9 Neuroinflammation Imaging in Neurodegenerative Diseases

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Introduction

Neuroinflammation is a natural response of a competent immune system to any type of CNS insult, and it includes both innate (e.g., monocytes) and adaptive components (lymphocytes). A special characteristic of the CNS is the presence of specialized resident immune cells, the microglia. When faced with a noxious stimulus or injury, microglial cells become activated, increase in size, assume an ameboid shape with shorter processes, and secrete a variety of cytokines and other neurotoxic compounds. An excessive reaction can result in a vicious cycle that eventually results in neuronal injury and death. Microglial activation, however, is only one part of the neuroinflammatory process, with additional contributions from astrocytes, peripherally derived macrophages, and sometimes T-cell lymphocytes (Fig. 9.1).

The potential contribution of neuroinflammation to CNS injury has been extensively studied using molecular imaging with positron emission tomography (PET) in many disease entities, including neurodegenerative diseases (NDDs). Most research using neuroinflammation imaging in NDDs has focused on Alzheimer's disease (AD), with fewer studies evaluating Parkinson's disease (PD) and other movement disorders. The overarching goal of such studies is to understand the role of neuroinflammation in disease pathophysiology and progression. Imaging can also be used to monitor treatment effects and to provide surrogate endpoints in clinical trials of strategies to modify neuroinflammation. While there are many targets that could be used to image neuroinflammation with PET, the most commonly studied target has been the 18-kDa translocator protein (TSPO), an outer mitochondrial membrane receptor that is expressed in many CNS and peripheral immune cells [1]. Basal TSPO expression in the brain parenchyma is low but it is upregulated in inflammatory states. As a result, imaging TSPO has been used to assess the neuroinflammatory process in various diseases including NDDs, and many radioligands have been developed to image TSPO with PET.

However, TSPO as a target to monitor neuroinflammation does have several shortcomings. In the CNS, TSPO is expressed in several cell types. These include resident microglia and monocyte-derived macrophages, astrocytes, and endothelial, choroid plexus and ependymal cells, with low but ubiquitous expression in the parenchyma [2]. Although

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D. J. Cross et al. (eds.), *Molecular Imaging of Neurodegenerative Disorders*,
https://doi.org/10.1007/978-3-031-35098-6_9

