REVIEW

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PET imaging of microglial pathology in multiple sclerosis

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Purpose of review:
This review evaluates recent advances in the development of translocator protein (TSPO) – and purinergic receptor–binding PET tracers and highlights the capacity of TSPO-PET-imaging to capture microglial activation across multiple regions of interest in multiple sclerosis brain. We discuss the added value of integrating PET-derived measures with fluid and metabolic biomarkers, as well as their successful application in recent clinical trials.

Recent findings:
Recent research highlights PET as a robust molecular imaging tool for detecting microglial activation and implicates dysregulated microglial activity as a key driver of smouldering multiple sclerosis pathology. PET-detectable microglial activation appears not merely as a secondary response to neuroaxonal injury but is increasingly recognized as an integral inflammatory component of ongoing pathological processes that lead to future brain atrophy and clinical deterioration.

Summary:
Recent advances establish PET as an essential research tool for evaluating the presence of smouldering inflammation in MS brain not detectable using MRI. Furthermore, PET-based methods have proven suitable for measuring glial responses to potentially neuroprotective therapies currently under development.

Keywords
microglia, multiple sclerosis progression, positron emission tomography, translocator protein

INTRODUCTION

Microglial activation is a central component of multiple sclerosis (MS) pathology involved in promoting both lesion evolution and diffuse neuroaxonal injury [1,2]. While conventional MRI is highly sensitive in capturing acute focal inflammatory activity and subsequent chronic lesion scars, it provides limited capacity to capture compartmentalized, chronic glial cell-driven inflammation which is characteristic for the pathology contributing to MS progression independent of relapse activity [3]. In research settings, positron emission tomography (PET) is increasingly used as a complementary imaging modality enabling *in vivo* assessment of glial pathology by utilization of radiotracers binding to molecules expressed in activated glia. Owing to the capacity to provide molecular-level specificity and the possibility to quantify the molecular targets in living human brain, PET imaging can be viewed as an ideal method to study the neuropathological processes in MS. Importantly, unlike in a conventional neuropathology setting, PET imaging can be performed longitudinally, and can thus provide dynamic insights of glial pathology otherwise not obtainable [4▪].

Most clinical PET studies in MS have focused on the assessment of the mitochondrial 18-kDa translocator protein (TSPO), which is upregulated in activated microglia and to a lesser extent in astrocytes [5]. Experimental evidence indicates that TSPO is involved in mitochondrial cholesterol transport, regulation of reactive oxygen species, calcium signalling and

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KEY POINTS

- Translocator protein (TSPO)-positron emission tomography (PET) sensitively detects increased microglial activation in multiple sclerosis (MS) and correlates with neurodegeneration-related biomarkers and disease progression.
- Longitudinal and interventional studies support TSPO-PET as a prognostic and outcome-reporting biomarker in progressive MS.
- Novel TSPO tracers, harmonized methods, and non-TSPO targets are being developed to overcome current limitations of TSPO-PET.

modulation of the mitochondrial permeability transition pore, linking it to cellular stress responses [6] but TSPO may also be functional in regulation of mitochondrial energy metabolism [7]. In chronic neurological conditions such as progressive MS, microglial cells, when activated, tend to get arrested in a proinflammatory, neurodegenerative state [8]. They congregate in areas of ongoing central nervous system (CNS) pathology, and the increased densities of the TSPO-expressing cells can be readily detected using PET and TSPO-binding radioligands, where they manifest as hot areas of increased radioligand binding (Fig. 1) [9]. Consequently, TSPO has become a robust target for imaging MS neuropathological activity [10]. Though PET tracers for TSPO have been utilized since 1984 [11], the continued development of TSPO-PET quantitation methodology, the ever increasing TSPO-PET-studied MS patient numbers and the possibility to combine TSPO-PET outcomes with other imaging and soluble biomarker outcomes in a multimodal fashion has proven uniquely informative for the understanding of the significance of the chronic and focal glial activation that characterize the MS disease [12].

