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NEUROIMAGING (DJ BROOKS, SECTION EDITOR)

Neuroinflammation in Neurodegenerative Disorders—a Review

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Abstract The potential for positron emission tomography (PET) to detect neuroinflammation in vivo has sparked a remarkable interest in various disciplines of neuroscience. Early PET radioligands, such as [^{11}C]PK(*R*)-11195 for the 18-kDa translocator protein (TSPO) and [^{11}C]L-deprenyl for monoamine oxidase B, have been used in studies designed to clarify the role of neuroinflammation in a variety of psychiatric and neurological disorders. Recent years have witnessed the development of several second-generation PET radioligands for TSPO and radioligands to measure endogenous targets that are active in various stages of the inflammatory cascade, such as cyclooxygenase and arachidonic acid. Here, we discuss some of the biomarkers for neuroinflammation that are available for quantification with PET, as well as recent findings from studies where neuroinflammation has been assessed in neurodegenerative disorders. In addition, we highlight the challenges to accurate interpretation of PET studies of neuroinflammation.

Keywords Positron emission tomography · Inflammation · Translocator protein · Neurodegeneration

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Introduction

Neuroinflammation

Neuroinflammation—or more specifically, activation of the neuroimmune cells microglia and astrocytes into proinflammatory states—has been implicated as a pathological contributor in several neurodegenerative diseases. Many of these diseases are defined pathologically by abnormal accumulation of specific protein species (for instance, paired helical filamental tau-containing tangles in Alzheimer's disease), hence the term "proteinopathy" to describe these disorders. In vitro studies and animal models have shown that many proteinopathies stimulate neuroimmune responses, and consequently, much work has been conducted to elucidate the role of neuroimmune activation in several disorders.

The brain has long been considered an "immunologically privileged" organ, as the peripheral immune cells are thought unable to penetrate the blood-brain barrier. Instead, the glial cells—microglia and astrocytes—are the primary constituents of a dedicated neuroimmune system, and its interaction with the peripheral immune system is poorly understood [1]. The glial cells provide pro- and anti-inflammatory functionality and participate in various functions under basal and disease conditions, including phagocytosis, steroid release, free radical reduction, and cellular repair. Proinflammatory functions, including release of cytokines and reactive oxygen species, may damage healthy neurons, causing synaptic dysfunction, loss of synapses, and neuronal death. Therefore, an imbalance between proinflammatory and reparatory functions of neuroimmune cells can result in CNS injury. While the damaging effects of such imbalance are recognized in classical neuroimmunological disease such as multiple sclerosis, growing evidence suggests that chronic low-level activation of glial cells may contribute to pathological changes found in many

neurodegenerative diseases. The possibility to quantify the current inflammatory state in a living human brain has sparked a remarkable interest through various disciplines of neuroscience, as it provides means to measure disease severity, study pathophysiological mechanisms, and identify novel targets for treatment (Fig. 1).

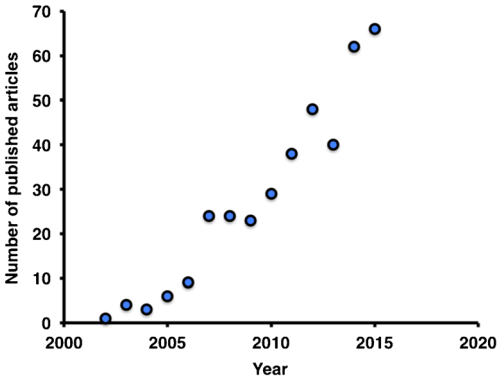

Fig. 1 Number of articles listed in PubMed that have listed as key words both "PET" and either "translocator protein (TSPO)" or "peripheral benzodiazepine receptor (PBR)"—the latter terms referring to a biomarker of inflammation

Positron Emission Tomography

Positron emission tomography (PET) is a molecular imaging modality capable of providing information of brain functionality. PET relies upon the employment of radioactively labeled pharmaceuticals (radioligands) that enter into the living organism. In PET studies of neuroinflammation, pharmaceuticals that bind specifically to 18-kDa translocator protein or monoaminoxidase B are often used, as the concentration of these proteins is believed to reflect ongoing neuroinflammation (discussed below). The PET system provides quantitative images reflecting the spatial and temporal distribution of the radioligand in vivo.