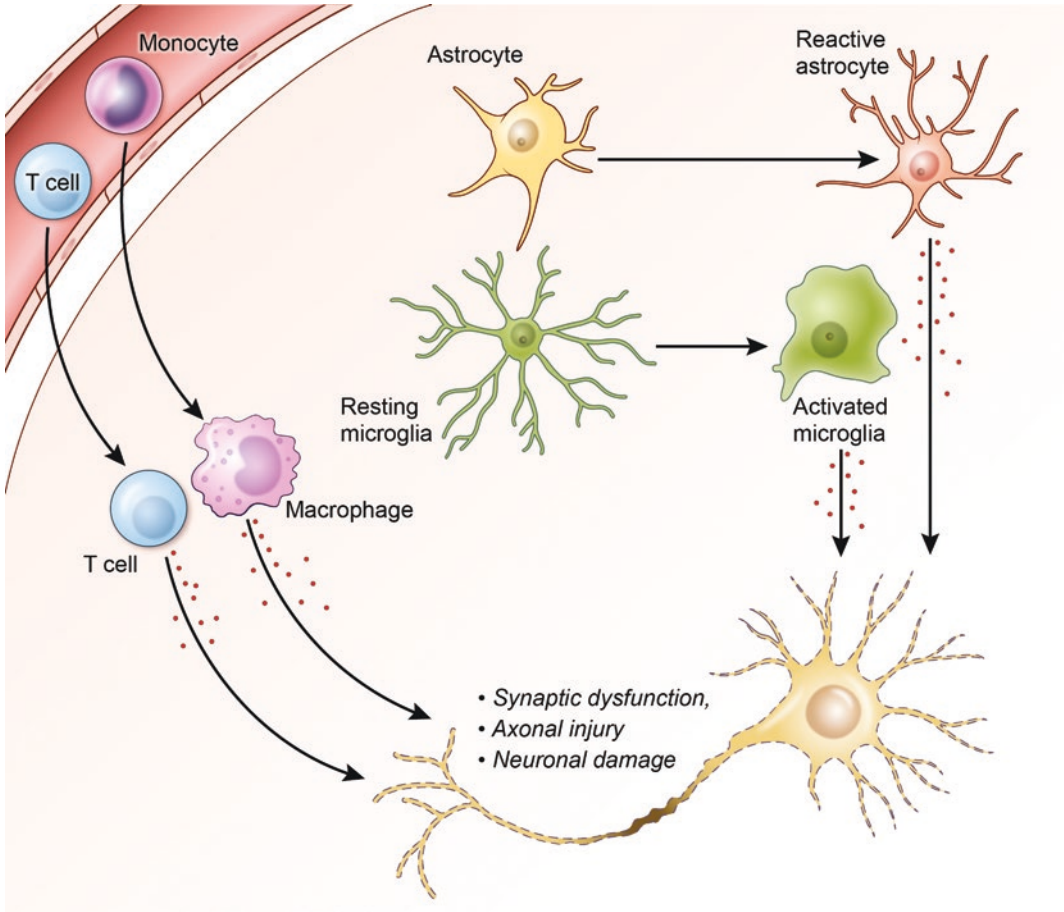

Fig. 9.1 Neuroinflammation and mechanism of neuronal injury: activated microglia, astrocytes, peripherally derived monocytes, and lymphocytes contribute to neuroinflammation. Excess production of cytokines, chemokines, and other neurotoxic molecules can result in synaptic loss, axonal degradation, and neuronal cellular damage

generally assumed not to be expressed in neurons, colocalization of TSPO staining with tyrosine hydroxylase has been reported, raising the possibility that dopaminergic neurons also express TSPO [3]. TSPO imaging also cannot distinguish between activated microglia that are harmful (pro-inflammatory M1 phenotype) versus neuroprotective (anti-inflammatory M2), and cannot differentiate microglia from astrocytes, which also participate in the neuroinflammatory process.

The original and most commonly used TSPO PET ligand is [^{11}C]-PK11195, an isoquinolone TSPO antagonist. However, it has several limitations as a PET radiotracer, including low blood–brain barrier permeability and high binding to plasma proteins, limiting tracer entry to brain, and low specific binding to the TSPO target with a poor signal-to-noise ratio in the PET images. As a result, many other ligands have since been and continue to be developed to improve neuroinflammation imaging (Fig. 9.2).

In general, TSPO ligands other than [^{11}C]-PK11195 are referred to as second- or third-generation ligands (Fig. 9.2), with improved affinity and higher specific-to-nonspecific binding. The use of second-generation ligands, however, was immediately hampered because almost

