11195 SUVR was further evaluated in the entire subcohort

Figure 1 Representative [11C]PK11195 PET SUVR Maps



[11C]PK11195 PET SUVR maps of 3 representative cases from the stable cognitively normal (A), progressor (B), and symptomatic Alzheimer disease (C) groups.

Figure 2 [11C]PK11195 PET SUVR in the Hippocampus and Precuneus Regions



with CSF biomarkers using Spearman correlations adjusting for age and sex. Significant negative correlations were found between CSF A β 42 and [11C]PK11195 SUVR in the hippocampus and precuneus and the whole cortex regions as well (Figures 4, A, E, and I). Significant negative correlations between CSF A β 42/A β 40 and [11C]PK11195 SUVR were noted in the precuneus (Figure 4J). No significant correlations between CSF p-tau181 or t-tau and [11C]PK11195

SUVR were found. The Spearman rho (R) and *p* values are shown in Figure 4.

[11C]PK11195 SUVR Predicts Cognitive Decline

The ability of TSPO PET imaging to predict future cognitive decline was evaluated. The mean period of cognitive follow-up for the 3 groups (stable cognitively normal, progressor, symptomatic AD) were 13.2 ± 3.9 , 7.4 ± 4.8 , and 4.1 ± 2.9 ,

Figure 3 CSF Measures of Amyloid and Tau

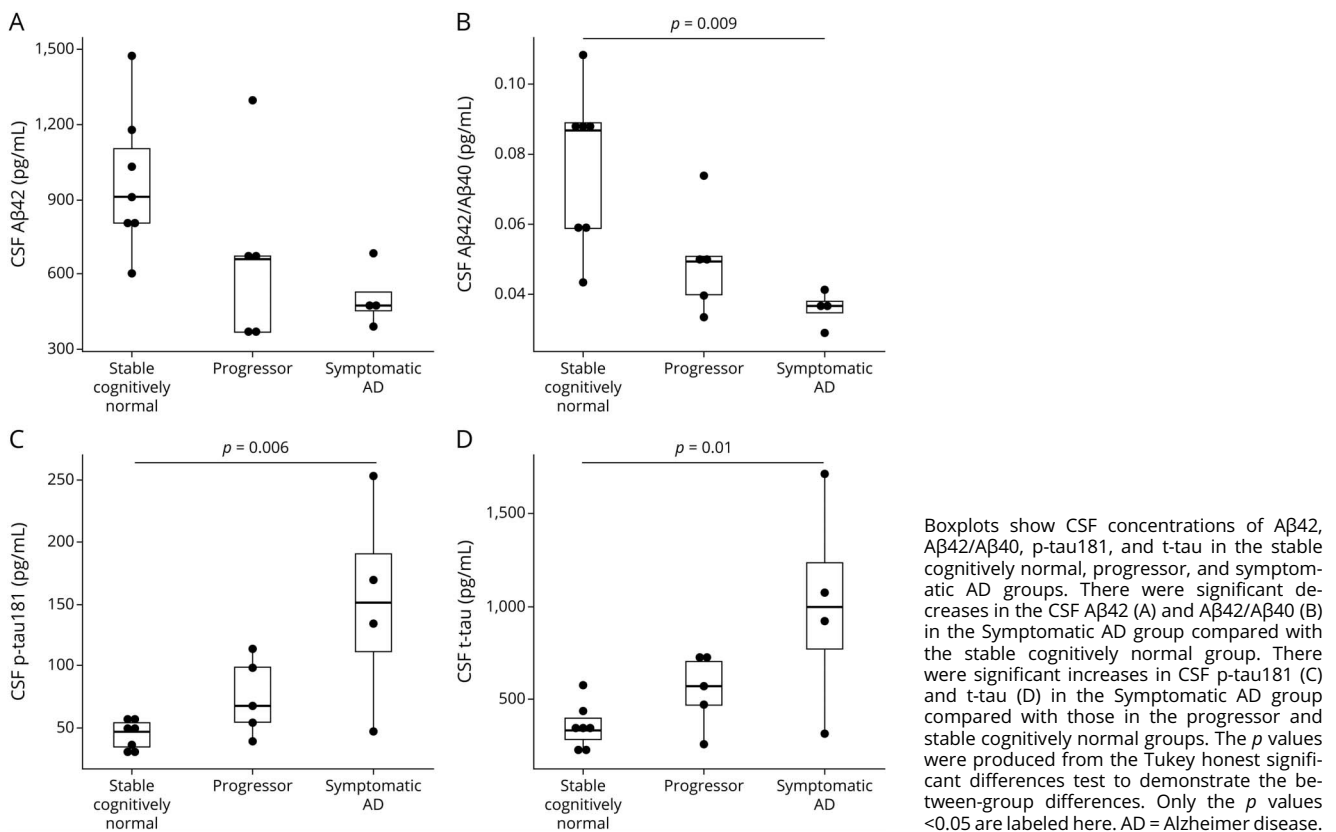
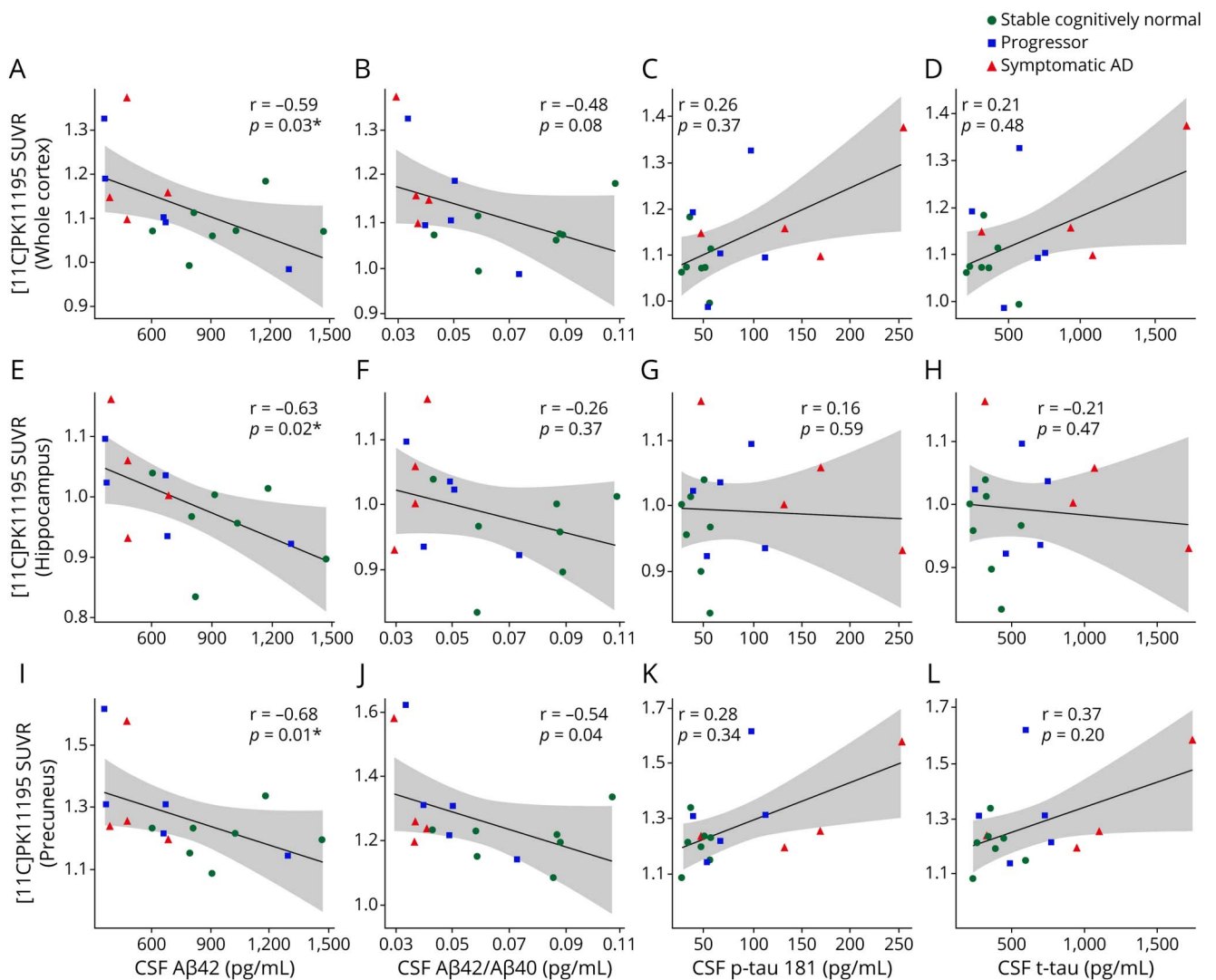


