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RESEARCH ARTICLE

Microglia measured by TSPO PET are associated with Alzheimer's disease pathology and mediate key steps in a disease progression model

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Abstract

INTRODUCTION: Evidence suggests microglial activation precedes regional tau and neurodegeneration in Alzheimer's disease (AD). We characterized microglia with translocator protein (TSPO) positron emission tomography (PET) within an AD progression model where global amyloid beta (Aβ) precedes local tau and neurodegeneration, resulting in cognitive impairment.

METHODS: Florbetaben, PBR28, and MK-6240 PET, T1 magnetic resonance imaging, and cognitive measures were performed in 19 cognitively unimpaired older adults and 22 patients with mild cognitive impairment or mild AD to examine associations among microglia activation, Aβ, tau, and cognition, adjusting for neurodegeneration. Mediation analyses evaluated the possible role of microglial activation along the AD progression model.

RESULTS: Higher PBR28 uptake was associated with higher Aβ, higher tau, and lower MMSE score, independent of neurodegeneration. PBR28 mediated associations between tau in early and middle Braak stages, between tau and neurodegeneration, and between neurodegeneration and cognition.

DISCUSSION: Microglia are associated with AD pathology and cognition and may mediate relationships between subsequent steps in AD progression.

KEYWORDS
AD progression, Alzheimer's disease, neuroinflammation, TSPO PET

1 | BACKGROUND

Diffuse amyloid β (Aβ) deposition throughout the neocortex[1] can occur as early as two decades before Alzheimer's disease (AD) symptom onset and is believed to facilitate the development of other AD pathologies, including the aggregation of hyperphosphorylated tau into neurofibrillary tangles.[2,3] The spread of tau pathology in AD has been well characterized into Braak stages at autopsy,[4] starting with early accumulation in the entorhinal cortex and hippocampal regions before spreading to other regions of the temporal, frontal, and

parietal regions. Of note, the spatiotemporal trajectory of tau aggregation precedes that of neurodegeneration (eg, neuronal death, synaptic loss), which gives rise to AD symptoms.[5] This model of Aβ deposition to tau aggregation across Braak stages to neurodegeneration to cognitive impairment will be referred to as the AD progression model throughout this article.

Neuroinflammation is an immune response in which glial cells in the brain, such as microglia, are recruited to protect tissue from pathogens, respond to injury, and help with the upkeep of tissue maintenance. Microglia are heterogeneous in their developmental origins as well as their varied response to stimuli during surveillance, including the adoption of different cellular morphologies and differential transcriptomic expression through aging, injury, and disease, suggesting context-dependent functionality over time within a single microglia.[6] Within the context of AD, microglial activity plays a complex role, where it may protect against disease pathology, promote the spread of disease pathology, or be a product of disease progression. Microglia may serve a protective function, such as clearing soluble Aβ or corralling larger Aβ deposits in the extracellular space, maintaining an innate immune memory; however, primed microglia can develop a complex neurotoxic phenotype with exaggerated immune responses leading to chronic inflammation or an attenuated immune response leading to unchecked pathology, depending on the stimuli, the microenvironment, and the cellular cross-talk with neurons and other inflammatory cells.[7,8] These dysfunctional microglia are associated with increased Aβ and AD risk.[9] Further, apolipoprotein E (*APOE*) and triggering receptor expressed on myeloid cells 2 (*TREM2*) mutations in microglia may promote amyloidosis and tauopathies through their role in leading to or suppressing microglial activation.[10] Microglial activation may also promote disease pathology and progression via cytokine release[9] and the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome,[2,11–17] preceding[13,14,18–20] and seeding[21–23] tau pathology to surrounding unaffected areas as well as contributing to amyloid-initiated, tau-dependent synaptic loss.[9,24] Microglia, as a product of disease progression, can perform cellular functions related to the upkeep of the extracellular space (ie, removing cellular waste and debris).[25] The accumulation of insoluble myelin debris within surveilling microglia can ultimately lead to microglia dysfunction, brain aging,[26] and cognitive impairment.[27] The complex age- and disease stage-dependent role of microglia likely contributes to the mixed results obtained in clinical trials of non-steroidal anti-inflammatory drugs (NSAIDs) to prevent or delay AD.[28–30] For a review of microglia heterogeneity and nomenclature, see Healy et al.[6] and Paolicelli et al.[8]