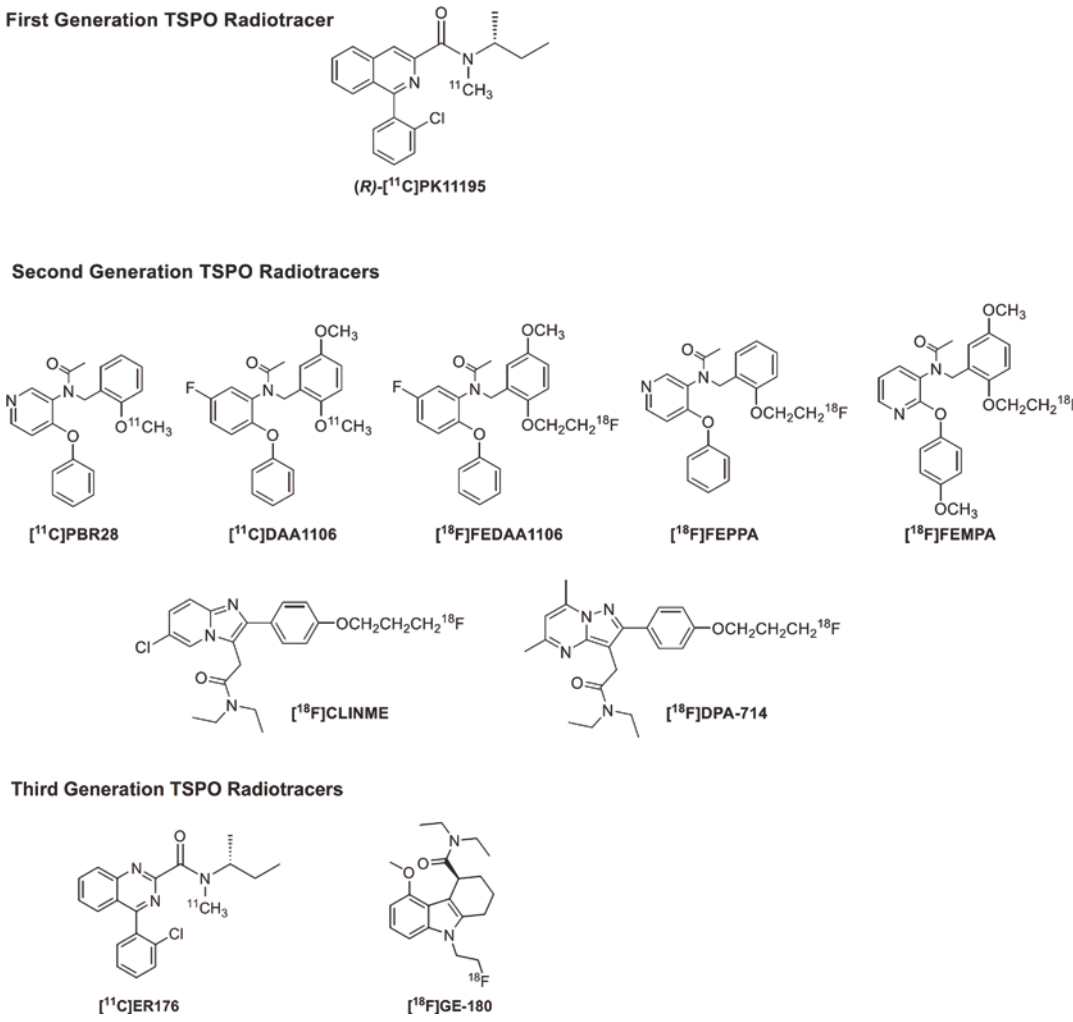

Fig. 9.2 Chemical structures of first-, second-, and third-generation TSPO PET ligands (adapted and reproduced with permission from [65])

10% of subjects showed no specific binding. Upon further evaluation, a polymorphism was discovered in exon 4 of the TSPO gene resulting in a nonconservative amino-acid substitution from alanine to threonine (Ala147Thr). This resulted in three possible binding levels: high-affinity binders (HAB) (C/C; Ala/Ala), medium-affinity binders (MAB) (C/T; Ala/Thr), and low-affinity binders (LAB) (T/T; Thr/Thr) [4, 5]. This necessitates genotyping before imaging and exclusion of almost 10% of the population, as well as the need to increase the sample number to match the binding levels between patients and controls.

Multiple third-generation ligands have subsequently been developed with claims of lower or no sensitivity to polymorphism [6, 7]. However, to our knowledge no ligand has been found that is completely insensitive to polymorphism.

Imaging Neuroinflammation in Alzheimer's Disease

One reason neuroinflammation has been considered a possible factor in the pathophysiology of AD is that the amyloid-β deposition hypothesis seems to be insufficient to explain all aspects of

disease pathogenesis. In addition, increased inflammatory markers have been described in AD, and the AD risk genes such as ApoE are known to be associated with innate immune function modulation [8]. Therefore, PET has been widely used to assess the role of neuroinflammation in AD pathogenesis. These PET studies typically include imaging with radiotracers for amyloid and tau to confirm the stage and relation to neuroinflammation of the underlying AD pathophysiological process. Unfortunately, the results of these studies have generally been inconsistent.

