Review

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Neuroinflammation in Neurodegenerative Diseases: A Narrative Update (2020–2026) on Metabolic, Molecular, Morphological, and Functional Imaging

Agostino Chiaravalloti[1,2,*]

[1]Department of Biomedicine and Prevention, University of Rome Tor Vergata, 00133 Rome, Italy
[2]IRCCS Neuromed, 86077 Pozzilli, Italy
*Correspondence: agostino.chiaravalloti@uniroma2.it (Agostino Chiaravalloti)
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Neuroinflammation is increasingly recognized as a biologically relevant component of neurodegenerative disease, yet its *in vivo* imaging remains difficult to interpret. This narrative update synthesizes original imaging studies published between January 1, 2020, and May 17, 2026, and examines how positron emission tomography (PET), magnetic resonance imaging (MRI), and hybrid or multimodal approaches characterize glial and neurovascular processes. The most extensive human evidence is available for Alzheimer's disease, in which translocator protein (TSPO) PET has been associated with tau burden, amyloid-β deposition, Braak-like propagation, cognitive decline, network dysfunction, and genotype-dependent disease biology. In frontotemporal dementia, progressive supranuclear palsy, corticobasal syndrome, dementia with Lewy bodies, Parkinson's disease, and multiple system atrophy, evidence is more limited and heterogeneous; nevertheless, selected studies support mechanistic phenotyping, prognostic enrichment, and, in multiple system atrophy, formal differential-diagnostic testing. Emerging targets include monoamine oxidase-B, colony-stimulating factor 1 receptor, P2X7 receptor, and acetate metabolism, whereas fluorodeoxyglucose (FDG) PET, diffusion MRI, quantitative susceptibility mapping, and blood-brain barrier imaging provide complementary metabolic, microstructural, and neurovascular information. Neuroinflammation imaging should therefore be interpreted as a collection of target-specific, stage-dependent biological readouts rather than as a unitary measure of inflammation. Because most studies report associations, colocalization, or prognostic models rather than diagnostic accuracy, sensitivity and specificity are discussed only when explicitly evaluated in the original study. Current evidence supports neuroinflammation imaging primarily for mechanistic investigation, patient stratification, and trial enrichment rather than routine clinical deployment.

Keywords: neuroinflammation; positron emission tomography; TSPO; microglia; astrocytes; Alzheimer's disease; Parkinson's disease; magnetic resonance imaging

Introduction

Neuroinflammation has become a major focus of neurodegenerative disease imaging because comparable burdens of amyloid-β, tau, α-synuclein-related pathology, vascular injury, or cortical atrophy may be associated with markedly different rates of progression and clinical phenotypes. Neuroinflammation, however, is not a single measurable process. Current imaging markers capture partially overlapping biological phenomena: translocator protein (TSPO) positron emission tomography (PET) reflects a mixed signal from glial and non-glial sources; monoamine oxidase-B (MAO-B) PET is more closely related to reactive astrogliosis but remains incompletely cell-specific; P2X7 receptor and colony-stimulating factor 1 receptor (CSF1R) PET may provide readouts more directly related to microglial biology but remain exploratory; and magnetic resonance imaging (MRI) markers characterize tissue microstructure, permeability, susceptibility, or network dysfunction rather than glial activation itself.

This narrative update covers original imaging studies published from January 1, 2020, through May 17, 2026. A structured search was used to improve transparency, but the article was not designed as a systematic review or meta-analysis. Its purpose is to synthesize and critically appraise recent evidence, identify the settings in which quantitative diagnostic or prognostic performance has been evaluated, and clarify the interpretive limits of each imaging approach.

Search Strategy and Scope of the Review

A structured literature search was conducted to improve transparency while preserving the narrative scope of the article. Scopus was the primary bibliographic database, and PubMed/MEDLINE was used to verify candidate records, abstracts, and bibliographic details. The final search was performed on May 17, 2026. The core query combined disease terms, inflammatory targets, and imaging modalities using variants of: (neuroinflamm* OR

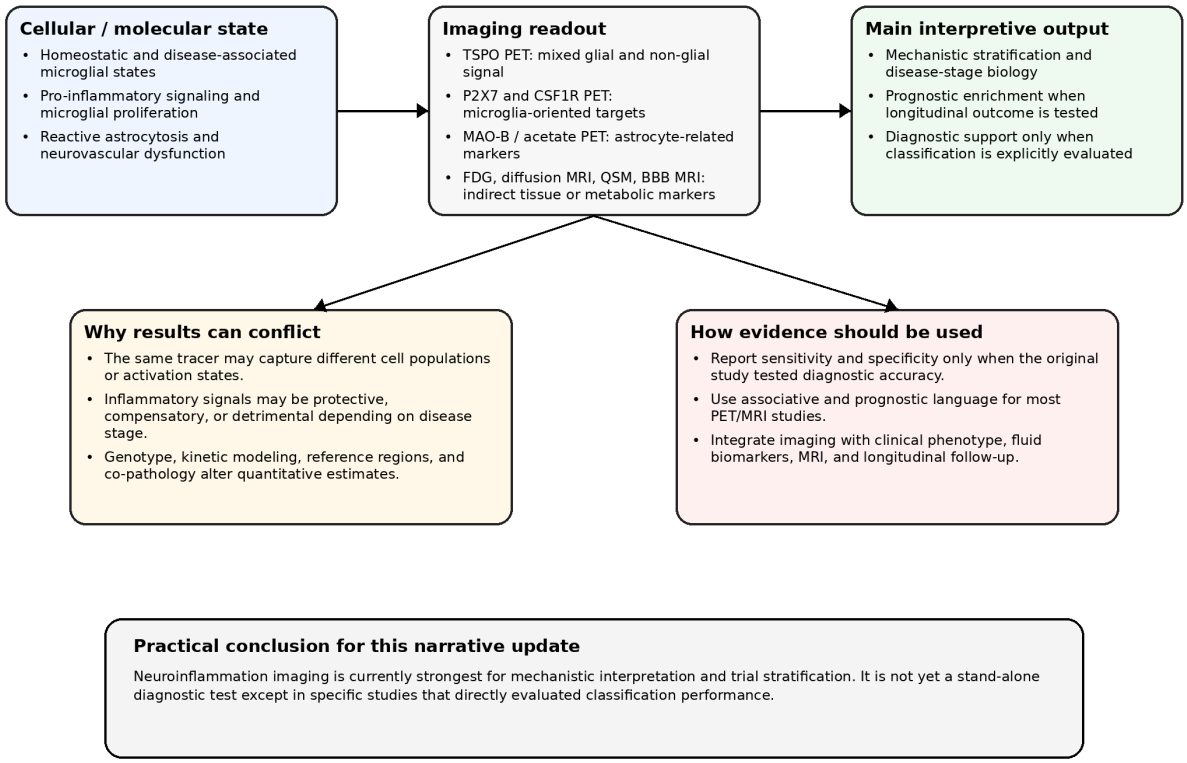

Fig. 1. Cellular targets, imaging readouts, and interpretive use of neuroinflammation imaging. Created by the author using Python 3.11.8 (Python Software Foundation, Wilmington, DE, USA) and Pillow 9.2.0 (Pillow contributors; open-source software).

microglia* OR astrocyt* OR astrogliosis OR TSPO OR MAO-B OR P2X7 OR CSF1R OR "blood-brain barrier" OR QSM OR "free water") AND (PET OR "positron emission tomography" OR MRI OR fMRI OR "diffusion MRI" OR FDG) AND (Alzheimer* OR "mild cognitive impairment" OR Parkinson* OR "Lewy body" OR "frontotemporal dementia" OR "progressive supranuclear palsy" OR "corticobasal syndrome" OR "multiple system atrophy" OR ALS), limited to publications dated from January 1, 2020, through May 17, 2026.