Moving beyond study designs that only include canonical Aβ, tau, and neurodegeneration biomarkers, recent advancements have made it possible to incorporate the role of neuroinflammatory markers throughout AD progression.[31] The 18 kDa translocator protein (TSPO) can be imaged in vivo using positron emission tomography (PET)[32]; an elevated signal from TSPO PET can indicate activated microglia and/or increased microglial density. Regional TSPO expression, induced by amyloid, propagates across Braak stages and may be a driver of tau aggregation and spread in patients with AD,[33] yet TSPO in activated microglia is also closely associated with neurodegeneration.[34] We sought to determine whether TSPO had both upstream (ie, preceding neurodegeneration) and downstream (ie, following neurodegeneration) associations with AD pathology. First, we examined the association of TSPO with measures of (1) global Aβ, (2) regional tau across different Braak stages, and (3) cognition, while accounting for neurodegeneration. Next, we considered the role of TSPO in AD based on a progression model that began with Aβ deposition and continues with tau aggregation and neurodegeneration in early, middle, and late Braak stages, followed by cognitive impairment.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (eg, PubMed) and cite these studies appropriately. The role of key proteins, including amyloid β (Aβ) and tau, has been well characterized in Alzheimer's disease (AD), while the mechanisms by which neuroinflammation is related to disease progression remain uncertain.
2. **Interpretation**: This study shows that neuroinflammation is not only related to measures of AD such as Aβ and tau burden but also may mediate important steps in the progression of disease pathology. These findings support the hypothesis that activated microglia contribute to the spread of AD pathology and, in turn, symptomology.
3. **Future directions**: Future studies should explore this in a longitudinal manner by repeating measures in the same patient to explore within-subject AD progression. A better understanding of AD progression will contribute to improved treatments and cognitive outcomes for those with the disease.

2 | METHODS

2.1 | Participants

Forty-one research participants underwent magnetic resonance imaging (MRI), multiple PET scans, and a cognitive assessment. These participants were retrospectively selected from and harmonized across studies (K23AG052633, R01AG026158, R56AG034189, P50AG008702, P01AG07232, R01AG037212, RF1AG054023),[35,36] based on the availability of imaging and cognitive measures. Of these participants, 19 were cognitively unimpaired, while 22 were cognitively impaired based on having a primary memory complaint and meeting clinical criteria for either amnestic mild cognitive impairment (MCI, single- or multiple-domain)[37] or AD,[38] as described previously.[36] Participants were evaluated with the Mini-Mental State Examination (MMSE[39]), and domain-specific tests including the Selective Reminding Test-Delayed Recall (SRT-DR[40]), Trail Making Test Part B (Trails B[41]),

and categorical fluency (CF-Animals[42]). Domain-specific cognitive test scores were transformed into *z*-scores using age-, sex-, and education-adjusted normative data derived from the National Alzheimer's Coordinating Center Uniform Dataset (NACC).[43] All participants (or their legally authorized representatives) provided informed consent according to the Declaration of Helsinki, and all study procedures were approved by the Columbia University Irving Medical Center Institutional Review Board.

2.2 | TSPO genotyping

TSPO binding affinity was determined at screening, as previously described.[36] Briefly, genomic DNA from each subject was used to genotype the rs6971 polymorphism using a TaqMan assay.[44] Participants were high-affinity binders (HH) or mixed-affinity binders (HL), and the proportion did not differ between controls and patients. Low-affinity binders (LL) were excluded.

2.3 | APOE genotyping

APOE information was only available in a subset of 17 participants (10 controls, seven patients). All patients were APOE ε4 non-carriers, which precluded robust interpretation of models when including APOE ε4 status. However, APOE ε4 carriers had significantly greater global ^{18}F-florbetaben (FBB) SUVR and MK6240 SUVR and lower global cognition, with slightly greater PBR28 SUVR and lower %GM (Table S1).

2.4 | Magnetic resonance imaging

MRI scans were acquired as previously described.[35,36] In short, all participants underwent T1-weighted MRI scanning on a 3T scanner. FreeSurfer 6.0 (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu) was used to segment the MRI scans and to determine gray matter (GM) volume. A global neurodegeneration measure (%GM) was calculated as the sum of the GM volume from composite AD-related regions (hippocampus, inferior frontal gyrus, middle-inferior and superior temporal cortex, medial temporal cortex, inferior and superior parietal cortex, precuneus, prefrontal cortex, and posterior cingulate) normalized by the total intracranial volume. Neurodegeneration measures were also calculated for early (I+II), middle (III+IV), and late (V+VI) Braak stages (Table S2). Divisions of Braak staging have been described elsewhere.[35,45]

2.5 | PET

2.5.1 | Image acquisition, processing, and quantification

^{18}F-Florbetaben (FBB)

FBB scans were acquired to evaluate Aβ as described previously.[36] In summary, image data from 50 to 70 min after FBB injection were aligned with the MRI, and regions of interest (ROIs) were defined using the Hammers-N30R83-1 MM atlas in the PNEURO module of PMOD 3.9 (PMOD Technologies[46]). Amyloid positivity was defined as previously described.[36] Partial volume correction (PVC) was completed using the region-based voxel-wise method (PMOD Technologies[47]). Standardized uptake value ratios (SUVRs) were calculated by normalizing the radioactivity in the ROIs to the activity in the GM of the cerebellum. A composite SUVR measure was calculated based on a volume-weighted average of representative AD-related regions consisting of the same regions as mentioned earlier for the composite MRI measure.