Two early studies using [^{11}C]-PK11195 suggested a role for neuroinflammation in AD and mild cognitive impairment (MCI). Cagnin et al. found that while in controls regional binding significantly increased with age in the thalamus, patients with AD showed significantly increased binding in the entorhinal, temporoparietal, and cingulate cortex [9]. Okello et al. showed that amyloid deposition and microglial activation can be detected in about 50% of patients with MCI. However, there was no correlation between regional levels of [^{11}C]-PK11195 and amyloid, suggesting that the two pathologies can co-exist but can also occur independently [10].

Many later studies using second-generation ligands often showed discordant results. Yasuno et al. showed increased [^{11}C]-DAA1106 binding in 10 AD patients [11] and Kreisl et al. found elevated [^{11}C]-PBR28 binding in AD but not in MCI [12]. Two other papers, however, using [^{11}C]-vinpocetine and [^{18}F]-FEDAA1106, showed no difference between AD subjects and age-matched controls [13, 14]. Interestingly, Kreisl et al. found a correlation between neuroinflammation (measured by [^{11}C]-PBR28) and amyloid (imaged with [^{11}C]-PIB), and between neuroinflammation and neurocognitive impairment in AD (although not in MCI patients), contrary to the findings of Okello et al. [10]. Since increased binding of [^{11}C]-PBR28 was seen only in AD, the authors proposed that neuroinflammation occurs after conversion of MCI to AD and worsens with disease progression, thus making its detection possibly useful in marking the conversion from MCI to AD and in assessing response to experimental treatments.

More recently, many studies using either [^{11}C]-PK11195 or second-generation ligands to assess MCI and AD also demonstrated conflicting results. Some showed no correlation between inflammation, cognition and/or pathologic correlates (amyloid and/or tau burden) [15–17]. However, others showed the opposite, albeit to different degrees or distributions, e.g., in different brain regions or using a global measure of neuroinflammation [18–25].

There are several possible explanations for these discrepant results. The use of different ligands with different imaging characteristics and sensitivities to detect TSPO expression likely is a major factor. This was elegantly demonstrated by Yokokura et al. who used the "gold standard" of receptor blocking experiments to determine the specific binding of two TSPO radiotracers. While [^{11}C]-PK11195 showed small differences between AD and controls in the precuneus, imaging with [^{11}C]-DPA713 demonstrated more impressive increased binding in multiple regions including the anterior and posterior cingulate gyri, thalamus, and precuneus [26] (Fig. 9.3).

Another factor likely underlying the conflicting PET imaging results is the use of different patient populations at different stages of the AD pathophysiological process, often with small sample numbers. A third factor is the use of different image analysis methods to estimate the level of TSPO binding. These include graphical analysis with a measured arterial plasma input function (e.g., [19]), simplified reference tissue methods with various brain regions used to provide information about the delivery of radiotracer to tissue (e.g., [27]), or a semi-quantitative approach using the ratio of local regional radioactivity to radioactivity in the cerebellum which is assumed not to be affected by the disease process (e.g., [28]).

To help reconcile these results, Bradburn et al. performed a meta-analysis of TSPO studies in AD and MCI [29]. The authors concluded that neuroinflammation is increased in AD, with more modest effects in MCI. In the parietal region, the neuroinflammatory effects correlated with Mini-