TSPO-PET imaging has consistently demonstrated increased signal not only in the context of focal chronic lesions but also in the normal-appearing white matter (NAWM) and grey matter, supporting the concept of widespread innate immune cell activation beyond MRI-visible focal pathology.

Recently published work has emphasized longitudinal change in TSPO-signal and its' associations with disability and neurodegeneration. Significant correlations with TSPO-binding and MS pathology-relevant soluble biomarkers measurable in blood have been demonstrated. This emerging work positions TSPO-PET as a specific and quantitative imaging biomarker of MS progression-related pathology. This review focuses on literature from 2024 to 2025, detailing how PET imaging of glial activity is evolving into a predictive biomarker for disease trajectory and therapeutic response.

PET REVEALS CHRONIC NEUROINFLAMMATION

Earlier abundant work has demonstrated that TSPO-binding in the NAWM is higher in MS patients compared to healthy controls, in males vs. females, and is associated with clinical and radiological measures of disease burden [13–16].

PET imaging outcomes addressing central nervous system pathology in multiple sclerosis

Using the third-generation TSPO radioligand ^{11}C-ER176 PET, Zeydan *et al*. found that PET signal was highest in PPMS patients, followed by patients with RRMS and lowest in controls, and that higher thalamus radioligand uptake correlated with increased disability [17▪]. Another study utilizing both proton magnetic resonance spectroscopy and ^{11}C-ER176 PET found that glial activation in the thalamus correlated with thalamic volume loss and increased disability in MS patients [18]. In a study of 23 MS patients and 13 HCs combining ^{11}C-PBR28-PET and DTI-MRI, TSPO expression was significantly associated with white matter (WM) degeneration [19], confirming previous findings [20,21].

In addition to widespread, compartmentalized microglial activation in areas of white and grey matter, lesion-associated microglial activation plays a significant role in promoting MS progression. A novel chronic active lesion phenotype linked to rapid MS progression, a broad rim lesion (BRL), was discovered in a post-mortem study of a large MS autopsy cohort (N = 186). Radiological BRLs (rBRLs) could be visualized using TSPO-PET in another cohort of 114 MS patients, where rBRLs similarly associated with more rapid disease progression, thus establishing the PET-detectable rBRLs as a potential imaging biomarker of significantly detrimental MS pathology [22▪].

Other imaging methods for chronic active lesions include susceptibility-weighted imaging for paramagnetic rim lesions (PRLs) [23] and identification of slowly expanding lesions (SELs) from consecutive conventional MRI scans using a Jacobian method [24]. Furthermore, TSPO-PET imaging can be used to quantitate microglial activation in chronic lesions. All three imaging methods, i.e. PRLs, SELs, and TSPO-rim-active lesions [25] capture detrimental pathology [26], but their exact respective pathological characteristics remain somewhat unexplored.