^{11}C-PBR28 (PBR28)

PBR28 scans were acquired to evaluate TSPO expression, as described previously.[36] In summary, image data from 60 to 90 min after PBR28 injection were aligned with the MRI, and ROIs were defined using the Hammers-N30R83-1 MM atlas in the PNEURO module of PMOD 3.9. PVC was completed using the region-based voxel-wise method in PMOD. SUVR measures were calculated by normalizing the radioactivity in the ROIs to the activity in the GM of the cerebellum, which was used as a reference region. A composite SUVR measure was calculated based on a volume-weighted average of representative AD-related regions consisting of the same regions as mentioned above for the composite FBB and MRI measures.

^{18}F-MK-6240 (MK-6240)

MK-6240 scans were acquired to evaluate the presence and extent of tau pathology, as described previously.[35] In summary, image data were collected from 90 to 110 min after MK-6240 injection. ROIs were defined in FreeSurfer. Tau positivity thresholds for early, middle, and late Braak stages (individual regions outlined in Table S2) were 1.40, 1.50, and 1.53 SUVR, respectively, and were previously derived in a sample of 100 cognitively unimpaired adults from a community-based study in Northern Manhattan.[35] PVC was implemented in MATLAB using the Muller-Gartner method[47] as performed in the previous study.[35] SUVR measures were calculated using the inferior GM of the cerebellum as a reference region, which avoids spill-in of radiotracer binding in the occipital lobe and off-target binding in the falx cerebelli. Regional SUVR measures were calculated for early (I+II), middle (III+IV), and late (V+VI) Braak stages, as described above for the regional MRI measures.

2.6 | Statistical analysis

Demographic characteristics between the control and patient groups were compared with *t*-tests for continuous variables and chi-squared tests for proportional variables for context related to AD progression, but data from both groups were combined for the association and mediation analyses. To test whether TSPO expression was associated with AD biomarkers and cognition independently of neurodegeneration, we used a series of linear regressions with PBR28 SUVR as the independent variable and AD biomarkers (FBB SUVR, MK-

6240 SUVR) or cognitive performance (MMSE, SRT-DR, Trails B, CF-Animals) as the dependent variable controlling for age, education, race, sex, and *TSPO* genotypes, with and without %GM in an AD composite region (Figure S1). To evaluate whether TSPO expression mediated pathways along the AD progression model, we performed a series of structural equation models (lavaan package, R version 4.1.2[48]; standard errors computed using Delta method[49]), adjusting each path for age, education, race, sex, and *TSPO* genotypes. For the AD progression model, regional %GM within early, middle, and late Braak stages was used rather than %GM in an AD composite region.

The main analyses were performed using PVC PET data to account for spill-out of PET signal due to neurodegeneration within a voxel; PVC methods may add noise to data,[50] and analyses using uncorrected PET data are shown in Figures S2 and S3 and Table S3. Some PET measures were skewed. While very high values in patients relative to controls are biologically plausible and meaningful, we repeated the analysis after log transformation. Reported results were not biased by the skewness of PET data. Corrections for multiple comparisons were not performed. All analyses were performed using R version 4.1.2.

3 | RESULTS

3.1 | Demographic characteristics

Age did not differ between controls and patients, and there were more men, more White participants, and greater years of education in the patient group (Table 1). As expected, the patient group had greater FBB SUVR, greater PBR28 SUVR, greater MK-6240 SUVR in early, middle, and late Braak stages, and lower MMSE, SRT-DR, Trails B, and CF-Animals scores. Notably, the patient group had the greatest MK-6240 SUVR in middle Braak regions and the lowest SRT-DR scores, as expected, but the greatest impairment (ie, lowest individual-level *z*-scores) in Trails B.

3.2 | TSPO correlates with AD PET and cognitive measures, independent of neurodegeneration

When correcting for %GM, greater PBR28 SUVR was associated with greater FBB SUVR (Figure 1; $\beta = 0.46$, $p = .002$). Greater PBR28 SUVR was also associated with greater MK-6240 SUVR in middle ($\beta = 0.45$, $p = .004$) and late ($\beta = 0.50$, $p = .002$) Braak regions, with a non-significant positive association in early Braak regions. Greater PBR28 SUVR was associated with lower MMSE ($\beta = -0.53$, $p = .006$), SRT-DR ($\beta = -0.39$, $p = .037$), and Trails B scores ($\beta = -0.50$, $p = .004$), but not categorical fluency scores. When not correcting for %GM, greater PBR28 SUVR was associated with greater MK-6240 SUVR in early Braak regions and lower CF-Animals score (Figure S1).