Figure 4 Correlations Between [11C]PK11195 SUVR and the CSF Biomarkers



Scatterplots show the significant correlations between [11C]PK11195 SUVR and CSF levels of amyloidosis (A, E, I, and J). There were no significant correlations between [11C]PK11195 SUVR and CSF levels of p-tau181 (C, G, and K) and t-tau (D, H, and L). *, $p < 0.05$; adjusted by age and sex.

respectively. We used the random coefficient model to investigate whether the baseline [11C]PK11195 SUVR predicts the cognitive decline. In this study, we report the estimate (β by type 3 sum of squares) and corresponding p values from the interaction term: time \times baseline PK from Equation 1. We found that higher [11C]PK11195 SUVR in the whole cortical regions ($p = 0.03$) predicted the cognitive decline in Knight ADRC-PACC score, but not in global composite score (Table 2). [11C]PK11195 SUVR in the hippocampus and precuneus regions did not predict the decline of global and Knight ADRC-PACC scores with $p > 0.05$ (Table 2). The same statistical analysis was performed on 16 participants who have the CSF measures. We found that higher [11C]PK11195 SUVR in the whole cortical regions predicted the cognitive decline in the global composite score ($p = 0.03$) and Knight ADRC-PACC score ($p = 0.01$) (eTable 1 in the supplement,

links.lww.com/NXI/A704). [11C]PK11195 SUVR in the precuneus but not in the hippocampus predicted cognitive decline in Knight ADRC-PACC score ($p = 0.01$) (eTable 1 in the supplement). When considering CSF A β 42/A β 40 and/or p-tau181 as covariates, [11C]PK11195 SUVR in the whole cortical regions still predicted the cognitive decline in global composite score and Knight ADRC-PACC score, and [11C]PK11195 SUVR in the precuneus predicted the cognitive decline in Knight ADRC-PACC score (eTables 2 and 3 in the supplement).

Classification of Evidence

This study provides Class II evidence that in patients with AD, higher baseline [11C]PK11195 SUVR averaged in the whole cortical regions was associated with longitudinal decline on cognitive tests.

Table 2 Baseline [11C]PK11195 SUVR Predicts Cognitive Decline

	Global composite score		Knight ADRC-PACC score	
	Estimate	p Value	Estimate	p Value
Cortex	-0.74	0.11	-1.09	0.03 ^a
Hippocampus	-0.53	0.24	-0.68	0.13
Precuneus	-0.34	0.24	-0.56	0.05

^a $p < 0.05$; adjusted by age and sex.

Discussion

The goal of this study was to investigate the relationships between microglial activation measured by [11C]PK11195, CSF biomarkers of AD, and cognitive decline. We found that individuals categorized in the progressor and symptomatic AD groups had higher [11C]PK11195 SUVR in the hippocampus and precuneus regions compared with the stable cognitively normal group. Lower CSF A β 42 and A β 42/A β 40, consistent with greater brain amyloidosis, was associated with higher [11C]PK11195 SUVR in the AD pathology-susceptible regions the hippocampus and precuneus. Of interest, no significant correlations CSF p-tau181 or t-tau were found with [11C]PK11195 SUVR in any region. Last, [11C]PK11195 SUVR in the overall cortical region predicted cognitive decline, as measured by the commonly used composite score, Knight ADRC-PACC score, in AD studies.

As one of the earliest developed PET TSPO radiotracers, [11C]PK11195 has been used to investigate the microglial activation in AD brains.²⁸ The lack of group differences of the mean cortical SUVR may be attributed to the limited sample size. However, our region-based analysis found elevated [11C]PK11195 SUVR in the hippocampus of the progressor and symptomatic AD groups compared with the stable cognitively normal group. The hippocampus is an important subcortical region that is known to be severely and consistently affected by AD pathologic processes and shows a considerable shrinkage, distortion, and loss of neurons.^{29,30} Our previous work has demonstrated that the hippocampus volume demonstrated higher clinical diagnostic performance than the traditional volumetric measures for AD.⁸ The elevated [11C]PK11195 binding in the progressor group in this region suggests that microglial activation may be an early event in the pathogenesis of AD that precedes symptom onset.^{7,12,31}

Although lower CSF A β 42 is well-established as a biomarker of amyloidosis,³² the ratio of A β 42 to A β 40 (A β 42/A β 40) is superior to A β 42 as a biomarker of brain amyloidosis.^{33,34} In this study, we investigated the relationship between microglial activation and amyloidosis measured by both CSF A β 42 and A β 42/A β 40. We found both CSF levels of A β 42 and A β 42/A β 40 were negatively correlated with [11C]PK11195 SUVR

in the hippocampus and precuneus, suggesting that brain amyloidosis and microglial activation may be linked.