Eligible publications were original English-language articles published between January 1, 2020, and May 17, 2026; human *in vivo* imaging studies or translational studies with direct imaging relevance; studies of neurodegenerative diseases or clearly defined prodromal or genetic-risk groups; and studies evaluating imaging modalities or biomarkers relevant to microglial activation, reactive astrogliosis, neurovascular dysfunction, or inflammation-associated tissue changes. Review articles, book chapters, editorials, guidelines, web pages, conference abstracts without full data, papers without imaging data, and studies focused primarily on non-neurodegenerative inflammatory disorders were excluded unless they were required to interpret tracer biology. Screening proceeded through title and abstract assessment, followed by full-text evaluation of studies central to the synthesis. The relationship among cellular targets, imaging readouts, and their principal interpretive uses is summarized in Fig. 1.

Imaging Targets and Glial Phenotypes

Divergent findings across imaging modalities and diseases are partly explained by the biology of the cellular targets. Microglia do not constitute a uniform proinflammatory population. They continuously survey the tissue environment and respond to amyloid-β, tau, α-synuclein, vascular injury, neuronal stress, and peripheral immune signals by adopting functional states associated with phagocytosis, synaptic remodeling, antigen presentation, cytokine signaling, trophic support, or tissue injury. Consequently, an increased inflammatory imaging signal may represent a harmful process, a compensatory response, or a mixture of both, depending on disease stage and anatomical context.

TSPO PET remains the most widely used approach, but TSPO expression is neither microglia-specific nor restricted to a single activation state. Associations of [11C]PBR28 with cerebrospinal fluid (CSF) soluble TREM2, regional TREM2 gene-expression patterns, amyloid-β, tau, and cognition support its biological relevance in Alzheimer's disease [1]; however, the signal does not identify whether the predominant microglial state is protective, proinflammatory, or phagocytic. By contrast, P2X7 receptor imaging is intended to capture a more proinflammatory microglial component, whereas CSF1R imaging is oriented toward microglial density and proliferation. Early Parkinson's disease studies using [11C]SMW139 and [11C]CPPC illustrate both the potential and the current

limitations of this phenotyping strategy [2,3]. Astrocyte-oriented approaches, including MAO-B and acetate PET, interrogate a different component of the inflammatory response and should not be interpreted as measures of microglial activation [4,5,6,7,8,9].

This distinction has practical consequences. Differences among molecular PET, FDG PET, and MRI should not automatically be interpreted as technical inconsistency; they may reflect different cell populations, disease stages, and tissue compartments. The same disorder may therefore show elevated TSPO binding without a robust clinical correlation, FDG hypometabolism in degenerating cortex, and diffusion or susceptibility changes on MRI that primarily reflect tissue injury rather than cellular activation.

Interpretive Framework

An initial distinction is required between diagnostic accuracy and biological association. Most neuroinflammation imaging studies were not designed as diagnostic-accuracy studies. Instead, they quantify regional tracer uptake, relate it to pathology, cognition, or disease progression, and test whether the signal contributes information beyond established biomarkers. Sensitivity and specificity should therefore be reported only when diagnostic classification was explicitly evaluated in the original study.

A second distinction concerns target specificity. First-generation TSPO ligands such as [11C]PK11195 have relatively low signal-to-noise ratios but are less affected by the rs6971 binding-affinity polymorphism than second-generation ligands. Second-generation ligands such as [11C]PBR28 and [18F]DPA-714 provide higher signal but require rs6971 genotyping or explicit modeling of binding-affinity status. Non-TSPO targets may improve cellular phenotyping, but they introduce separate requirements for biological and kinetic validation. Metabolic and MRI measures should be interpreted as complementary indicators of tissue state rather than as direct measurements of neuroinflammation.

Alzheimer's Disease: Strongest Evidence, but Stage-Dependent Interpretation

The Alzheimer's disease literature provides the most extensive quantitative and longitudinal evidence. Multimodal studies have related TSPO PET to tau burden, amyloid-β deposition, cognitive decline, network dysfunction, APOE genotype, neuropsychiatric symptoms, and transcriptomic patterns. The most informative studies extend beyond case-control comparisons by testing whether glial imaging contributes information beyond amyloid, tau, and atrophy.

Malpetti and colleagues [10] used tau PET, [11C]PK11195 PET, and MRI to predict longitudinal cognitive decline across the Alzheimer's disease clinical spectrum. Posterior tau and anterior temporal neuroinflammation remained in the final prognostic model, whereas the MRI atrophy component was not retained; the adjusted R^2 was 0.418. Ewers and colleagues [11] reported that higher CSF soluble TREM2 and higher baseline TSPO signal in a mouse model were associated with slower amyloid-β accumulation. This observation counters a uniformly deleterious interpretation of neuroinflammation. Pascoal and colleagues [1] studied 130 high-affinity TSPO binders and found that [11C]PBR28 correlated with CSF soluble TREM2, amyloid PET, and tau PET; the combined presence of amyloid, tau, and microglial abnormalities was strongly associated with cognitive impairment.

Other Alzheimer's disease studies refine this interpretation. Wang and colleagues [12] linked baseline [11C]PK11195 uptake to amyloidosis and subsequent cognitive decline in a small longitudinal cohort. Zhang and colleagues [13] integrated [18F]DPA-714 PET with amyloid PET and peripheral transcriptomics and reported associations with amyloid burden, Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR), medial temporal atrophy, and CD200 expression. Gouilly and colleagues [14] found heterogeneous inflammatory PET profiles in early Alzheimer's disease and no straightforward association with cognition after correction for multiple comparisons. Appleton and colleagues [15] reported strong inflammation-tau colocalization in early-onset mild cognitive impairment (MCI), with a mean within-participant correlation of 0.63 ± 0.24.

Longitudinal and early-stage studies are particularly informative. Ismail and colleagues [16] followed participants with MCI using serial amyloid and neuroinflammation PET and identified different trajectories according to amyloid and tau status, supporting a stage-dependent rather than monotonic inflammatory model. Tondo and colleagues [17] combined [18F]FDG and [11C]PK11195 PET in early-onset Alzheimer's disease and found a significant association between local hypometabolism and microglial activation ($r = 0.667$, $p = 0.018$). Toppala and colleagues [18] found an association between amyloid and [11C]PBR28 in amyloid-negative older adults but not after amyloid positivity, suggesting an early disease window in which microglial PET may be most informative.