3.3 | TSPO significantly mediates pathways along AD progression model

In a series of mediation analyses (Figure 2, Table 2), greater PBR28 SUVR mediated the association between greater MK-6240 SUVR in early Braak regions and greater MK-6240 SUVR in middle Braak regions (indirect effect = 0.118, *z*-score = 2.169, $p = .030$) and the association between greater MK-6240 SUVR in middle Braak regions and greater neurodegeneration in middle Braak regions (indirect effect = −0.225, *z*-score = −2.214, $p = .027$). Greater PBR28 SUVR mediated the association between greater neurodegeneration in both early (indirect effect = 0.233, *z*-score = 2.307, $p = .021$) and middle Braak regions (indirect effect = 0.204, *z*-score = 2.185, $p = .029$) and lower MMSE score. Greater PBR28 SUVR also mediated the association between greater neurodegeneration in both early (indirect effect = 0.283, *z*-score = 2.579, $p = .009$) and middle Braak regions (indirect effect = 0.228, *z*-score = 2.379, $p = .017$) and lower Trails B score.

4 | DISCUSSION

We examined the associations of microglial recruitment and/or density, measured by TSPO expression, and key AD biomarkers and cognitive measures with two goals – to disentangle components of neuroinflammation that drive pathology from those that respond to neurodegenerative processes and to elucidate the role of neuroinflammation along an AD progression model. Our findings add to the growing body of evidence that neuroinflammation tracks in severity with Aβ and tau pathology and cognition, independently of the microglial response to neurodegenerative processes. The findings additionally demonstrate that neuroinflammation may be the mechanistic link by which tau spreads across Braak regions and between tau burden, neurodegeneration, and cognitive impairment.[51] Neuroinflammation should be incorporated into large-scale, multimodal studies of AD to understand the role of activated microglia in the links between Aβ and tau, tau burden across Braak stage regions, and tau and downstream neurodegeneration and cognitive impairment such that specific inflammatory processes can be targeted at specific points along the AD continuum.

We found that greater TSPO expression was associated with AD severity in terms of neuropsychological testing results, GM volumes, and both Aβ and tau burden, aligning with previous studies.[33,52–54] However, previous studies did not correct for neurodegeneration, so whether microglia were driving AD pathogenesis or responding to neurodegeneration had not been previously established. The current study suggests that the relationships between TSPO expression, AD biomarkers, and cognition are present regardless of the role of microglia in removing cellular debris and other neurodegeneration-related products. While we did not have the statistical power to test associations within controls and patients separately, it should be noted that a range of TSPO expression was present at low levels of tau in controls (Figure 1), potentially suggesting that neuroinflammation