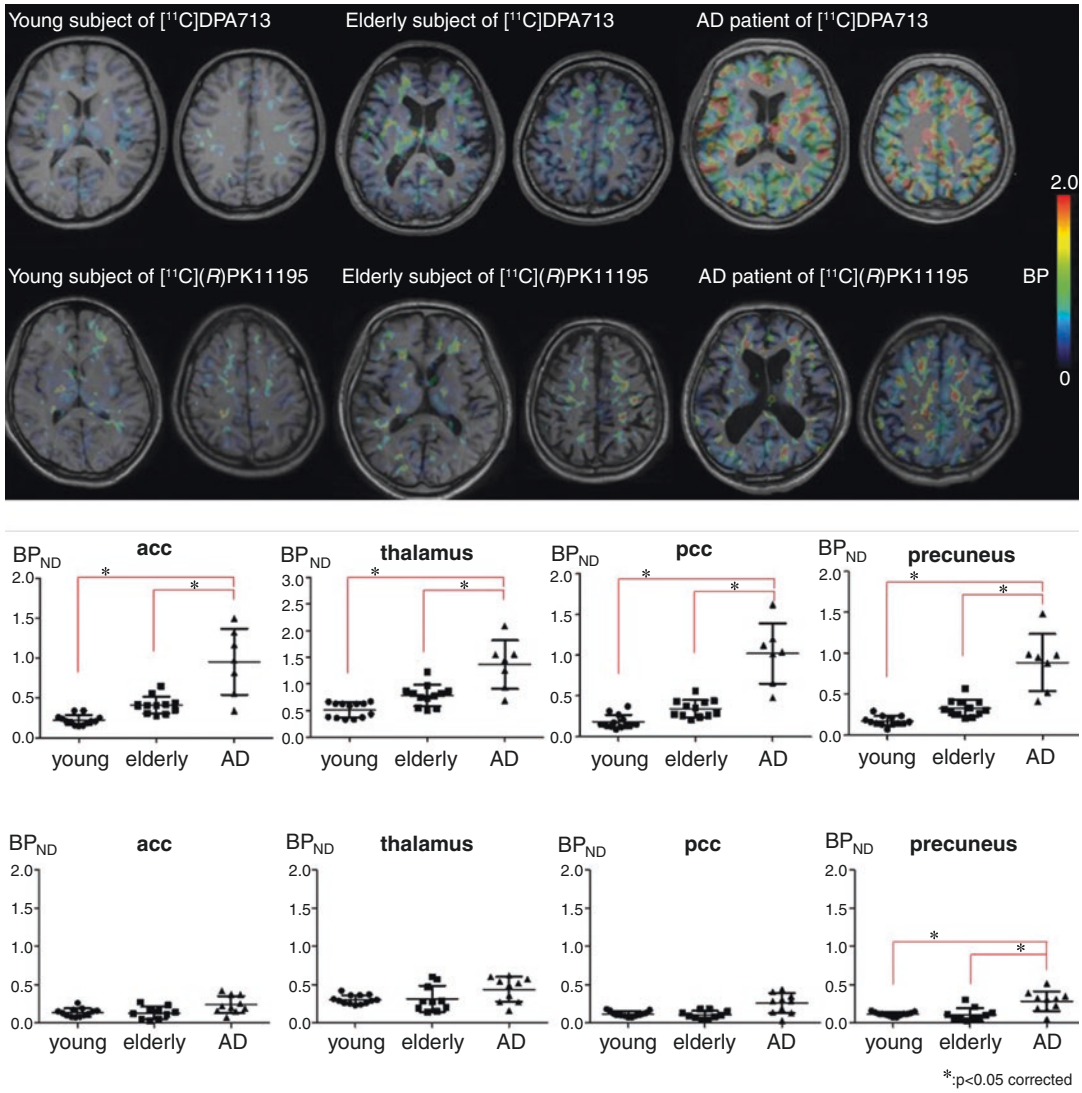

Fig. 9.3 Discrepancy of imaging results between first- and second-generation TSPO PET imaging in AD subjects. While [11C]-PK11195 showed small differences between AD and controls in the precuneus, [11C]-DPA713 demonstrated increased binding in multiple regions, including the anterior and posterior cingulate gyri, thalamus, and precuneus (adapted and reproduced with permission from [26])

Mental State Examination scores in AD. This meta-analysis was published in 2019; the inclusion of more recent studies could provide different results.