Genetic, behavioral, and spatial studies further broaden the interpretation. Ferrari-Souza and colleagues [19] identified APOE ε4-associated microglial activation in early Braak regions independently of amyloid and tau. Schaffer Aguzzoli and colleagues [20] linked neuropsychiatric symptom severity, particularly irritability, to microglial activation across the Alzheimer's disease continuum. Rossano and colleagues [21] reported associations among TSPO PET, amyloid, middle- and late-Braak tau, and cognition within a disease-progression model. Sanchez-Rodriguez and colleagues [22] linked inflammatory transcriptomic mechanisms to the combined effects of amyloid and tau on neuronal activity. Additional studies

Table 1. Key Alzheimer's disease studies and their principal interpretive contributions.

Study	Cohort/design	Principal result
Malpetti et al., 2020 [10]	AD/MCI; longitudinal multimodal PET/MRI	Posterior tau and anterior temporal PK11195 predicted ACE-R decline; adjusted $R^2 = 0.418$.
Ewers et al., 2020 [11]	300 participants; CSF and amyloid PET	Higher soluble TREM2 was associated with slower amyloid PET accumulation ($p = 0.010$).
Pascoal et al., 2021 [1]	130 high-affinity TSPO binders	PBR28 correlated with amyloid and tau; the combined abnormality was strongly associated with cognitive impairment.
Wang et al., 2022 [12]	24 participants; longitudinal cognition	Whole-cortex PK11195 predicted PACC decline (estimate –1.09, $p = 0.03$).
Zhang et al., 2024 [13]	85 participants; PET and transcriptomics	DPA-714 correlated with amyloid, cognition, CDR, MTA, and CD200 expression.
Gouilly et al., 2023 [14]	29 early AD patients	Corrected analyses did not support a straightforward relationship between cognition and SUVR.
Appleton et al., 2025 [15]	Early-onset MCI	Inflammation-tau colocalization exceeded inflammation-amyloid colocalization.
Ismail et al., 2020 [16]	43 MCI; serial PET	Inflammatory trajectories differed by amyloid and tau stage, supporting stage dependence.
Tondo et al., 2020 [17]	12 early-onset AD	FDG hypometabolism correlated with PK11195 signal in interaction regions (r = 0.667).
Toppala et al., 2021 [18]	54 older adults without dementia	Amyloid-PBR28 association present in amyloid-negative but not amyloid-positive participants.
Ferrari-Souza et al., 2023 [19]	118 high-affinity binders	APOE ε4 was associated with medial temporal PBR28 independently of amyloid and tau.
Schaffer Aguzzoli et al., 2023 [20]	109 participants	NPI-Q severity and irritability associated with microglial activation.

AD, Alzheimer's disease; MCI, mild cognitive impairment; PET, positron emission tomography; MRI, magnetic resonance imaging; ACE-R, Addenbrooke's Cognitive Examination–Revised; CSF, cerebrospinal fluid; TSPO, 18-kDa translocator protein; TREM2, triggering receptor expressed on myeloid cells 2; PACC, Preclinical Alzheimer Cognitive Composite; CDR, Clinical Dementia Rating; MTA, medial temporal atrophy; SUVR, standardized uptake value ratio; FDG, fluorodeoxyglucose; APOE ε4, apolipoprotein E ε4 allele; NPI-Q, Neuropsychiatric Inventory Questionnaire.

related olfactory impairment to tau pathology and neuroinflammation [23], examined the spatial relationships among amyloid deposition, gray-matter volume, and neuroinflammation [24], and used magnetic resonance spectroscopic imaging (MRSI)/PET to relate microglial activation to neuronal health [25].

In Alzheimer's disease, the strongest evidence supports neuroinflammation imaging for mechanistic stratification and prognosis rather than routine diagnosis. TSPO PET is most informative when interpreted alongside amyloid, tau, genotype, cognition, and longitudinal outcome. Its principal limitation is biological specificity: a disease-related TSPO signal does not define the underlying microglial phenotype. Negative and heterogeneous findings in early disease argue against using a single uptake threshold or isolated regional value for clinical staging. Representative Alzheimer's disease studies and their principal interpretive contributions are summarized in Table 1 (Ref. [1,10,11,12,13,14,15,16,17,18,19,20]).

Network and Functional Imaging

Network-level studies shift the focus from regional uptake to systems biology. Rauchmann and colleagues [26] evaluated amyloid-positive early Alzheimer's disease and controls using [18F]GE-180 PET, resting-state functional MRI, and diffusion MRI; TSPO standardized uptake value ratios were higher in Alzheimer's disease, and interregional TSPO covariance preferentially followed functional connectivity. Canario and colleagues [27] combined [11C]PiB, [11C]PK11195, and task-based functional MRI in patients with Alzheimer's disease and controls; posterior cingulate PK11195 binding was higher in patients and correlated with task-related activity. Leng and colleagues [28] found that [11C]PBR28 uptake was independently associated with lower structural-network integrity and lower local efficiency after adjustment for amyloid burden and cortical thickness.

Functional and network studies support a contribution of neuroinflammation to systems-level dysfunction in Alzheimer's disease. Their principal value is mechanistic

rather than diagnostic. Sample sizes remain modest, and task-based functional MRI, resting-state functional MRI, and structural-network measures should not be treated as interchangeable endpoints.

Frontotemporal Dementia, Four-Repeat Tauopathies, and the ALS/FTD Spectrum

In frontotemporal dementia (FTD), clinical and molecular heterogeneity limits the utility of any single inflammatory marker. Bevan-Jones and colleagues [29] reported colocalization of [11C]PK11195 and [18F]AV-1451 across the FTD spectrum and showed that inflammatory topography contributed to syndrome-level classification. In a prognostic FTD study, left frontal [11C]PK11195 binding potential predicted subsequent decline on the Addenbrooke's Cognitive Examination-Revised (estimate –0.70, $p = 0.01435$; false-discovery-rate-adjusted $p = 0.0287$), whereas gray-matter volume was not retained as a comparable predictor [30]. These findings support prognostic enrichment but not molecular diagnosis.

The four-repeat tauopathy literature provides more direct evidence for topographic classification. Palleis and colleagues [31] reported increased [18F]GE-180 TSPO signal in corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), with subcortical involvement in both disorders and additional motor and supplementary-motor cortical signal in CBS; a multiregion classifier identified CBS and PSP with sensitivities of 80% and 79%, respectively, at 92% specificity. In a subsequent amyloid-negative CBS cohort, tau PET and plasma neurofilament light predicted faster progression, whereas higher global TSPO PET was associated with slower progression [32]. This inverse association should be interpreted as evidence of stage-dependent biology rather than a uniformly protective inflammatory effect.