TABLE 1 Descriptive statistics of demographic characteristics and primary outcomes.

		Control ($N = 19$)	Patient ($N = 22$)	All ($N = 41$)	p value
Age	Mean (SD)	70 .0 (4.3)	68.1 (8.7)	69.0 (7.0)	.401
	Range	60 to 76	53 to 83	53 to 83	
Sex	Female	10 (53%)	5 (22%)	15 (37%)	.047
	Male	9 (47%)	17 (77%)	26 (63%)	
Race	Black/African-American	5 (26%)	0 (0%)	5 (12%)	.010
	White	14 (74%)	22 (100%)	36 (88%)	
Education	Mean (SD)	15.4 (2.7)	17.1 (2.4)	16.3 (2.7)	.033
	Range	10 to 20	12 to 20	10 to 20	
TSPO genotype	HH	13 (68%)	13 (59%)	26 (63%)	.536
	HL	6 (32%)	9 (41%)	15 (37%)	
APOE $\varepsilon 4$ status	Non-carriers	8 (42%)	2 (9%)	10 (24%)	<.001
	Carriers	7 (37%)	0 (0%)	7 (17%)	
	Missing	4 (21%)	20 (91%)	24 (59%)	
Amyloid status	Negative	12 (63%)	8 (36%)	20 (49%)	.087
	Positive	7 (37%)	14 (64%)	21 (51%)	
Early tau status	Negative	10 (53%)	2 (9%)	12 (29%)	.002
	Positive	9 (47%)	20 (91%)	29 (71%)	
Middle tau status	Negative	13 (68%)	4 (18%)	17 (41%)	.001
	Positive	6 (32%)	18 (82%)	24 (59%)	
Late tau status	Negative	14 (74%)	6 (27%)	20 (49%)	.003
	Positive	5 (26%)	16 (73%)	21 (51%)	
Composite ^{18}F-FBB PVC SUVR	Mean (SD)	1.47 (0.33)	1.88 (0.46)	1.69 (0.45)	.003
	Range	1.12 to 2.17	1.11 to 2.81	1.11 to 2.81	
Composite ^{11}C-PBR28 PVC SUVR	Mean (SD)	1.10 (0.11)	1.21 (0.10)	1.16 (0.12)	.001
	Range	0.77 to 1.22	1.06 to 1.45	0.77 to 1.45	
Early Braak ^{18}F-MK-6240 PVC SUVR	Mean (SD)	1.50 (0.51)	2.46 (0.91)	2.02 (0.886)	<.001
	Range	0.97 to 2.91	1.00 to 3.82	0.97 to 3.82	
Middle Braak ^{18}F-MK-6240 PVC SUVR	Mean (SD)	1.41 (0.21)	2.85 (1.54)	2.18 (1.34)	<.001
	Range	1.11 to 1.90	1.02 to 5.79	1.02 to 5.79	
Late Braak ^{18}F-MK-6240 PVC SUVR	Mean (SD)	1.39 (0.19)	2.55 (1.41)	2.01 (1.18)	<.001
	Range	1.09 to 1.75	0.98 to 5.99	0.98 to 5.99	
%GM volume	Mean (SD)	0.44 (0.01)	0.43 (0.01)	0.44 (0.01)	.017
	Range	0.43 to 0.46	0.39 to 0.45	0.39 to 0.46	
MMSE	Mean (SD)	29.2 (1.31)	25.6 (3.20)	27.3 (3.07)	<.001
	Range	26 to 30	18 to 30	18 to 30	
SRT-DR z-score	Mean (SD)	0.53 (1.09)	−3.11 (0.66)	−1.42 (2.04)	<.001
	Range	−1.60 to 2.27	−3.87 to 1.53	−3.87 to 2.27	
Trails B z-score	Mean (SD)	0.15 (0.64)	−2.79 (2.57)	−1.43 (2.42)	<.001
	Range	−1.23 to 1.02	−6.28 to 0.42	−6.26 to 1.02	
CF-Animals z-score	Mean (SD)	−0.24 (0.88)	−1.65 (1.17)	−0.98 (1.25)	<.001
	Range	−2.06 to 1.26	−3.31 to 2.38	−3.31 to 2.38	