Two such studies are noteworthy because they included a large number of subjects who were studied longitudinally [22, 30]. Hamelin et al. used [18F]-DPA714 to evaluate patients who were classified either as prodromal AD (amyloid positive, Clinical Dementia Rating (CDR) score = 0.5) or demented (amyloid positive, CDR ≥ 1.0 [30]). Follow-up scans in 1–2 years showed two distinctive dynamic patterns of microglial activation: higher initial [18F]-DPA714 binding followed by a slower increase in subjects with slower disease progression, and lower initial [18F]-DPA714 binding followed by a more rapid increase in subjects with accelerated disease progression. This suggested a possible protective role of microglial activation in early stages of AD. This was pro-

posed by Leng and Edison who suggested that an initial microglial response might be protective, thus slowing disease progression (Fig. 9.4). However, subsequent chronic activation eventually causes phenotypic changes in microglia and shifts their behavior toward a pro-inflammatory phenotype, which causes damage to neuronal networks and disease progression. On the other hand, AD patients with defective microglial functioning at the onset of disease would undergo a quicker progression and an exaggerated late-stage inflammatory response [31].

Pascoal et al. imaged 130 HAB subjects over the normal aging and AD clinical spectrum, lon-

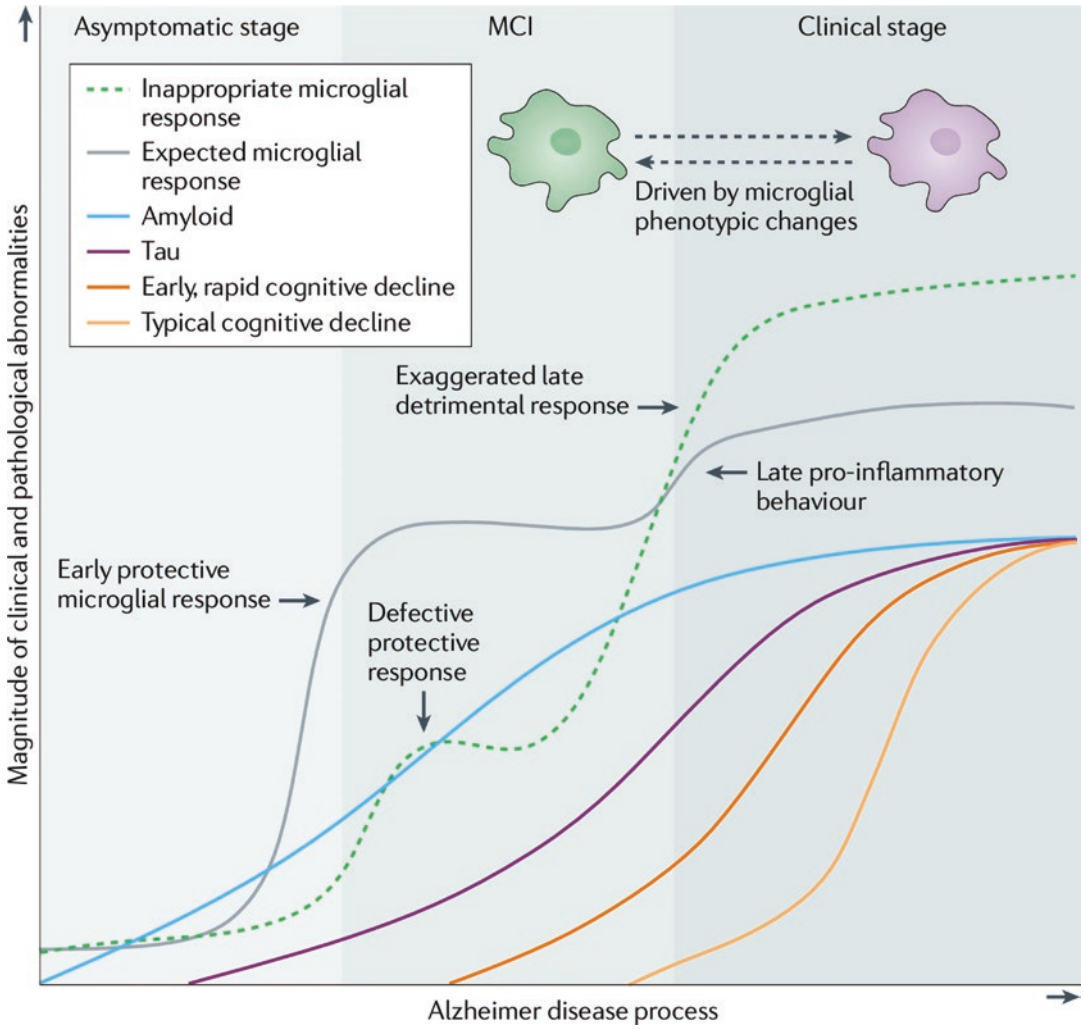

Fig. 9.4 Proposed effect of microglial activation on Alzheimer disease progression [31]. The authors suggest that individual clinical presentation at a given pathological stage in AD might be partly determined by different microglial responses in the early versus late stages of the disease. When microglial activity is deficient, i.e., not protective, at the onset of disease, AD patients might develop cognitive decline at an earlier stage in response to tau and amyloid deposition. This suggests that the initial microglial activation to pathological changes is protective. However, chronic microglial activation eventually causes phenotypic changes in microglia toward a pro-inflammatory phenotype, with secondary neuronal damage and accelerated symptomatology. In patients with inappropriate early microglial responses, a weak initial protective response results in a quicker transition to worse phenotypes as well as an exaggerated late-stage inflammatory response. MCI: mild cognitive impairment (reproduced with permission from [31])