The amyotrophic lateral sclerosis (ALS)/FTD spectrum further illustrates why metabolic and molecular inflammatory signals should be distinguished. Tondo and colleagues [33] identified [11C]PK11195 abnormalities in SOD1 mutation carriers, including asymptomatic and symptomatic participants. Zanovello and colleagues [34] found that brainstem FDG hypermetabolism in ALS/FTD was associated with shorter survival. Metabolic hyperactivity is therefore relevant to the review, but it should not be interpreted as a specific molecular marker of neuroinflammation.

In FTD and related tauopathies, neuroinflammation imaging is most useful for mechanistic phenotyping and prognostic enrichment. Formal classification has been explored in selected CBS and PSP cohorts, but broad diagnostic use is not supported. The principal limitations are molecular heterogeneity, mixed tau and TDP-43 pathology, off-target tau-tracer binding, and small samples.

Lewy Body Disease, Parkinson's Disease, and Multiple System Atrophy

In dementia with Lewy bodies, Nicastro and colleagues [35] combined [11C]PK11195 PET with diffusion and structural MRI in 19 patients with probable dementia with Lewy bodies and 20 controls. Patients showed widespread gray-matter and diffusion abnormalities, yet higher parietal PK11195 binding was associated with relatively preserved white-matter diffusion measures and better cognition. This finding cautions against assuming that a stronger inflammatory signal invariably indicates tissue injury.

Findings in Parkinson's disease are heterogeneous. Lavisse and colleagues [36] reported higher [18F]DPA-714 binding in the midbrain, frontal cortex, and contralateral putamen, but no robust correlation with motor severity or dopamine-transporter loss. Yacoubian and colleagues [37] found higher [18F]DPA-714 binding in the putamen, thalamus, substantia nigra, and several cortical regions in untreated de novo Parkinson's disease, together with systemic immune differences. Mullin and colleagues [38] reported increased nigral [11C]PK11195 binding in GBA mutation carriers without Parkinson's disease, whereas Farmen and colleagues [39] related monocyte markers to nigral PK11195 binding and putaminal [18F]DOPA uptake in isolated rapid eye movement sleep behavior disorder. These data support early immune involvement but do not establish a validated diagnostic threshold. Additional pilot studies evaluated [18F]NOS as a marker of oxidative inflammatory signaling and the interaction between neuroinflammation and amyloid-β in Parkinson's disease-related cognitive decline [40,41].

The clearest formal diagnostic-accuracy study compared multiple system atrophy (MSA) with Parkinson's disease using [11C]PBR28 PET and machine learning [42]. Visual majority reading distinguished MSA from Parkinson's disease with 100% specificity and 83% sensitivity; machine learning based on normalized volume of distribution increased sensitivity to 96% while maintaining 100% specificity. These estimates are appropriate to report because classification was a prespecified study objective, but they should not be generalized to other diseases, tracers, or analytic pipelines.

In synucleinopathies, neuroinflammation imaging is biologically informative but inconsistent. MSA versus Parkinson's disease represents the clearest diagnostic application in the current evidence base. In Parkinson's disease and dementia with Lewy bodies, the evidence is more relevant to mechanism, prodromal biology, and risk stratification than to diagnosis. Key limitations include small cohorts, variation in disease stage, inconsistent handling of binding-affinity genotype, and weak or inconsistent associations with motor and cognitive severity.

Non-TSPO Targets and Astrocyte-Oriented Imaging

Non-TSPO PET targets have progressed from tracer development to early human studies. Mills and colleagues [2] investigated [11C]CPPC as a CSF1R-targeted marker in early Parkinson's disease; postmortem data showed colocalization of CSF1R with IBA1-positive cells, and selected *in vivo* regional measures correlated with motor disability, although the PET cohort was small. Rikken and colleagues [3] reported increased [11C]SMW139 P2X7 binding in the putamen and whole cortex in Parkinson's disease, but no significant association with Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III scores or disease duration. Together, these studies illustrate the potential of alternative targets to resolve different components of microglial biology, while also demonstrating the need for direct cellular validation, larger cohorts, and standardized kinetic analysis.

Astrocyte-related imaging provides a necessary complement to microglial imaging. [18F]SMBT-1 studies support the feasibility of MAO-B PET for reactive astrogliosis, although MAO-B is not specific to astrocytes [4,5,6]. Ballweg and colleagues [7] evaluated [18F]F-DED PET in an Alzheimer's disease mouse model and a pilot human cohort; in mice, the signal correlated with MAO-B and glial fibrillary acidic protein immunohistochemistry and preceded TSPO and amyloid PET changes. Jaisa-Aad and colleagues [8] provided neuropathological evidence that MAO-B is informative but not a pure marker of reactive astrogliosis. Nam and colleagues [9] used [11C]acetate and FDG PET to investigate astrocyte-neuron interactions, while plasma glial fibrillary acidic protein and [18F]SMBT-1 studies support complementary blood-imaging approaches [43]. A multitracer study further emphasized the heterogeneity of reactive astrogliosis [44], and kinetic modeling work defined requirements for quantitative interpretation of [18F]SMBT-1 in the human brain [45].

Emerging targets may improve glial phenotyping, but none is yet a fully validated clinical biomarker. CSF1R and P2X7 PET remain early human approaches to microglial phenotyping. MAO-B, acetate, and glial fibrillary acidic protein-related methods address astrocytic responses, but their interpretation remains dependent on brain region, disease stage, and analytic method.

MRI and Metabolic Imaging: Indirect but Scalable Information

MRI markers are attractive because they are noninvasive, repeatable, and widely available, but they do not measure glial activation directly. Free-water diffusion, cortical diffusivity, quantitative susceptibility mapping (QSM), perivascular spaces, blood-brain barrier (BBB) water exchange, and CSF markers of BBB dysfunction characterize microstructural, vascular, or susceptibility changes that may overlap with inflammatory biology [46,47,48,49,50,51,52,53,54,55,56]. Autopsy-linked diffusion and susceptibility studies are especially valuable because they connect imaging measurements to tissue-level pathology rather than to clinical diagnosis alone [47,51].

FDG PET should be treated as a metabolic comparator rather than as a primary inflammatory biomarker. Tondo and colleagues [17] demonstrated a relationship between microglial activation and hypometabolism in early-onset Alzheimer's disease, and Nam and colleagues [9] reported inverse acetate-FDG relationships in Alzheimer's disease-related regions. Conversely, focal or regional FDG hypermetabolism may occur in inflammatory, immune-mediated, epileptogenic, or reparative processes. FDG uptake therefore requires interpretation in conjunction with MRI, the clinical phenotype, electroencephalography when relevant, and longitudinal follow-up.

MRI and FDG PET extend the clinical reach of neuroinflammation research, but they are less biologically specific than molecular PET. Their principal role is to contextualize tissue injury, neurovascular dysfunction, and metabolic-neuronal relationships. They should not be presented as direct cellular measurements of neuroinflammation. Representative MRI and metabolic surrogate studies are summarized in Table 2 (Ref. [46,47,48,49,50,51,52,53,55]).