Abbreviations: CF, categorical fluency; MMSE, Mini-Mental State Examination; SRT-DR, Selective Reminding Test-Delayed Recall; SUVR, standardized uptake value ratio; TSPO, translocator protein.

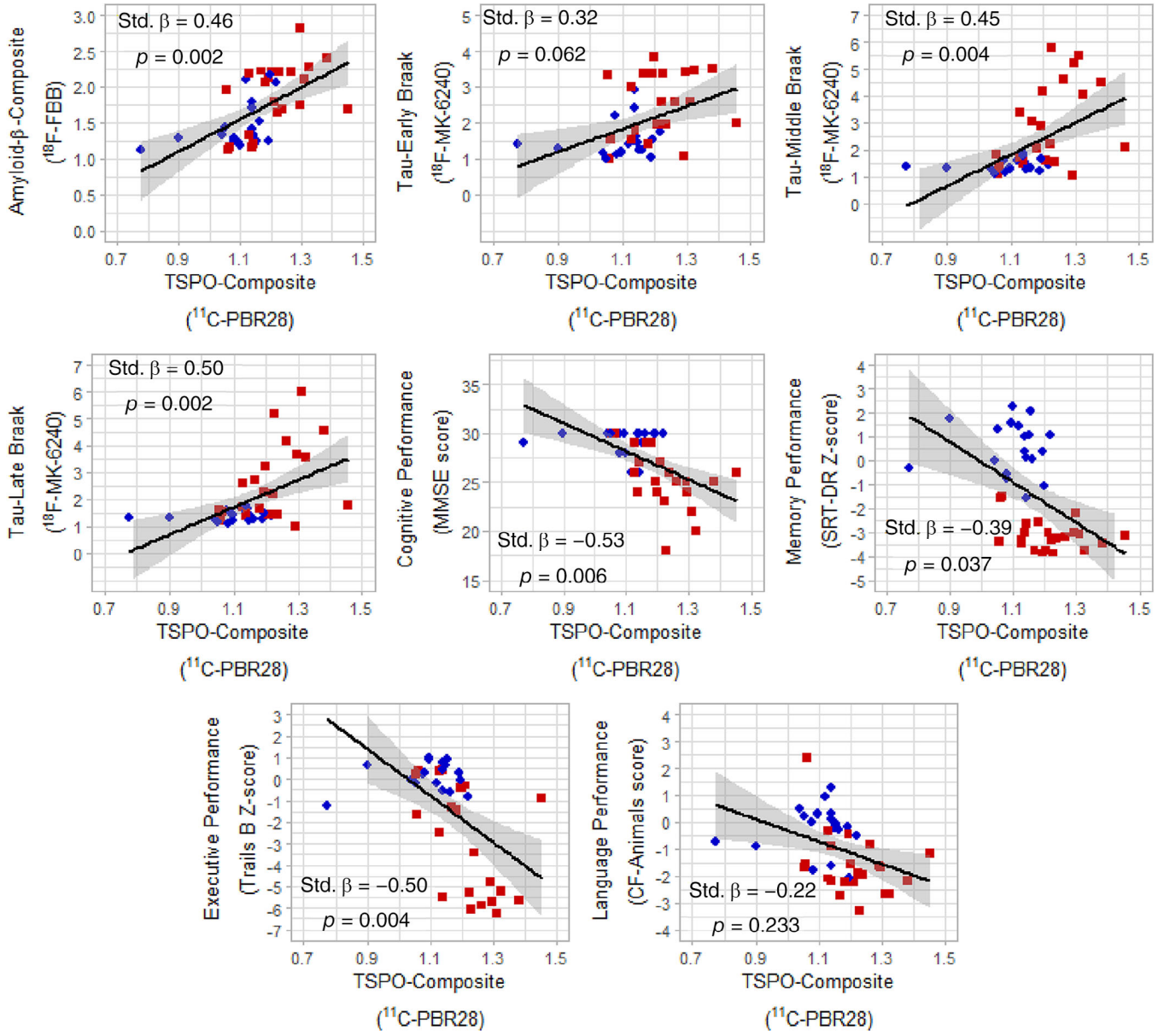

FIGURE 1 TSPO expression by ^{11}C-PBR28 uptake (SUVR) correlated with AD-related PET and cognitive measures across controls (blue circles) and patients (red squares). All associations were corrected for age, sex, race, education, *TSPO* genotype, and neurodegeneration (%GM in AD composite region). PET, positron emission tomography; SUVR, standardized uptake value ratio; TSPO, translocator protein.

precedes tau accumulation. Within patients, greater tau burden was observed in the presence of greater TSPO expression across Braak stage regions, and the association across controls and patients was independent of neurodegenerative processes in middle and late Braak stage regions. The association between greater TSPO expression and greater tau burden in early Braak stage regions did not survive adjustment for neurodegeneration. As tau spreads from across Braak stage regions, tau continues to increase in early Braak stage regions; tau burden in early Braak stage regions across controls and patients may reflect disease progression in a similar way to neurodegeneration. Therefore, there may be a mechanistic link between TSPO and tau in early Braak stage regions, but it may be too collinear with neurodegeneration across the clinical AD continuum to be identified using cross-sectional data. Further work investigating regional TSPO, AD biomarkers, neurodegeneration, and cognition at distinct stages of the AD continuum is needed (eg, using amyloid-positive controls to test associations in early Braak stage regions).

We found that TSPO expression mediated the association between tau in early and middle Braak stage regions, between tau and neurodegeneration in middle Braak stages, and between neurodegeneration and cognitive impairment in early and middle Braak stages. To our knowledge, this is the first study to examine this type of TSPO mediation in an AD progression model from Aβ through tau, neurodegeneration, and cognition. Our results do not show a mediation effect of TSPO on the relationships between Aβ and tau in early Braak stages, between tau in early Braak stages and neurodegeneration, or