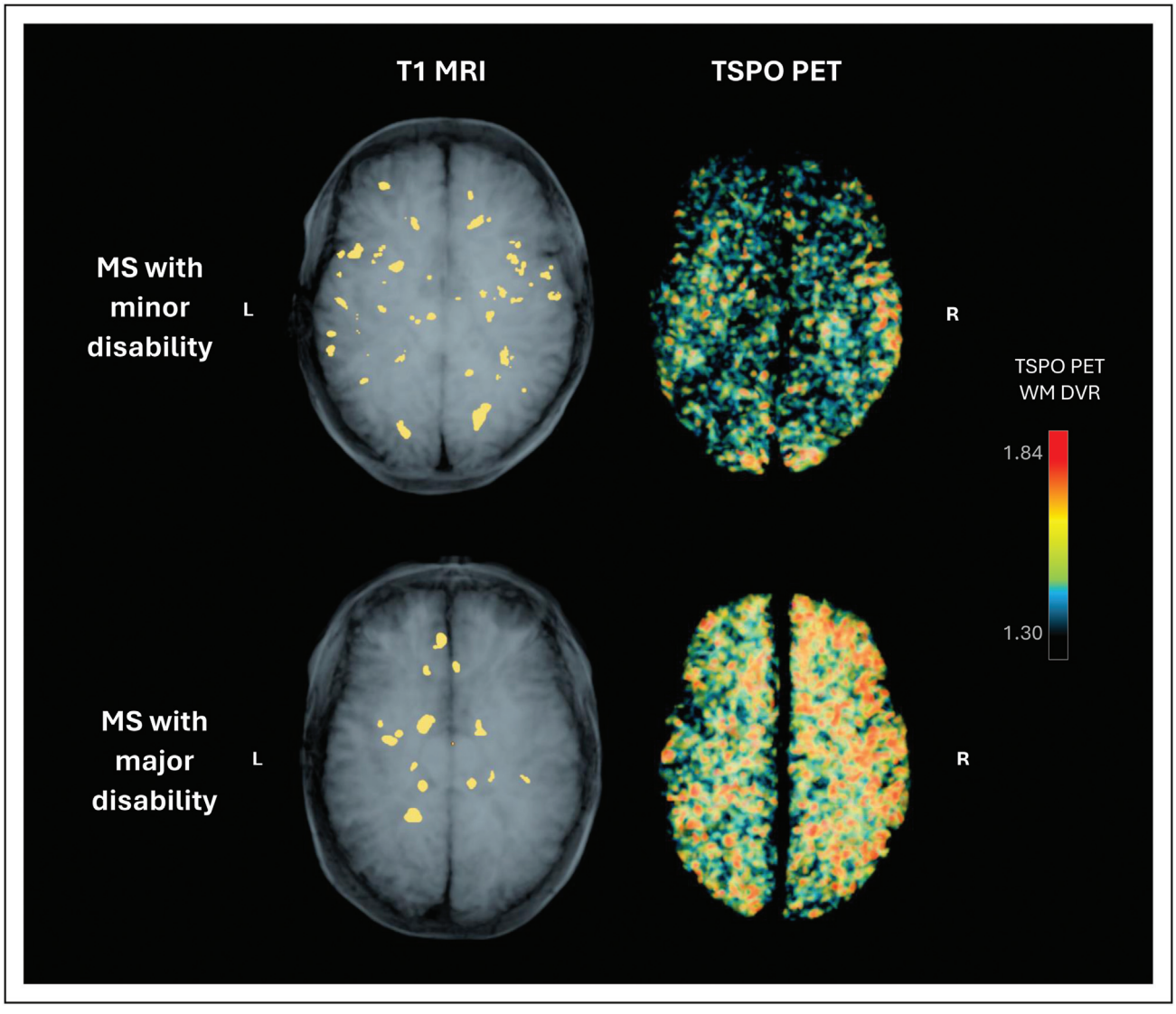

FIGURE 1. Lesion locations and areas of high microglial activation in the white matter of female MS patients with either minor disability (EDSS 1.0, disease duration 9.6 years) or major disability (EDSS 6.0, disease duration 7.6 years). Microglial activation, as measured by TSPO distribution volume ratio (DVR), extends beyond focal MRI lesions and reveals smouldering inflammatory activity invisible to MRI particularly in the patient with major disability. Volumetric MRI and white matter (WM) TSPO PET images are rendered with transparency to visualize lesion locations and TSPO availability throughout the WM volume. T1 MRI image is overlayed with MS lesion locations.

While a potential correlation of SELs and TSPO-binding is yet to be reported, a study including 30 MS patients and 21 healthy controls utilizing 7 T MRI and ^{11}C-PBR28 PET, showed a correlation between the number of PRLs and PET overall-active lesions. However, no association between the number of peripherally active lesions with PET and PRLs was observed and standard uptake value (SUV) ratio means were similar between PRL and non-PRL lesions. Furthermore, PET-detectable inflammation showed the strongest association with neurological disability highlighting its superior sensitivity in revealing compartmentalized inflammation [27].