Negative and Conflicting Evidence

A separate synthesis of negative and conflicting evidence is essential because this field is vulnerable to overstatement. In Alzheimer's disease, Gouilly and colleagues [14] found no straightforward corrected association between early-disease TSPO PET and cognition. Ismail and colleagues [16] reported declining cortical inflammation in high-amyloid MCI despite increasing amyloid, whereas other subgroups showed positive amyloid-inflammation or tau-inflammation relationships. Toppala and colleagues [18] observed an amyloid-PBR28 association in amyloid-negative but not amyloid-positive older adults. Collectively, these findings support a stage-dependent inflammatory trajectory rather than a single linear model.

Conflicting observations are equally important in non-Alzheimer disorders. In dementia with Lewy bodies, higher PK11195 binding was associated with relative preservation of white matter and cognition [35]. In Parkinson's disease, Lavisse and colleagues [36] and Yacoubian and colleagues [37] reported increased regional TSPO binding, but clinical correlations were inconsistent. Rikken and colleagues [3] found increased P2X7 binding without an association with disease severity or duration. In CBS, higher TSPO signal was associated with slower, rather than faster, progression in one cohort [32]. These findings are integral to the interpretation and should not be treated as isolated exceptions.

Neuroinflammation imaging should therefore be interpreted as stage-, target-, and disease-dependent. Divergent

Table 2. MRI and metabolic surrogate markers relevant to neuroinflammation.

Study	Modality/setting	Interpretive contribution
Nakaya et al., 2022 [46]	Free-water diffusion; THK5351/PiB PET	Free water was associated with tau/neuroinflammation-related PET signal and cognition.
Torso et al., 2023 [47]	Autopsy-linked cortical diffusion	Diffusion measures associated with Thal phase, Braak stage, ADNC, and locus coeruleus hypopigmentation.
Preis et al., 2024 [48]	BBB dysfunction imaging	BBB dysfunction associated with AD pathology, cognition, and inflammatory markers.
Yang et al., 2025 [49]	QSM and transcriptomics	Iron-sensitive QSM patterns were linked to genes enriched for metal-ion transport and expressed in microglia and glutamatergic neurons.
Hosseini et al., 2026 [50]	QSM and inflammatory biomarkers	Alzheimer's disease-related QSM changes correlated with immune biomarkers rather than with amyloid or tau alone.
Wang et al., 2023 [51]	QSM/R2* and postmortem SNc pathology	Susceptibility measures were associated with glial density and tau burden, but not neuronal density.
Padrela et al., 2026 [52]	Multi-echo ASL BBB water exchange	Tex lower in SCD and MCI; not associated with amyloid after adjustment.
Sumra et al., 2025 [53]	Free-water diffusion across disorders	Free-water features predicted plasma GFAP more strongly than NfL.
Barisano et al., 2025 [55]	PVS and white matter lesion MRI	Automated multicenter measures were associated with dementia risk and accelerated atrophy.

ADNC, Alzheimer's disease neuropathologic change; BBB, blood-brain barrier; QSM, quantitative susceptibility mapping; SNc, substantia nigra pars compacta; ASL, arterial spin labeling; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; PVS, perivascular spaces.

Table 3. Disease-level conclusions and current clinical readiness.

Disease field	Strongest current use	Main evidence	Greatest limitation	Clinical readiness
Alzheimer's disease	Mechanistic and prognostic	Longitudinal and multimodal PET evidence linking TSPO to tau, amyloid, cognition, and networks	Target specificity; stage-dependent and heterogeneous signal	Research stratification and trial enrichment; not routine diagnosis
FTD, PSP, and CBS	Mechanistic and prognostic; limited diagnostic use in classifiers	Frontal PK11195 predicts decline in FTD; four-repeat tauopathy classifiers show discrimination	Molecular heterogeneity, off-target tau PET, and small samples	Potential trial enrichment; selected differential support only
DLB/PD	Mechanistic and prodromal biology	Regional TSPO/P2X7/CSF1R abnormalities and prodromal immune associations	Weak clinical correlations; disease-stage variability	Research use; not a standalone diagnostic tool
MSA versus Parkinson's disease	Diagnostic discrimination in one PET/ML study	PBR28 visual reading and machine learning yielded sensitivity and specificity estimates	Requires external validation and harmonized kinetic pipelines	Most plausible near-term diagnostic application
Astrogliosis and MRI	Complementary phenotyping	MAO-B/acetate PET and diffusion, QSM, and BBB measures extend biological characterization	Indirect or incompletely cell-specific measures	Useful adjuncts for mechanism and longitudinal monitoring

results do not necessarily represent failures of reproducibility; they may reflect differences in cellular state, disease phase, tracer kinetics, reference-region selection, genotype, or co-pathology.

Disease-Level Synthesis and Clinical Readiness

The strongest current applications, principal limitations, and present level of clinical readiness for each disease field are summarized in Table 3.

Table 4. Diagnostic and prognostic performance reported in selected original studies.

Question	Method	Reported performance/association	Interpretive implication
MSA versus Parkinson's disease [42]	Visual PET majority read	Specificity 100%; sensitivity 83%; Cohen kappa 0.72	Diagnostic accuracy was explicitly tested.
MSA versus Parkinson's disease [42]	Machine learning using normalized VT	Specificity 100%; sensitivity 96%; Cohen kappa 0.92	Highest discriminative performance among the included studies.
MSA-C versus MSA-P [42]	Visual majority read	Specificity 91%; sensitivity 74%; Cohen kappa 0.65	Subtype discrimination was weaker than MSA vs PD.
CBS/PSP detection [31]	Multiregion classifier	CBS sensitivity, 80%; PSP sensitivity, 79%; specificity, 92%	Promising, but independent validation is required.
AD cognitive prognosis [10]	Multimodal PET regression	Adjusted R^2 = 0.418; posterior tau, p = 0.025; anterior temporal PK11195, p = 0.017	Prognostic association model, not diagnostic accuracy.
AD network dysfunction [28]	PBR28 PET plus DTI/rs-fMRI	PBR28 associated with structural integrity (β = –0.375) and local efficiency (β = –0.468)	Biological association rather than classification.
Parkinson's disease non-TSPO PET [2,3]	CSF1R and P2X7 PET	Regional CSF1R measures correlated with motor disability; P2X7 showed putaminal and cortical group effects	Exploratory cohorts; no validated diagnostic thresholds.

Diagnostic and Prognostic Performance

Most contemporary neuroinflammation imaging studies evaluate biological association or prediction rather than diagnostic accuracy. The clearest diagnostic-performance study in the present evidence base is the use of [11C]PBR28 PET and machine learning to distinguish MSA from Parkinson's disease [42]. In Alzheimer's disease, FTD, PSP, and Parkinson's disease, current evidence more strongly supports prognostic enrichment or biological stratification than routine diagnostic use. Selected diagnostic and prognostic performance data are summarized in Table 4 (Ref. [2,3,10,28,31,42]).

Clinical and Research Implications

The immediate clinical role of neuroinflammation imaging remains limited. Amyloid PET, tau PET, FDG PET, and structural MRI have more clearly established positions in dementia practice. TSPO, MAO-B, CSF1R, P2X7, QSM, and BBB imaging are better regarded as tools for research phenotyping, trial enrichment, and mechanistic stratification. Their most plausible role is not to replace established diagnostic biomarkers, but to identify biologically active disease stages and patient subgroups in which immune-modulating, astrocyte-targeted, or microglia-targeted interventions may be most informative.