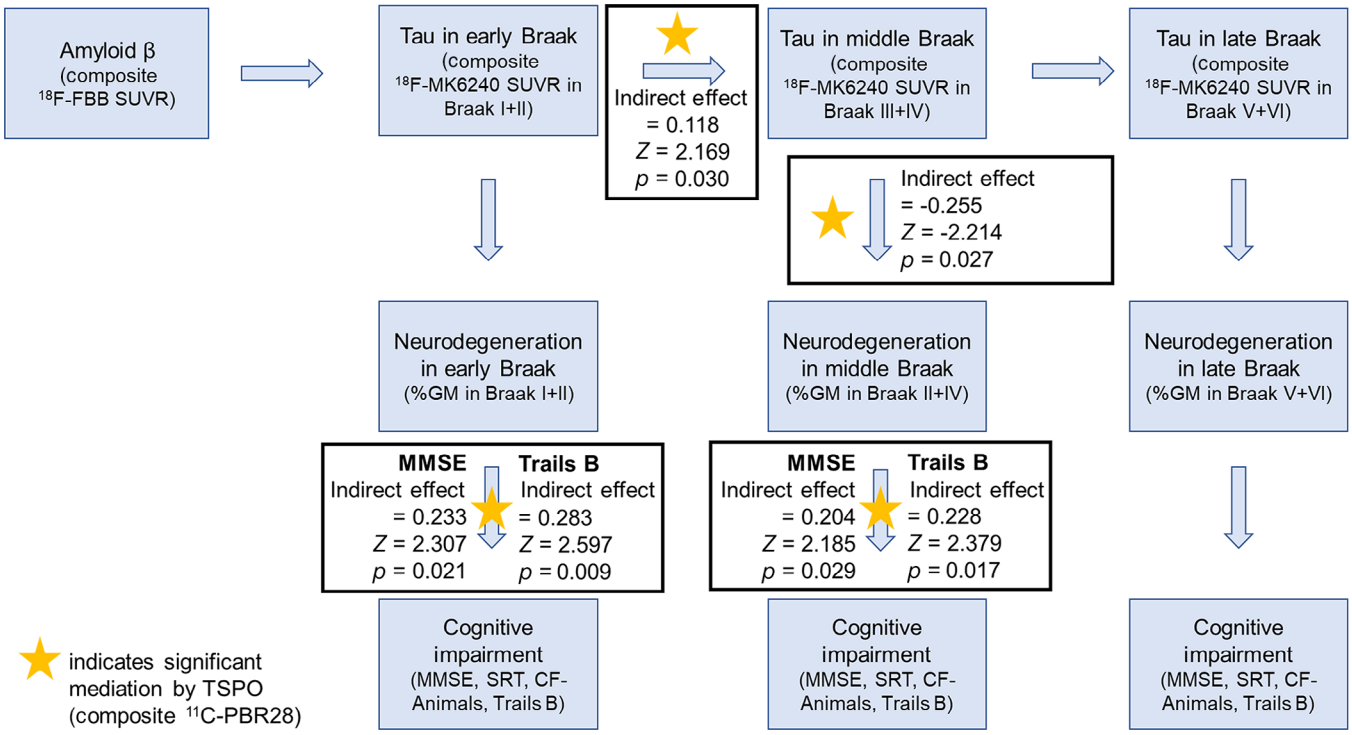

FIGURE 2 TSPO expression by ^{11}C-PBR28 uptake (SUVR) significantly mediated pathways along AD progression model. SUVR, standardized uptake value ratios; TSPO, translocator protein.

throughout any steps in the late Braak pathway. Patients had the greatest tau burden in middle Braak stage regions and the greatest range of impairment in Trails B; it may be the case that the current sample did not have advanced enough tau pathology in late Braak stage regions to elucidate the roles of tau and neurodegeneration in late Braak stage regions but advanced enough tau pathology for measures in early Braak stages to have plateaued. Regardless, these analyses are an important step toward characterizing neuroinflammation in AD progression.

The findings of this study are in agreement with the extant literature and current research frameworks of AD, for example, AT(N)[2,3] and ATX(N)[31], which were the basis of the longitudinal AD progression model investigated here. Our well-characterized sample with and without clinical impairment leveraged multiple studies and centers to perform broad neuroimaging characterization of TSPO PET in AD progression. Given that the results represented here are a secondary analysis of previously published data, PET methods (ROI definitions and PVC methods) for tau were defined differently than those of Aβ and TSPO; however, consistency within radioligands is more important than consistency across radioligands for each participant, particularly as each method has been shown to reliably quantify the underlying pathology.[55–57] In the current sample, approximately 35% of patients were amyloid-negative. This aligns with previous reports of the mismatch between clinical AD and *post mortem* histopathological confirmation.[58] Participants who were amyloid-negative but tau-positive were similar to amyloid-positive and tau-positive participants in terms of age, cortical thickness, memory-biomarker associations, and more.[59]

The study's limitations include its small sample size, lack of *APOE* information, and TSPO PET as a general marker. The inclusion of only a few participants in the early stages of AD pathogenesis, that is, cognitively normal but amyloid-positive and tau-negative, may limit our ability to detect early effects (eg, TSPO-mediating amyloid to tau associations). Therefore, our results may be capturing a microglial pathway specific to tau (eg, TSPO-mediated tau spreading and downstream neurodegeneration and cognitive impairment) that is simply apparent in this range of the AD continuum. Alternatively, there may be a specific microglial response to tau that differs from that to amyloid,[60] and the pathway from amyloid to tau may depend on other aspects of neuroinflammation, including astrocyte reactivity, in cognitively normal, amyloid-positive individuals.[61] APOE ε4 plays a modulatory role in neuroinflammation, such that APOE ε4 attenuates[62] or exaggerates[63] microglial activation, but the missingness pattern of *APOE* information precludes its inclusion in models. Simple main effects demonstrated higher PBR28 SUVR in APOE ε4 carriers, in addition to its known effects on amyloid, tau, neurodegeneration, and cognition. While TSPO is upregulated in microglial activation in rodent models, TSPO is not upregulated in humans due to a species-specific promoter region on the TSPO gene.[64] Further, TSPO is expressed mostly in microglia[65] but to a lesser extent in astrocytes and endothelial cells.[64,66,67] However, changes in TSPO PET signal have been reported across many different neurodegenerative diseases,[68] and the majority of TSPO

TABLE 2 Results of mediation analyses for composite ^{11}C-PBR28 SUVR in AD progression model.