Although studies have demonstrated an association of neuroinflammation and CSF measures of tau,⁴ we did not find any significant correlations between [11C]PK11195 SUVR and CSF p-tau181 or t-tau. However, not reaching the significant level, the trends of positive associations between [11C]PK11195 SUVR and CSF measures of p-tau and tau in the whole cortex and precuneus regions have been shown in Figure 4, suggesting neuroinflammation could increase with the increase in tau pathology in AD. Notably, our participants exhibited very early AD. Accumulating evidence suggests that neuroinflammation may play a neuroprotective role in early AD, but this role may change and become pathologic in later stages of AD.^{7,35} Therefore, measures of neuroinflammation may vary in a nonlinear fashion across different disease stages, complicating studies. Large sample sizes and longitudinal evaluations are necessary to characterize changes in neuroinflammation over time.

Although several previous studies have found that TSPO PET uptake correlates inversely with cognitive measures,^{36,37} the relationship between [11C]PK11195 uptake and longitudinal cognitive decline has not been fully explored. Consistent with a recent study that demonstrated the ability of [11C]PK11195 to predict cognitive decline,³⁸ we also found that [11C]PK11195 SUVRs in the whole cortical region predicted cognitive decline. Similar results were found on the subset participants who have CSF measures (eTable 1 in the supplement, links.lww.com/NXI/A704). A further analysis of whether microglial activation at baseline remains a significant predictor of subsequent cognitive decline after including amyloid and tau at baseline as independent predictors was performed. [11C]PK11195 SUVRs in the whole cortical region predicting cognitive decline still remained (eTables 2 and 3 in the supplement), suggesting microglial activation is a strong predictor of cognitive decline.

A linear regression model was also implemented to investigate the relationship between the baseline [11C]PK11195 binding and the rate of change in cognitive measures. The results were summarized in eTable 4 in the supplement, links.lww.com/NXI/A704. Significant negative correlations were found between the [11C]PK11195 binding and the rate of change in Global and Knight ADRC-PACC scores in the hippocampus region. The negative correlations between the [11C]PK11195 binding and the rate of change in cognitive measures in the whole cortex and precuneus regions were found but not reaching statistical significance. Those results also support our findings using the random coefficient model that the baseline [11C]PK11195 binding predicts cognitive decline in AD. The inverse correlation between [11C]PK11195 SUVR and the rate of change in cognitive composite score Knight ADRC-PACC found in this study suggests that a high level of microglial activation accelerates the cognition decline in AD. Although associations between amyloid deposition,

tau load, and microglial activation have been established in both postmortem and in vivo neuroimaging studies,^{39,40} how those key AD pathologies independently or jointly promote the clinical progression of AD remains unclear. One recent study considered the interaction of those AD pathologies found the combined contribution of temporo-parietal tau pathology and anterior temporal neuroinflammation in predicting cognitive decline in patients with symptomatic AD.³⁸ Further studies with larger sample size are desired along this direction.

There are several limitations in this study. First, the sample size is small. Studies with larger sample sizes are required to evaluate the interactions of AD pathologies in the prediction of cognitive decline. In addition, this study focused on the 2 earliest-affected AD pathology-sensitive regions—the hippocampus and precuneus. Further analysis on the whole brain will be necessary to deepen our understanding of the spatial relationships among these AD pathologies. Finally, CSF measures of amyloidosis and tauopathy do not provide information on the regional distribution of AD pathology. Future studies analyzing PET imaging of amyloid, tau, and microglial activation on the voxel level will enable the detailed investigation of the spatial relationships among amyloid, tau, and neuroinflammation in AD progression.

In summary, our results indicate a first-generation TSPO PET tracer developed to image microglial activation in AD. [11C]PK11195 demonstrates higher binding both in individuals with symptomatic AD and individuals who are cognitively normal at baseline and progress to symptomatic AD. We found that [11C]PK11195 binding correlated with global amyloidosis measured by CSF biomarkers in the hippocampus and precuneus, suggesting that microglial activation is associated with brain amyloidosis in early AD. Furthermore, regional [11C]PK11195 binding in the overall cortical region predicted cognitive decline in AD.

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Disclosure

Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures.

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Continued

Appendix (continued)

Name	Location	Contribution
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