Future studies should prioritize longitudinal designs, head-to-head tracer comparisons, standardized reporting of genotype and kinetic models, and validation against fluid biomarkers, histopathology, and complementary imaging whenever possible. Effect sizes, uncertainty estimates, and diagnostic-performance measures should be reported only when supported by the study design.

Conclusion

Original imaging studies published between January 1, 2020, and May 17, 2026, show that neuroinflammation is closely linked to neurodegenerative pathology, particularly in Alzheimer's disease, where microglial PET signals relate to tau propagation, amyloid-β deposition, network dysfunction, genotype, and cognitive decline. Evidence in FTD, PSP, CBS, dementia with Lewy bodies, Parkinson's disease, and MSA extends the biological relevance of glial imaging beyond Alzheimer's disease, although the strength and consistency of evidence vary by disorder. Emerging targets such as MAO-B, CSF1R, P2X7, acetate metabolism, and MRI-based tissue markers may facilitate more specific glial and neurovascular phenotyping.

Neuroinflammation imaging is not yet ready for broad clinical deployment as a standalone diagnostic tool. Its present value is greatest when interpreted quantitatively within a multimodal framework. Sensitivity and specificity should be reported only for studies that directly evaluated diagnostic performance; for most of the available evidence, the appropriate concepts are association, colocalization, prediction, stage-specific biology, and patient stratification.

Availability of Data and Materials

Not applicable.

Author Contributions

AC is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpreta-

tion of data; the preparation of the manuscript; approval of the final version of the manuscript for publication; and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

References

[1] Pascoal TA, Benedet AL, Ashton NJ, Kang MS, Therriault J, Chamoun M, et al. Microglial activation and tau propagate jointly across Braak stages. Nature Medicine. 2021; 27: 1592–1599. https://doi.org/10.1038/s41591-021-01456-w

[2] Mills KA, Du Y, Coughlin JM, Foss CA, Horti AG, Jenkins KR, et al. Exploring [11C]CPPC as a CSF1R-targeted PET imaging marker for early Parkinson's disease severity. Journal of Clinical Investigation. 2025; 135: e186591. https://doi.org/10.1172/JCI186591

[3] Rikken RM, van de Giessen E, Brumberg J, Aarnio R, Joling M, Forsberg Moren A, et al. Imaging proinflammatory microglia in Parkinson disease using [11C]SMW139 PET: a multicenter study. Journal of Nuclear Medicine. 2025; 66: 1646–1651. https://doi.org/10.2967/jnumed.125.269671

[4] Harada R, Hayakawa Y, Ezura M, Lerdsirisuk P, Du Y, Ishikawa Y, et al. [18F]SMBT-1: a selective and reversible PET tracer for monoamine oxidase-B imaging. Journal of Nuclear Medicine. 2021; 62: 253–258.

[5] Villemagne VL, Harada R, Dore V, Furumoto S, Mulligan R, Kudo Y, et al. First-in-humans evaluation of [18F]SMBT-1, a novel [18F]-labeled monoamine oxidase-B PET tracer for imaging reactive astrogliosis. Journal of Nuclear Medicine. 2022; 63: 1551–1559. https://doi.org/10.2967/jnumed.121.263254

[6] Villemagne VL, Harada R, Dore V, Furumoto S, Mulligan R, Kudo Y, et al. Assessing reactive astrogliosis with [18F]SMBT-1 across the Alzheimer disease spectrum. Journal of Nuclear Medicine. 2022; 63: 1560–1569. https://doi.org/10.2967/jnumed.121.263255

[7] Ballweg A, Klaus C, Vogler L, Katzdobler S, Wind K, Zatcepin A, et al. [18F]F-DED PET imaging of reactive astrogliosis in neurodegenerative diseases: preclinical proof of concept and first-in-human data. Journal of Neuroinflammation. 2023; 20: 68. https://doi.org/10.1186/s12974-023-02749-2

[8] Jaisa-Aad M, Muñoz-Castro C, Healey MA, Hyman BT, Serrano-Pozo A. Characterization of monoamine oxidase-B (MAO-B) as a biomarker of reactive astrogliosis in Alzheimer's disease and related dementias. Acta Neuropathologica. 2024; 147: 66. https://doi.org/10.1007/s00401-024-02712-2

[9] Nam MH, Ko HY, Kim D, Lee S, Park YM, Hyeon SJ, et al. Visualizing reactive astrocyte-neuron interaction in Alzheimer's disease using 11C-acetate and 18F-FDG. Brain: a Journal of Neurology. 2023; 146: 2957–2974. https://doi.org/10.1093/brain/awad037

[10] Malpetti M, Kievit RA, Passamonti L, Jones PS, Tsvetanov KA, Rittman T, et al. Microglial activation and tau burden predict cognitive decline in Alzheimer's disease. Brain: a Journal of Neurology. 2020; 143: 1588–1602. https://doi.org/10.1093/brain/awaa088

[11] Ewers M, Biechele G, Suárez-Calvet M, Sacher C, Blume T, Morenas-Rodriguez E, et al. Higher CSF sTREM2 and microglia activation are associated with slower rates of beta-amyloid accumulation. EMBO Molecular Medicine. 2020; 12: e12308. https://doi.org/10.15252/emmm.202012308

[12] Wang Q, Chen G, Schindler SE, Christensen J, McKay NS, Liu J, et al. Baseline Microglial Activation Correlates With Brain Amyloidosis and Longitudinal Cognitive Decline in Alzheimer Disease. Neurology(R) Neuroimmunology & Neuroinflammation. 2022; 9: e1152. https://doi.org/10.1212/NXI.0000000000001152

[13] Zhang M, Qian XH, Hu J, Zhang Y, Lin X, Hai W, et al. Integrating TSPO PET imaging and transcriptomics to unveil the role of neuroinflammation and amyloid-β deposition in Alzheimer's disease. European Journal of Nuclear Medicine and Molecular Imaging. 2024; 51: 455–467. https://doi.org/10.1007/s00259-023-06446-3

[14] Gouilly D, Salabert AS, Bertrand E, Goubeaud M, Catala H, Germain J, et al. Clinical heterogeneity of neuro-inflammatory PET profiles in early Alzheimer's disease. Frontiers in Neurology. 2023; 14: 1189278. https://doi.org/10.3389/fneur.2023.1189278

[15] Appleton J, Finn Q, Zanotti-Fregonara P, Yu M, Faridar A, Nakawah MO, et al. Brain inflammation co-localizes highly with tau in mild cognitive impairment due to early-onset Alzheimer's disease. Brain: a Journal of Neurology. 2025; 148: 119–132. https://doi.org/10.1093/brain/awae234