X	Mediator	Y	Indirect effect (std. β, z, p)	Direct effect (std. β, z, p)	Total effect (std. β, z, p)
Global Aβ burden	Global TSPO expression	Tau in early Braak	0.017, 0.195, .845	0.748, 5.259, .000	0.765, 6.895, 0.000
Tau in early Braak		Neurodegeneration in early Braak	−0.157, −1.917, .055	−0.229, −1.591, .112	−0.386, −2.870, 0.004
Neurodegeneration in early Braak		Cognitive impairment – MMSE	0.233, 2.307, .021	0.207, 1.310, .190	0.440, 2.821, 0.005
		Cognitive impairment – SRT-DR	0.117, 1.536, .125	0.492, 3.368, .001	0.609, 4.553, 0.000
		Cognitive impairment – CF-Animals	0.076, 0.982, .326	0.391, 2.456, .014	0.468, 3.276, 0.001
		Cognitive impairment – Trails B	0.283, 2.597, .009	−0.057, −0.384, .701	0.226, 1.443, .149
Tau in early Braak		Tau in middle Braak	0.118, 2.169, .030	0.634, 7.078, .000	0.752, 8.750, .000
Tau in middle Braak		Neurodegeneration in middle Braak	−0.255, −2.214. .027	−0.087, −0.506, .613	−0.342, −2.295, .022
Neurodegeneration in middle Braak		Cognitive impairment – MMSE	0.204, 2.185, .029	0.347, 2.277, .023	0.552, 3.768, .000
		Cognitive impairment – SRT-DR	0.158, 1.794, .073	0.310, 1.959, .050	0.469, 3.198, .001
		Cognitive impairment – CF-Animals	0.061, 0.804, .422	0.454, 2.909, .004	0.515, 3.727, .000
		Cognitive impairment – Trails B	0.228, 2.379, .017	0.211, 1.439, .150	0.439, 3.037, .002
Tau in middle Braak		Tau in late Braak	0.029, 0.956, .335	0.917, 18.22, .000	0.947, 23.03, .000
Tau in late Braak		Neurodegeneration in late Braak	−0.168, −1.382, .167	0.015, 0.077, .938	−0.153, −0.966, .334
Neurodegeneration in late Braak		Cognitive impairment – MMSE	0.0146, 1.588, .112	0.157, 1.074, .283	0.303, 1.850, .064
		Cognitive impairment – SRT-DR	0.114, 1.497, .134	0.191, 1.283, .200	0.305, 1.933, .053
		Cognitive impairment – CF-animals	0.071, 1.251, .211	0.297, 1.983, .047	0.368, 2.450, .014
		Cognitive impairment – Trails B	0.144, 1.603, .109	0.136, 1.003, .316	0.280, 1.180, .070

Note: Rows of significant mediations are shown in bold.
Abbreviations: CF, categorical fluency; MMSE, Mini-Mental State Examination; SRT-DR, Selective Reminding Test-Delayed Recall; std, standardized; SUVR, standardized uptake value ratio; TSPO, translocator protein.

PET signals[69,70] likely reflect microglial recruitment and/or density rather than an explicit microglial activation process. Whether microglia are maintaining their homeostatic state, responding properly to a given stimulus in a given circumstance, or responding improperly to a given stimulus in a given circumstance is unknown with TSPO PET. Regardless, we have identified tau spreading and tau-related neurodegeneration and cognitive impairment as a critical time point to further investigate with cell type- and function-specific methods such as glycogen synthase kinase 3 (GSK-3), cyclooxygenase-1 (COX-1), or COX-2[71] in larger longitudinal studies.

Neuroinflammatory processes have been implicated in late-onset AD,[72,73] early-onset AD,[74,75] autosomal-dominant AD,[76] and AD in adults with Down syndrome.[77] In our work, neuroinflammation may play a critical role in tau spreading across Braak stages as well as downstream neurodegenerative and cognitive consequences of tau burden, independently of neuroinflammatory processes that clear neurodegeneration-related products. Other studies have also suggested that elevated TSPO signal precedes tau deposition throughout Braak staging.[33] Specific pathways in the AD progression model (eg, tau burden in early and middle Braak stages) may be more or less relevant depending on disease stage and severity of the study sample, and further work should elucidate the specific neuroinflammatory processes and microglial activation states on which to intervene.[10,78] Disease-modifying drugs, particularly the recent U.S. Food and Drug Administration-approved Aβ-targeting antibodies, aducanumab[79,80] and lecanemab,[81,82] need to be better characterized in relation to the inflammatory responses that are induced to clear Aβ oligomers and protofibrils. Monitoring and controlling the inflammatory response

may lead to a reduction in amyloid-related imaging abnormalities (ARIA).[83] As other therapeutics are developed in clinical trials, treatment response stratification will be critical. One potential way to perform such stratification might be based on patterns of neuroinflammation that may precede distinct subtypes of tau burden[84,85] and neurodegeneration,[86,87] which have differential rates of cognitive decline.[88] Overall, neuroinflammation may be the mechanism by which tau spreads across Braak stage regions and leads to downstream neurodegeneration and cognitive impairments. TSPO PET using either ^{11}C-PBR28 or third-generation TSPO radioligands, such as ^{11}C-ER176[71], offers a suitable method of identifying key regionally and temporally specific neuroinflammatory processes in AD and related dementias.

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CONFLICT OF INTEREST STATEMENT

WCK has a consulting agreement with Cerveau Technologies. However, Cerveau was not involved in the study design or interpretation of these results. No authors have conflicts of interest to report. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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