PET imaging comes with several caveats. First, the spatial and temporal resolution associated with emission tomography is limited; thus, small structures are typically not easily quantifiable [2]. Second, the PET system cannot distinguish between different sources of radioactivity. Enzymes in the liver and other tissues break down the pharmaceutical, leading to the generation of radioactive metabolites. If these metabolites enter the brain, they will contribute to the signal, potentially confounding accurate quantification. Another, and often complicated problem, is the presence of nonspecific binding sites. The PET image represents the sum of signals originating from different binding sites, and binding to the specific target of interest represents only a fraction of the signal [3, 4]. For instance, as radiopharmaceuticals must be lipophilic to passively cross the blood-brain barrier, they often bind nonspecifically to the lipid-rich myelin sheaths of white matter tracts. Since it is not always possible to estimate the fraction of specifically bound tracer, a high ratio of specific to nonspecific binding is favorable. Last, full quantification of PET data requires that the concentration of unchanged radioligand in arterial plasma (also known as the input function) is measured during the PET examination. Estimation of the input function necessitates arterial cannulation and specialized staff and instrumentation typically only available in dedicated PET research centers. Consequently, many PET studies rely on simplified acquisition and analysis procedures, often by calculating ratios between different brain regions.

For the subset of radioligands for which there exists a brain region with negligible specific binding to the target of interest (referred to as a reference region), these ratio calculations produce outcome measures that are well-correlated with those obtained from full quantification, omitting the need for arterial sampling [5, 6]. Because the targets currently used for studying neuroinflammation are expressed throughout the brain, no true reference region can be designated. Therefore, quantification using an arterial input function is considered the "gold standard" for PET studies of neuroinflammation.

Biomarkers for Neuroinflammation

The 18-kDa Translocator Protein

The 18-kDa translocator protein (TSPO) is a commonly targeted biomarker with PET [7]. TSPO is a transmembrane protein found mainly in the outer mitochondrial membrane. The protein was formerly called the peripheral benzodiazepine receptor (PBR) because it binds diazepam, and was first discovered as a high affinity receptor for Ro-4864 in kidney, liver, and lung [8]. The name PBR was chosen to distinguish it from the central benzodiazepine receptor. Results from subsequent studies showed that this protein binds to cholesterol and porphyrins and evidence supports a role in transporting substrates across membranes [9, 10]. Therefore, the name was changed to TSPO to avoid confusion with the central benzodiazepine receptor [11]. However, recent reports of viable mice genetically depleted of TSPO have cast doubts on its role in some of these functions [12–16]. TSPO is expressed in low levels in immune-competent cells, macrophages, and leukocytes in the periphery, as well as in microglia and astrocytes [17]. In response to cellular injury, the glial cells become activated and this morphological and functional change results in increased expression of TSPO [18].

Increased TSPO density has been observed in several neurological disorders. Not surprisingly, such increases are evident in classic neuroimmunological disorders such as multiple sclerosis and HIV encephalopathy [19]. Increased TSPO density has however also been demonstrated in brain tissue from patients with neurodegenerative diseases.

Monoamine Oxidase B

The monoamine oxidases (MAO) A and B are isoenzymes, functioning by oxidatively deaminating neurotransmitter and xenobiotic amines [20]. The subtype MAO-B hydrolyzes trace amine, phenylethylamine, and dopamine, and as a by-product, reactive oxygen species are excreted which in excessive concentrations have damaging effects [21]. MAO-B expression increases with age, which is thought to contribute to age-related neurodegeneration [22, 23].

There is evidence that astrocytes play an important role in regulating MAO-B activity under normal and pathological conditions [24–27]. Thus, it has been hypothesized that the concentration of MAO-B can reflect the current state of astrocytosis, which in turn serves as a biomarker for ongoing neuroinflammation.

Other Targets

Besides TSPO and MAO-B, a few other targets have been used in PET studies of neuroinflammation. Arachidonic acid (AA) is polyunsaturated omega-6 fatty acid, highly abundant in the phospholipid bilayer membranes in the brain, where it serves as a second messenger involved in the regulation of several signaling enzymes. The cascade by which regulatory compounds (prostaglandins) are formed from the breakdown of AA was awarded the Nobel Prize in 1982, and today, it is widely accepted that AA plays an important role in the inflammatory response. For the CNS specifically, binding of microglial derived cytokines to calcium channel coupled receptors on astrocytes results in activations of phospholipase enzymes that liberate AA from membrane lipoproteins. Thus, the mobilization of AA has been suggested to be a useful biomarker of neuroinflammation.