gitudinally, for TSPO expression and amyloid and tau levels. Neuroinflammation and tau pathology correlated hierarchically with each other following Braak-like stages of neuropathological disease progression. The strongest predictor of cognitive impairment was the co-occurrence of amyloid, tau, and microglial abnormalities. They concluded that amyloid and activated microglia interaction might determine the rate of tau spread across disease stages [22].

In conclusion, neuroinflammation seems to play an important role in the pathophysiology of AD, but a better understanding of this role is needed, especially since many trials of anti-inflammatory drugs did not slow disease progression [32–34]. This is key for future AD clinical trials to suppress pro-inflammatory changes or enhance microglial anti-inflammatory properties, along with anti-amyloid or -tau approaches. Imaging of neuroinflammation in AD should be further refined to serve as a quantitative surrogate endpoint in clinical trials.

Imaging Neuroinflammation in Parkinson's Disease and Other Movement Disorders

Another NDD in which neuroinflammation is suspected to play a role is PD, which is characterized by the degeneration of dopaminergic neurons in the substantia nigra and the pathologic presence of abnormal cytoplasmic inclusions, Lewy bodies, containing alpha-synuclein. PD is classically described as a movement disorder, with bradykinesia, resting tremor, rigidity, and postural instability [35]. More recently, however, it is being thought of as a multi-system disorder, where neuroinflammation and immune dysfunction play a major role, and with non-motor symptoms such as sleep and mood disorders [36] and gastrointestinal dysfunction [37] preceding motor manifestations. Many PD patients also develop dementia in the later stages of the disease.

PET imaging of neuroinflammation in PD patients was first reported by Gerhard et al. who showed increased [^{11}C]-PK11195 binding, although the degree of microglial activation did not correlate with clinical severity or putaminal [^{18}F]-DOPA uptake [38]. A study using a second-generation ligand ([^{18}F]-FEPPA), however, showed no effect of disease or disease x TSPO genotype interaction on ligand binding in any brain region [39]. Interestingly, the same group subsequently showed an interaction between neuroinflammation and amyloid deposition in PD with cognitive decline. They noted that further research is needed to determine whether amyloid deposits cause neuroinflammation and further neurodegeneration, or if increased microglia activation is a protective response [40]. These results likely overlap with prior work showing neuroinflammation in AD.