Beyond the aforementioned brain regions, Herranz *et al.* showed increased ^{11}C-PBR28 binding in the meningeal tissue and cortex of 49 MS patients compared to 21 age-matched controls. These findings were further validated using immunohistochemistry of post-mortem secondary progressive MS (SPMS) cases and controls, indicating a role of meningeal inflammation in MS pathology [28].

Finally, in contrast to the abundance of reported positive correlations of TSPO uptake and MS pathology, a study of 5 MS patients and 23 HCs investigating the two isozymes of cyclooxygenase, i.e. COX-1 expressed in microglia and COX-2 localized in neurons and

induced by inflammatory stimuli, found no difference in ^{11}C-PS13 binding for COX-1 or ^{11}C-MC1 binding for COX-2 between MS patients and HCs or between lesions and normal-appearing brain tissue [29].

Utilization of TSPO-PET imaging for predicting multiple sclerosis progression

There is increasing evidence that microglial activation relates to later downstream neurodegeneration and clinical progression metrics. A study by Nylund *et al.* reported that accumulation of glial activation relates to later brain atrophy on longer follow-up 4–11 years after PET, supporting TSPO-PET as a readout of compartmentalized inflammation that is relevant to neurodegeneration [4▪]. In line with this, RRMS patients who converted to SPMS during a 5-year follow-up had increased TSPO binding in the NAWM, thalamus, and perilesional area at baseline compared to those who remained in the RRMS phase [30▪].

Correlation between soluble biomarkers and TSPO-PET imaging outcomes

PET imaging of glial activation is technically challenging and expensive and presently mostly suitable for use in research settings. There is thus a great demand for more easily accessible biomarkers for assessment of aspects of smouldering CNS inflammation particularly in the context of progressive MS. Combining PET imaging with analysis of soluble biomarkers has potential to inform on the nature of the CNS pathology associated with alterations in biomarkers measurable in blood.

Increased serum neurofilament light chain concentration (sNfL) correlated with increased TSPO-PET signal in the NAWM and chronic active lesions, suggesting that microglial activation, when present, contributes to neuroaxonal damage leading to increased sNfL in blood [31]. Blood glial fibrillary acidic protein (GFAP), a marker of astrogliosis, on the other hand demonstrated a positive correlation with a greater volume of lesions harbouring increased TSPO-binding among a mixed cohort of MS patients. This suggests that in this context, GFAP concentration in blood might reflect mixed microglia and astrocyte pathology within chronic lesions, as TSPO is also expressed on a subset of astrocytes in addition to microglial cells. These findings associated with more unfavourable brain volume and overall lesion volume metrics measured by MRI [32]. Furthermore, higher levels of plasma chitinase-3-like protein 1, expressed both by activated astrocytes and microglia, correlated with higher brain TSPO uptake in a cohort of 55 MS patients [33].

Longitudinal TSPO-PET imaging in multiple sclerosis

A number of studies have addressed the usability of longitudinal TSPO-PET imaging in clinical therapeutic settings, allowing dynamic evaluation of in situ glial activation in living patients with or without treatment [34–36]. Recently, the first publication reporting a longitudinal change in TSPO-binding in an untreated MS cohort was published. Here, SPMS patients had higher baseline TSPO-binding compared to RRMS in the NAWM. Over a one-year follow-up, the radioligand binding increased among SPMS but not RRMS patients [4▪]. The findings implicate a gradual increase in glial activation over time in patients prone to progression. The effect of chimeric antigen receptor T-cell (CAR-T) therapy on microglia activity was studied in a small open-label study including 5 MS patients treated with anti-B-cell maturation antigen CAR-T. The study showed a reduction in ^{11}C-PBR28 uptake in three of the five patients and no change in the other two [37].