Cyclooxygenases (COX) are enzymes that catalyze the breakdown of AA into prostaglandins. The two isoforms (COX-1 and COX-2) are constitutively expressed in the mammalian brain but not co-localized. Under normal circumstances, COX-1 is predominantly found in microglia and some vascular tissue, whereas COX-2 is expressed postsynaptically, predominantly in neurons in the cortex, amygdala, and hippocampus [28]. COX is believed to be involved in the inflammatory cascade, and inhibition of the enzymes is often used for therapeutic anti-inflammatory treatment. Upregulation of COX has thus been suggested as a biomarker for neuroinflammation.

Radioligands for Neuroinflammation

Radioligands for TSPO

The prototypical PET radioligand for TSPO is [^{11}C](*R*)-PK11195. [^{11}C](*R*)-PK11195 has TSPO antagonist properties based on thermodynamic studies [29] and binds to TSPO within a tryptophan-rich pocket [30]. Autoradiography studies have shown an increase in [^{3}H]PK11195 binding in Alzheimer's disease (AD) patients, particularly in areas of reduced choline acetyltransferase activity [31, 32]. Radiolabeling with ^{11}C has allowed in vivo detection of TSPO expression, and numerous clinical PET studies have been performed using this radioligand in neurodegenerative diseases.

While [^{11}C](*R*)-PK11195 is the most highly represented TSPO radioligand in the literature, this radioligand has limitations. [^{11}C](*R*)-PK11195 has high lipophilicity, which promotes nonspecific binding to lipids in the brain [33]. In addition, [^{11}C](*R*)-PK11195 may bind to the acute phase reactant α1-acid glycoprotein [34]. Due to low amounts of TSPO under normal conditions, nonspecific binding can represent a significant contribution to the PET signal. A pharmacological blocking study using nonlabeled PK11195 showed that specific binding of [^{11}C](*R*)-PK11195 in monkey brain is only 1.3 times the nonspecific binding [35], and thus, nonspecifically bound radioligand cannot be assumed to be negligible.

Several second-generation TSPO radioligands have been developed [36], and most have lower lipophilicity than [^{11}C](*R*)-PK11195 and improved specific to nonspecific binding. However, a limitation shared by all tested second-generation radioligands is differential affinity to TSPO dependent on the polymorphism expressed. This was first discovered with [^{11}C]PBR28, where a 40-fold difference in in vitro binding affinity was observed between "binders" and "nonbinders" [35]. Displacement assays later revealed a trimodal distribution of binding, classified as high, mixed, and low affinity binders (HABs, MABs, LABs) [37, 38]. Clear association between LAB and the rs6971 SNP led to the conclusion that this SNP is causing the differential binding [39]. Since the rs6971 SNP confers codominant expression, heterozygotes have reduced [^{11}C]PBR28 binding, while homozygotes have negligible binding. Determination of binding affinity, through genotype analysis or in vitro binding assay, must therefore be performed. The differential affinity can be accounted for statistically, allowing inclusion of HABs and MABs in clinical studies [40]. However, requisite exclusion of LABs, which make up ~9% of subjects of European and African American descent, is disadvantageous. To date, all tested second-generation radioligands are sensitive to this SNP [37].

In addition to the aforementioned radioligand [^{11}C]PBR28, other second-generation radioligands include [^{18}F]PBR06, [^{18}F]PBR111, [^{18}F]DPA-714, [^{18}F]FEPPA, [^{11}C]DAA1106, and [^{11}C]ER176 (see [41] for a review).

Radioligands for MAO-B

Much work has been done to develop PET radioligands for MAOs [42]. To develop radioligands with affinity for only one isoform has proven challenging, and there currently exists only

one reliable radioligand for MAO-B. L-deprenyl (selegiline) is a MAO-B inhibitor and its radiolabeled form [^{11}C]L-deprenyl was first applied in clinical applications in humans in 1987 [43]. Irreversible [^{11}C]L-deprenyl binding, however, induces problems when quantitating uptake [44], which motivated the development of a deuterium analogue, [^{11}C]L-deprenyl-D2, with more favorable pharmacokinetics. Although other radioligands are being developed [45, 46], [^{11}C]L-deprenyl-D2 is today the preferred radioligand for MAO-B [47].

Radioligands for Arachidonic Acid and COX

In contrast to radioligands for TSPO or MAO-B, in vivo PET studies targeting AA use radiolabeled AA itself as a marker of the compound turnover, rather than studying its binding sites [48, 49]. AA is involved in several brain functions [50], and thus, altered binding of [^{11}C]AA is not easily interpretable.