[16] Ismail R, Parbo P, Madsen LS, Hansen AK, Hansen KV, Schaldemose JL, et al. The relationships between neuroinflammation, beta-amyloid and tau deposition in Alzheimer's disease: a longitudinal PET study. Journal of Neuroinflammation. 2020; 17: 151. https://doi.org/10.1186/s12974-020-01820-6

[17] Tondo G, Iaccarino L, Caminiti SP, Presotto L, Santangelo R, Iannaccone S, et al. The combined effects of microglia activation and brain glucose hypometabolism in early-onset Alzheimer's disease. Alzheimer's Research & Therapy. 2020; 12: 50. https://doi.org/10.1186/s13195-020-00619-0

[18] Toppala S, Ekblad LL, Tuisku J, Helin S, Johansson JJ, Laine H, et al. Association of early beta-amyloid accumulation and neuroinflammation measured with [11C]PBR28 in elderly individuals without dementia. Neurology. 2021; 96: e1608–e1619. https://doi.org/10.1212/WNL.0000000000011612

[19] Ferrari-Souza JP, Lussier FZ, Leffa DT, Therriault J, Tissot C, Bellaver B, et al. *APOE*ε4 associates with microglial activation independently of Aβ plaques and tau tangles. Science Advances. 2023; 9: eade1474. https://doi.org/10.1126/sciadv.ade1474

[20] Schaffer Aguzzoli C, Ferreira PCL, Povala G, Ferrari-Souza JP, Bellaver B, Soares Katz C, et al. Neuropsychiatric Symptoms and Microglial Activation in Patients with Alzheimer Disease. JAMA Network Open. 2023; 6: e2345175. https://doi.org/10.1001/jamanetworkopen.2023.45175

[21] Rossano SM, Johnson AS, Smith A, Ziaggi G, Roetman A, Guzman D, et al. Microglia measured by TSPO PET are associated with Alzheimer's disease pathology and mediate key steps in a disease progression model. Alzheimer's & Dementia: the Journal of the Alzheimer's Association. 2024; 20: 2397–2407. https://doi.org/10.1002/alz.13699

[22] Sanchez-Rodriguez LM, Khan AF, Adewale Q, Bezgin G, Therriault J, Fernandez-Arias J, et al. In-vivo neuronal dysfunction by Aβ and tau overlaps with brain-wide inflammatory

mechanisms in Alzheimer's disease. Frontiers in Aging Neuroscience. 2024; 16: 1383163. https://doi.org/10.3389/fnagi.2024.1383163

[23] Klein J, Yan X, Johnson A, Tomljanovic Z, Zou J, Polly K, et al. Olfactory Impairment Is Related to Tau Pathology and Neuroinflammation in Alzheimer's Disease. Journal of Alzheimer's Disease: JAD. 2021; 80: 1051–1065. https://doi.org/10.3233/JAD-201149

[24] Jorge L, Martins R, Canário N, Xavier C, Abrunhosa A, Santana I, et al. Investigating the Spatial Associations Between Amyloid-β Deposition, Grey Matter Volume, and Neuroinflammation in Alzheimer's Disease. Journal of Alzheimer's Disease: JAD. 2021; 80: 113–132. https://doi.org/10.3233/JAD-200840

[25] Zhang Y, Qian XH, Zhuang H, Zhang W, Hu J, Zhao Y, et al. Dual association patterns between microglial activation and neuronal health in Alzheimer's disease: a whole-brain MRSI/PET study. Alzheimer's & Dementia: the Journal of the Alzheimer's Association. 2026; 22: e71229. https://doi.org/10.1002/alz.71229

[26] Rauchmann BS, Brendel M, Franzmeier N, Trappmann L, Zaganjori M, Ersoezlue E, et al. Microglial Activation and Connectivity in Alzheimer Disease and Aging. Annals of Neurology. 2022; 92: 768–781. https://doi.org/10.1002/ana.26465

[27] Canário N, Jorge L, Martins R, Santana I, Castelo-Branco M. Dual PET-fMRI reveals a link between neuroinflammation, amyloid binding and compensatory task-related brain activity in Alzheimer's disease. Communications Biology. 2022; 5: 804. https://doi.org/10.1038/s42003-022-03761-7

[28] Leng F, Hinz R, Gentleman S, Hampshire A, Dani M, Brooks DJ, et al. Neuroinflammation is independently associated with brain network dysfunction in Alzheimer's disease. Molecular Psychiatry. 2023; 28: 1303–1311. https://doi.org/10.1038/s41380-022-01878-z

[29] Bevan-Jones WR, Cope TE, Jones PS, Kaalund SS, Passamonti L, Allinson K, et al. Neuroinflammation and protein aggregation co-localize across the frontotemporal dementia spectrum. Brain: a Journal of Neurology. 2020; 143: 1010–1026. https://doi.org/10.1093/brain/awaa033

[30] Malpetti M, Cope TE, Street D, Jones PS, Hezemans FH, Mak E, et al. Microglial activation in the frontal cortex predicts cognitive decline in frontotemporal dementia. Brain: a Journal of Neurology. 2023; 146: 3221–3231. https://doi.org/10.1093/brain/awad078

[31] Palleis C, Sauerbeck J, Beyer L, Harris S, Schmitt J, Morenas-Rodriguez E, et al. In Vivo Assessment of Neuroinflammation in 4-Repeat Tauopathies. Movement Disorders: Official Journal of the Movement Disorder Society. 2021; 36: 883–894. https://doi.org/10.1002/mds.28395

[32] Palleis C, Franzmeier N, Weidinger E, Bernhardt AM, Katzdobler S, Wall S, et al. Association of neurofilament light chain, [18F]PI-2620 tau-PET, TSPO-PET, and clinical progression in patients with beta-amyloid-negative CBS. Neurology. 2024; 102: e207901. https://doi.org/10.1212/WNL.0000000000207901

[33] Tondo G, Iaccarino L, Cerami C, Vanoli GE, Presotto L, Masiello V, et al. ^{11} C-PK11195 PET-based molecular study of microglia activation in SOD1 amyotrophic lateral sclerosis. Annals of Clinical and Translational Neurology. 2020; 7: 1513–1523. https://doi.org/10.1002/acn3.51112

[34] Zanovello M, Sorarù G, Campi C, Anglani M, Spimpolo A, Berti S, et al. Brain Stem Glucose Hypermetabolism in Amyotrophic Lateral Sclerosis/Frontotemporal Dementia and Shortened Survival: An ^{18}F-FDG PET/MRI Study. Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 2022; 63: 777–784. https://doi.org/10.2967/jnumed.121.262232

[35] Nicastro N, Mak E, Williams GB, Surendranathan A, Bevan-Jones WR, Passamonti L, et al. Correlation of microglial activation with white matter changes in dementia with Lewy bodies. NeuroImage. Clinical. 2020; 25: 102200. https://doi.org/10.1016/j.nicl.2020.102200

[36] Lavisse S, Goutal S, Wimberley C, Tonietto M, Bottlaender M, Gervais P, et al. Increased microglial activation in patients with Parkinson disease using [18F]-DPA714 TSPO PET imaging. Parkinsonism & Related Disorders. 2021; 82: 29–36. https://doi.org/10.1016/j.parkreldis.2020.11.011