Currently, a number of early-phase intervention studies targeting glial activation and utilizing TSPO-PET imaging as a primary endpoint are on-going. Disease-modifying therapies in these studies include cladribine [38], ocrelizumab [39], ofatumumab [40], foralumab[41], *N*-acetyl cysteine [42], istradefylline [43], and hydroxychloroquine[44].

Emerging TSPO-PET radioligands

First-, second-, and third-generation TSPO radioligands have proven valuable in imaging microglial activation in MS research, but suffer from compromises in TSPO specificity, sensitivity, low signal-to-noise ratio, brain permeability and clearance kinetics, haplotype affinity and effective dose. ^{18}F-FEDAC was developed to match the high TSPO affinity of other second-generation TSPO radioligands while improving on slow clearance of radioactivity from the brain [45]. The first human study with seven healthy participants found ^{18}F-FEDAC to have a similar biodistribution to other second-generation TSPO radioligands whilst exhibiting minimal accumulation in healthy brain [46]. Subsequent work in rat stroke models confirmed ^{18}F-FEDAC's sensitivity to neuroinflammation-associated increases in TSPO expression [47]. ^{18}F-BIBD-239, a novel tracer with reduced polymorphism sensitivity, was recently developed to overcome the short half-life that limits current ^{11}C-labeled third-generation radioligands. In the first *in vivo* human study ^{18}F-BIBD-239 was shown to rapidly permeate into the healthy brain and to accumulate in inflamed TSPO-expressing glioma tissue [48].

^{18}F- FEDAC and ^{18}F-BIBD-239 both demonstrate preliminary suitability as PET imaging biomarkers of microglial activation with potential application in neuroinflammatory conditions such as MS. In addition, ^{11}C-DPA-813 and ^{18}F-DPA-814 are two other novel third-generation TSPO-PET tracers showing high binding to TSPO on human MS tissues in autoradiography but are also yet to be tested in MS patients [49▪].

Emerging PET microglia markers beyond TSPO

While TSPO robustly associates with microglial activation in the MS brain as demonstrated by transcriptomic and neurohistological evidence [50▪▪], TSPO is additionally expressed to a lesser extent by other cell types such as astroglial cells, leading to inherent unspecificity of radioligand signal. Furthermore, TSPO-PET does not differentiate between anti-inflammatory neuroprotective and pro-inflammatory neurotoxic microglial activation. Novel PET targets more closely linked to pro-inflammatory microglial phenotypes are under active investigation, although clinical validation remains limited. Such targets include purinergic receptors such as the P2X7 molecule. In a study using the radioligand ^{11}C-SMW139, binding to P2X7 receptor did not differ between MS patients and controls. Differences in tracer binding in NAWM or perilesional area were noted across some demographic measures, namely sex, age, and disease duration as well as MS disease type (new-onset or SPMS) but high variability and tracer limitations related to free fraction and quantification stability potentially hinder utilization of this ligand [51].

CSF1R (colony-stimulating factor-1 receptor) regulates glial differentiation and is expressed in microglia and macrophages. CSF1R transcript and protein expression is elevated in MS patient NAWM, perilesional area and CSF, and its inhibition attenuates detrimental neuroinflammation and demyelination in MS models [52] To improve on the specificity and radiological stability of a previously developed CSF1R PET tracer ^{11}C-CPPC, an analogous ^{11}C-radioligand, ^{11}C-1, was recently developed. It labels CSF1R with higher specificity but had poor brain uptake in live mice and non-human primates, deeming it unsuitable for in vivo CNS PET studies [53]. In contrast, another CSF1R inhibitor, ^{18}F-JNJ-CSF1R-1, demonstrated the desirable high brain uptake in both mice and non-human primates [54].