The only applied PET radioligand for COX is [^{11}C] ketoprofen and its methyl ester, which binds selectively to COX-1 [51]. Several preclinical studies in rats have demonstrated the utility of [^{11}C]ketoprofen to quantify COX-1 levels [52, 53], but for humans, it has only been trialed in healthy volunteers [54] and in a small cohort of AD patients [55]. Unfortunately, this latter study revealed no differences between patients and controls, concluding that [^{11}C]ketoprofen methyl ester is not a suitable diagnostic marker for AD.

With regard to COX-2, none of the evaluated tracers has been found to be useful for the study of neuroinflammation [56–58].

Neuroinflammation in Neurodegenerative Disorders

Alzheimer's Disease

Several studies have implicated neuroimmune responses as a pathological contributor to AD pathophysiology [59–63]. In vitro and animal model studies have shown that β-amyloid and hyperphosphorylated tau aggregation induce proinflammatory conditions [64–68]. Activated microglia and reactive astrocytes are present in AD brain and have been shown to overexpress TSPO when proximal to β-amyloid plaques [19].

Most PET studies using [^{11}C](*R*)-PK11195 have shown increased binding in patients with a clinical diagnosis of AD [69–71]. Studies have reported that cortical [^{11}C](*R*)-PK11195 binding correlates with clinical severity [69–71]. While no association between [^{11}C](*R*)-PK11195 binding and amyloid binding has been observed in cross-sectional studies [71, 72], a recent longitudinal study showed that an increase in [^{11}C](*R*)-PK11195 binding correlated with an increase in amyloid burden over time [73•].

Some studies have reported no difference in [^{11}C](*R*)-PK11195 binding between AD patients and controls [74–76]. In one such study, the "controls" included seven patients with unilateral gliomas, and the unaffected hemisphere was used as comparison data [74]. Another study showed no difference between controls and patients in the prodromal stage of AD—i.e., mild cognitive impairment (MCI)—regardless of whether the MCI patients progressed to dementia or remained clinically stable [76]. This study also found no correlation between [^{11}C](*R*)-PK11195 binding and cognitive scores.

These conflicting results could be due to several factors. First, none of the above studies used absolute quantification of [^{11}C](*R*)-PK11195 binding. Instead, clinical [^{11}C](*R*)-PK11195 studies often identify a "pseudo-reference" region by extracting clusters of the subject's PET voxels whose pharmacokinetics resembles that of nondisplaceable binding in normal gray matter. Although the technique appears useful in some cases, the reference region inevitably includes TSPO, and the resulting underestimation bias may reduce sensitivity to detect group differences. Second, the derivation of the reference cluster relies on predefined kinetic classes obtained from previous PET studies, sometimes even from other PET centers. Differences in instrumentation and injection protocol can influence the cluster pharmacokinetics, and it is therefore unclear how valid a representation of nonspecific binding is provided. Finally, the cost of PET often limits the number of subjects for imaging, and false negative results from underpowered studies are probable.

Some studies using second-generation TSPO radioligands have been conducted. First, [^{11}C]PBR28 binding was found to be greater in amyloid-positive AD patients than amyloid-positive MCI patients or controls, particularly in temporo-parietal regions [77]. [^{11}C]PBR28 binding correlated with volume loss and several cognitive indices, but not with amyloid load. These findings were later confirmed in a larger follow-up study that also indicated that the cerebellum could be useful as a pseudo-reference region [78•].

Autoradiography studies reported increased [^{3}H]DAA-1106 binding in brain tissue from transgenic AD mice [79] and AD patients [80, 81], although no correlation with clinical severity was observed [81]. Further, increased [^{11}C]DAA-1106 binding has been seen in the striatum and several cortical structures in MCI and AD patients [82]. Interestingly, only the MCI patient with the lowest level of [^{11}C]DAA-1106 at baseline did not covert to dementia. While the [^{11}C]DAA-1106 studies were performed without correction for TSPO genotype, the low prevalence of rs6971 SNP in Japanese suggests that these results may not have been confounded by physiological affinity differences.

In contrast to [^{11}C]DAA-1106, [^{18}F]FEDAA1106 did not detect differences between AD patients and controls [83]. These results could be due in part to (a) selection of relatively mildly affected patients and (b) an absence of correction for TSPO genotype. In contrast to the [^{11}C]DAA-1106 study, subjects who had [^{18}F]FEDAA PET were recruited from centers in Sweden and so more likely to carry the rs6971 SNP.