Using another second-generation ligand, [^{18}F]-DPA714, a third group showed binding that suggested neuroinflammation in the nigrostriatal pathway, more so on the more affected side. However, this did not correlate with symptom severity, dopamine transporter (DAT) binding or disease duration. In the frontal cortex, neuroinflammation did correlate with disease duration [41]. The authors suggested this discrepancy between regions could reflect spreading of pathology in the later stage of the disease [41]. Finally, a study published in 2019 using [^{11}C]-PBR28 in PD patients showed no neuroinflammation despite DAT imaging demonstrating dopaminergic degeneration [42].

A recent meta-analysis of neuroinflammation studies in PD clearly showed the effect of ligand choice on the results. While neuroinflammation was seen in multiple brain regions using [^{11}C]-PK11195, only the midbrain showed significant increases when second-generation ligands were used [43]. Heterogeneity in results was found in many brain regions. This could be due to different ligands, different analysis approaches (e.g., the use of the cerebellum as a reference region), or suboptimal reporting of detailed clinical variables. Of note, the nonspecific binding of [^{11}C]-PK11195 has been reported to be lower in PD patients; this could affect the results of certain analysis methods [44]. Therefore, there is a need for a more uniform approach to performing PET studies and for using large-cohort longitudinal studies to better understand the role of neuroin-

flammation in PD pathophysiology and progression.

Neuroinflammation imaging has been performed to a lesser extent in other NDDs. In Huntington's disease, for example, several studies identified neuroinflammatory changes, mainly in the globus pallidus and putamen in affected patients [45–47]. In one study, even premanifest HD gene carriers showed increased TSPO expression, although the changes were not significant when compared to controls and affected subjects [46]. In another study, the authors observed further distinct regional and subregional imaging features, which seemed to correspond to phenotypical variability [45]. Imaging studies using first- and second-generation TSPO ligands also identified neuroinflammatory changes in progressive supranuclear palsy patients [23, 48, 49]. In a study by Palleis et al., patients with corticobasal degeneration were also included and showed even more extensive inflammatory changes compared to progressive supranuclear palsy (PSP) subjects. TSPO upregulation, however, was not correlated with measures of disease progression in either PSP or corticobasal degeneration [49]. This contradicts the findings of Malpetti et al., where neuroinflammation (measured with [^{11}C]-PK11195) and tau burden in the brainstem and cerebellum correlated with the subsequent annual rate of PSP disease progression [50]. Additional work is thus needed to better understand the interaction between neuroinflammatory changes and disease progression in different NDDs.

Conclusions

The use of TSPO as an imaging target in NDDs and other CNS diseases remains challenging at multiple levels, and the interpretation of study results should be done with caution. A better understanding of the cellular regulation of TSPO expression and how it changes in relationship to disease progression in NDDs might help determine whether TSPO is an appropriate marker for those diseases, especially AD [51]. Meanwhile, alternative biological targets and radioligands for imaging neuroinflammation are being developed and may prove superior in the assessment of pro- and anti-inflammatory activity in NDDs [52]. One such radioligand is ^{11}C-BU99008, a novel PET tracer that selectively targets activated astrocytes. A recent study showed higher ^{11}C-BU99008 uptake in eight amyloid positive subjects compared to nine controls in the frontal, temporal, medial temporal, and occipital lobes (regions with high Aβ load) as well as across the whole brain [53], suggesting activated astrocytes in those locations. Other promising targets for imaging neuroinflammation that could be used to evaluate NDDs include cyclooxygenases [54–57], purinergic receptors [58], cannabinoid receptors [59, 60], colony stimulating factor receptor (CSF-1R) [61], inducible nitric oxide synthase (iNOS) [62], and triggering receptor expressed on myeloid cells 1 (TREM1) [63, 64].

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