[37] Yacoubian TA, Fang YHD, Gerstenecker A, Amara A, Stover N, Ruffrage L, et al. Brain and Systemic Inflammation in De Novo Parkinson's Disease. Movement Disorders: Official Journal of the Movement Disorder Society. 2023; 38: 743–754. https://doi.org/10.1002/mds.29363

[38] Mullin S, Stokholm MG, Hughes D, Mehta A, Parbo P, Hinz R, et al. Brain Microglial Activation Increased in Glucocerebrosidase (GBA) Mutation Carriers without Parkinson's disease. Movement Disorders: Official Journal of the Movement Disorder Society. 2021; 36: 774–779. https://doi.org/10.1002/mds.28375

[39] Farmen K, Nissen SK, Stokholm MG, Iranzo A, Østergaard K, Serradell M, et al. Monocyte markers correlate with immune and neuronal brain changes in REM sleep behavior disorder. Proceedings of the National Academy of Sciences of the United States of America. 2021; 118: e2020858118. https://doi.org/10.1073/pnas.2020858118

[40] Doot RK, Young AJ, Nasrallah IM, Wetherill RR, Siderowf A, Mach RH, et al. [18F]NOS PET brain imaging suggests elevated neuroinflammation in idiopathic Parkinson's disease. Cells. 2022; 11: 3081. https://doi.org/10.3390/cells11193081

[41] Ghadery C, Koshimori Y, Christopher L, Kim J, Rusjan P, Lang AE, et al. The Interaction Between Neuroinflammation and β-Amyloid in Cognitive Decline in Parkinson's Disease. Molecular Neurobiology. 2020; 57: 492–501. https://doi.org/10.1007/s12035-019-01714-6

[42] Jucaite A, Cselenyi Z, Kreisl WC, Rabiner EA, Varrone A, Carson RE, et al. Glia imaging differentiates multiple system atrophy from Parkinson's disease: a positron emission tomography study with [11C]PBR28 and machine learning analysis. Movement Disorders. 2022; 37: 119–129. https://doi.org/10.1002/mds.28814

[43] Chatterjee P, Doré V, Pedrini S, Krishnadas N, Thota R, Bourgeat P, et al. Plasma Glial Fibrillary Acidic Protein Is Associated with 18F-SMBT-1 PET: Two Putative Astrocyte Reactivity Biomarkers for Alzheimer's Disease. Journal of Alzheimer's Disease: JAD. 2023; 92: 615–628. https://doi.org/10.3233/JAD-220908

[44] Fontana IC, Kumar A, Okamura N, Nordberg A. Multitracer Approach to Understanding the Complexity of Reactive Astrogliosis in Alzheimer's Brains. ACS Chemical Neuroscience. 2024; 15: 328–336. https://doi.org/10.1021/acschemneuro.3c00646

[45] Lopresti BJ, Stehouwer J, Reese AC, Mason NS, Royse SK, Narendran R, et al. Kinetic modeling of the monoamine oxidase-B radioligand [18F]SMBT-1 in human brain with positron emission tomography. Journal of Cerebral Blood Flow & Metabolism. 2024; 44: 1262–1276. https://doi.org/10.1177/0271678X241254679

[46] Nakaya M, Sato N, Matsuda H, Maikusa N, Shigemoto Y, Sone D, et al. Free water derived by multi-shell diffusion MRI reflects tau/neuroinflammatory pathology in Alzheimer's disease. Alzheimer's & Dementia (New York, N. Y.). 2022; 8: e12356. https://doi.org/10.1002/trc2.12356

[47] Torso M, Ridgway GR, Valotti M, Hardingham I, Chance SA, National Alzheimer's Coordinating Center, et al. In vivo cortical diffusion imaging relates to Alzheimer's disease neuropathology. Alzheimer's Research & Therapy. 2023; 15: 165. https:

//doi.org/10.1186/s13195-023-01309-3

[48] Preis L, Villringer K, Brosseron F, Düzel E, Jessen F, Petzold GC, et al. Assessing blood-brain barrier dysfunction and its association with Alzheimer's pathology, cognitive impairment and neuroinflammation. Alzheimer's Research & Therapy. 2024; 16: 172. https://doi.org/10.1186/s13195-024-01529-1

[49] Yang A, Luan J, Xu M, Du L, Lv K, Hu P, et al. Regional brain iron correlates with transcriptional and cellular signatures in Alzheimer's disease. Alzheimer's & Dementia: the Journal of the Alzheimer's Association. 2025; 21: e14459. https://doi.org/10.1002/alz.14459

[50] Hosseini SA, Servaes S, Macedo AC, Aumont E, Rahmouni N, Chan T, et al. Quantitative susceptibility mapping of the brain is associated with inflammatory changes in Alzheimer's disease related areas. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2026; 46: 1841–1856. https://doi.org/10.1177/0271678X261417193

[51] Wang EW, Brown GL, Lewis MM, Jellen LC, Pu C, Johnson ML, et al. Susceptibility Magnetic Resonance Imaging Correlates with Glial Density and Tau in the Substantia Nigra Pars Compacta. Movement Disorders: Official Journal of the Movement Disorder Society. 2023; 38: 464–473. https://doi.org/10.1002/mds.29311

[52] Padrela BE, Tecelão S, Kirsebom BE, Geier O, Tranfa M, Masserini F, et al. Blood-brain barrier water exchange in relation to amyloid, cognition and cerebrovascular burden. NeuroImage. Clinical. 2026; 49: 103926. https://doi.org/10.1016/j.nicl.2025.103926

[53] Sumra V, Hadian M, Dilliott AA, Farhan SMK, Frank AR, Lang AE, et al. Regional free-water diffusion is more strongly related to neuroinflammation than neurodegeneration. Journal of Neurology. 2025; 272: 478. https://doi.org/10.1007/s00415-025-13201-1

[54] Torso M, Ridgway GR, Hardingham I, Schwarz AJ, Chance SA. In Vivo Detection of Changes Related to Cortical Columnar Organization and Neuroinflammation Across the AD Continuum. The Journal of Prevention of Alzheimer's Disease. 2022; 9: 769–779. https://doi.org/10.14283/jpad.2022.59

[55] Barisano G, Iv M, Choupan J, Hayden-Gephart M, Alzheimer's Disease Neuroimaging Initiative. Robust, fully-automated assessment of cerebral perivascular spaces and white matter lesions: a multicentre MRI longitudinal study of their evolution and association with risk of dementia and accelerated brain atrophy. EBioMedicine. 2025; 111: 105523. https://doi.org/10.1016/j.ebiom.2024.105523

[56] Vrillon A, Ashton NJ, Bouaziz-Amar E, Mouton-Liger F, Cognat E, Dumurgier J, et al. Dissection of blood-brain barrier dysfunction through CSF PDGFRβ and amyloid, tau, neuroinflammation, and synaptic CSF biomarkers in neurodegenerative disorders. EBioMedicine. 2025; 115: 105694. https://doi.org/10.1016/j.ebiom.2025.105694