Three longitudinal studies using TSPO radioligands have been performed in AD to determine how neuroinflammation changes during disease progression. However, each study used a different radioligand. Studies using [^{11}C](*R*)-PK11195 and [^{11}C]PBR28 showed that TSPO binding increases with progression of AD [73•, 84]. Kreisl et al. [84] also found that patients who showed clinical progression at follow-up had greater increase in [^{11}C]PBR28 binding than patients who remained clinically stable. A study using [^{18}F]DPA-714 found that baseline TSPO binding was greater in both MCI and AD patients than in controls [85]. Somewhat contrary to studies using [^{11}C]PBR28, the study of Hamelin et al. [85] found greater baseline binding of [^{18}F]DPA-714 in the most mildly affected patients and in those who had slower progression of disease. Larger studies involving serial imaging with harmonized TSPO imaging methodology will likely be necessary to clarify the relationship between TSPO and progression of Alzheimer's disease.

PET studies using [^{11}C]L-deprenyl have repeatedly shown elevated binding in AD and MCI patients [86–89], indicating an early presence of astrocytosis in AD pathogenesis. [^{11}C]L-deprenyl has also been used to assess the levels of MAO-B inhibitor binding by potential neuroprotective agents such as EVT301 [88] and sembragiline [90], in a bid to slow disease progression.

With the exception of the aforementioned study which concluded that [^{11}C]ketoprofen methyl ester is not useful [55], no study has to our knowledge been conducted assessing COX in AD.

The only study where [^{11}C]AA was used in humans [91] showed higher uptake in the eight AD patients than in nine age-matched controls. Although this indeed provides some support for upregulation of AA in AD, it is not evident how to interpret this finding based on the various roles of AA in the brain.

Synucleinopathies

Synucleinopathies are a collective group of neurodegenerative disorders that share a common proteinopathy. Abnormal accumulation of α-synuclein is associated with loss of synapses and neuronal death, with the location of the proteinopathy determining the clinical phenotype. In Parkinson's disease (PD), α-synuclein aggregates target dopamine neurons in the midbrain, forming Lewy bodies [92]. In dementia with Lewy bodies (DLB), these aggregates are additionally found in neurons in the cerebral cortex where they are associated with cognitive impairment, hallucinations, and neuropsychiatric symptoms [93]. In multiple system atrophy (MSA), aggregates are found primarily in oligodendrocytes in varying proportions in the midbrain, brainstem, cerebellum, and basal ganglia [94, 95]. MSA patients therefore develop either a Parkinsonian or olivo-ponto-cerebellar disorder. In these disorders, α-synuclein aggregates may be found in additional structures such as olfactory bulb [96], ganglia of the autonomic nervous system [97], and gastrointestinal tract [98].

Increased [^{11}C](*R*)-PK11195 binding was observed in PD patients without cognitive impairment in the pons, basal ganglia, and frontal and temporal cortices [99]. Of the 18 patients included, 8 were followed for 2 years and, at follow-up, had no change in [^{11}C](*R*)-PK11195 binding despite their disability rating with the Unified Parkinson's Disease Rating Scale worsening from 19 to 25.

In a study comparing [^{11}C](*R*)-PK11195 binding in patients with PD and Parkinson's disease dementia (PDD), both PD and PDD patients showed binding that was elevated in frontal, temporal, and occipital cortices, and inversely correlated with Mini Mental State Exam score among the PDD patients [100]. [^{18}F]FDG imaging in the same cohort showed areas of hypometabolism that overlapped with [^{11}C](*R*)-PK11195 binding.

When comparing patients with PD and DLB, [^{11}C](*R*)-PK11195 binding was increased (compared to controls) in basal ganglia and substantia nigra for both patient groups [101]. DLB patients had additional increases in the cortex and cerebellum. All patients were within 1 year of symptom onset, suggesting that increases in TSPO density can be seen in the early stages of disease.

Increased [^{11}C](*R*)-PK11195 binding has also been reported in MSA patients in the cortical, subcortical, and brainstem regions [102]. In a clinical trial, two out of three patients treated with minocycline for 24 weeks showed lower [^{11}C](*R*)-PK11195 binding at follow-up, while elevated binding was observed in most placebo-treated patients [103].