Methodological improvements

Lack of harmonization across radioligands and quantification methods has hindered execution of multicentre studies applying TSPO-PET imaging in MS. The INFLANET project aims to establish a methodological framework to harmonize quantification and analysis of PET imaging across six centres in France using the second-generation TSPO radiotracer ^{18}F-DPA-714 [55]. Extending this framework to include even more study centres that may use different scanners and tracers could facilitate further collaboration, potentially building on a novel blood-free and reference-free method recently introduced by Maccioni *et al.* [56] The supervised clustering algorithm has been implemented as a blood-free method for first-generation (^{11}C-PK11195) [57] and some second-generation TSPO radioligands, such as ^{11}C-PBR28 [58], ^{18}FDPA-714 [59] and most recently, ^{11}C-DPA-713 [60▪▪].

Other efforts to improve upon existing PET methods include a radiation dosimetry study of the existing radioligand ^{18}F-PBR111 [61] and development of a novel logarithmically transformed "glial activity load on PET" score (lnGALP). The score is calculated as the sum of voxel-by-voxel z -scores $\geq$4 based on SUV-measurements of ^{11}C-PBR28 radioligand binding in voxels within predefined regions of interest. In a cross-sectional study of 22 MS patients and 8 healthy controls re-addressing the presence of compartmentalized inflammation in MS vs. healthy controls, higher lnGALP scores in cortical grey matter and WM were measured in MS patients compared to healthy controls [62]. The usability and reliability of the lnGALP method still awaits validation against conventional modelling methods [58].

Other PET targets relevant to multiple sclerosis pathology

Radioligands to evaluate synaptic density, myelin content and glucose metabolism have recently been actively studied in MS. Synaptic density measured with ^{11}C-UCB-J PET imaging quantifying the synaptic vesicle glycoprotein 2A was reduced in the cortical grey matter of 10 patients with MS compared to 8 healthy controls, with correlation to cognitive impairment [63▪]. Similarly, in a study using the radioligand ^{18}F-UCB-H and MRI, PET imaging was far more sensitive in detecting cortical pathology in 31 MS patients compared to MRI [64▪]. Also here, the extent of PET-defined areas of cortical synapse pathology was associated with disability and cognitive performance [64▪].

Myelin density in MS has been studied using a variety of PET radioligands. The radiolabelled derivative of 4-diaminopyridine, ^{18}F-3F4AP that binds to potassium channels in demyelinated axons, showed potential in differentiating MS patients (n = 3) from healthy controls (n = 3) and lesions with and without

axonal damage [65▪▪]. A study by Barrios-López *et al.* suggested that amyloid PET for assessing myelin integrity may have potential as a biomarker in MS as they reported higher ^{18}F-fluorbetaben uptake in damaged WM compared to NAWM and correlations between SUV in the damaged WM and clinical parameters [66]. Yazdan-Panah *et al.* demonstrated the feasibility of assessing cerebral blood flow and myelin content simultaneously using ^{11}C-PiB PET imaging, building on the previously reported correlation of ^{11}C-PiB PET with 15O-H_2O PET perfusion measures in the cortex [67]. Yet another PET tracer for myelin imaging, ^{11}C-MeDAS, showed lower uptake in the spinal cord of MS patients vs. HCs and its distribution corresponded with known myelin distribution in the spinal cord. However, its sensitivity in detecting spinal MRI lesions was low [68].

Finally, Brier et al. addressed glucose metabolism in the MS brain with fluorodeoxyglucose PET in combination with MRI and showed increased NAWM glycolysis in MS patients compared HCs and that glycolysis increased with increased disability [69].

CONCLUDING REMARKS

Collectively, PET imaging of microglial pathology offers a unique window into mechanisms of chronic inflammation in MS and holds promise for improving disease stratification, understanding treatment effects and refining biomarkers of progression. PET imaging is expected to have a significant role in future Phase II proof-of-concept trials targeting glial activation to slow down MS progression. Importantly, unlike MRI measures of atrophy, which represent irreversible tissue loss, PET captures the active inflammatory state behind the blood-brain-barrier, offering a potential therapeutic window to halt progression before permanent neurodegeneration occurs.

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Conflicts of interest

There are no conflicts of interest.

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