[^{11}C]PBR28 has been used in clinical drug trials to determine target engagement of novel anti-inflammatory therapeutics in patients with PD. In a phase 2 study [104•], 24 PD patients received either placebo or treatment with AZD4231, an irreversible myeloperoxidase inhibitor. In the treated patients, [^{11}C]PBR28 binding was 13–16% lower at 4 and 8 weeks than at baseline, whereas it remained unchanged in patients given placebo, suggesting that myeloperoxidase inhibition reduces TSPO expression. Whether [^{11}C]PBR28 binding is diffusely increased in the brain in PD is not yet known, although a study using [^{18}F]FEPPA reported no difference [105].

To our knowledge, no PET studies using radioligands for MAO-B or COX-1 have been undertaken to study α-synucleinopathies.

Frontotemporal Lobar Degeneration and Related Tauopathies

The term frontotemporal lobar degeneration (FTLD) refers to a collection of diseases that cause synaptic dysfunction and neuronal loss in the frontal and temporal lobes and are pathologically distinct from AD and the α-synucleinopathies. Clinical designations include behavioral variant frontotemporal dementia, progressive nonfluent aphasia, and

semantic dementia [106, 107]. Sporadic and familial forms of FTLD often, but not always, result from aggregation of abnormal tau filaments [108–113]. Primary progressive palsy and corticobasal gangiolonic degeneration, collectively labeled "Parkinson's plus" disorders due to their shared nigrostriatal cell loss, are pathologically defined by tau aggregation and therefore often considered in the FTLD spectrum [114].

Increased [^{11}C](*R*)-PK11195 binding was reported in five patients with a clinical diagnosis of FTLD [115], but the quantification was performed without either blood sampling or use of a valid reference region. In another study, four patients with CBD showed increased [^{11}C](*R*)-PK11195 binding in the striatum, brainstem, and several cortical regions [116]. In a similarly powered study, four patients with progressive supranuclear palsy (PSP) showed increased [^{11}C](*R*)-PK11195 in the striatum, thalamus, brainstem, cerebellum, and frontal lobe [117]. In these two studies, the primary visual cortex and occipital white matter were used as references for nonspecific binding, as the authors claimed that these regions are unaffected in CBD and PSP, albeit not free from TSPO. This methodology is prone to biased outcome measures. Nevertheless, the location of increased binding overlapped with distribution of tau pathology commonly seen in CBD [118]. To our knowledge, no PET study using second-generation radioligands for TSPO, or any radioligands for MAO-B or COX-1, has been conducted in patients with frontotemporal lobar degeneration or related taupathies.

Huntington's Disease

Huntington's disease (HD) is an autosomal dominantly inherited disorder, caused by a mutation in the IT15 gene. The mutation causes abnormal accumulation of the huntingtin protein, leading to gradual neuronal damage [119]. Activated microglia have been found in vitro to be upregulated in the striatal, hypothalamic, thalamic, and cortical brain regions in all grades of pathology [120]. All PET studies to date have been conducted using [^{11}C](*R*)-PK11195, and the data acquired without arterial input functions. Instead, cluster-based approaches to identify a pseudo-reference tissue have been employed, resulting in semiquantitative outcomes.

Two different studies carried out by the same group showed increased levels of [^{11}C](*R*)-PK11195 binding in both premanifest gene carriers and symptomatic patients [121, 122]. When the combined data from these studies were reanalyzed, the authors concluded that hypothalamic dysfunction may be related to the nonmotor-related symptoms of HD [123]. Using an independent cohort, the group later showed very little change in [^{11}C](*R*)-PK11195 binding between presymptomatic gene carriers and symptomatic patients, suggesting that microglia activation is primarily an early contributor to the pathophysiology of HD and does not increase further during disease progression [124]. To our knowledge, no PET study in HD has been conducted using second-generation radioligands or arterial sampling to accurately quantify TSPO levels in vivo. Although the existing PET studies indeed corroborate the in vitro findings, the same group has conducted all studies.

Amytrophic Lateral Sclerosis

Amytrophic lateral sclerosis (ALS) is characterized by the gradual degeneration of motor neurons, commonly over up to 5 years. No effective treatment strategies exist; thus, the disease typically progresses until death occurs due to respiratory failure. Although the role of neuroinflammation in ALS is unknown, there is evidence for associated microglial activation [125].

The first published PET study in ALS showed greater [^{11}C](*R*)-PK11195 binding in patients than controls in motor cortex, pons, dorsolateral prefrontal cortex, and thalamus [126]. Although quantification was conducted without blood samples, the binding correlated with upper motor neuron symptoms and supports a previous autoradiography study [127].

Second-generation TSPO radioligands have also been used in ALS. Increased [^{18}F]DPA-714 binding was found in cortical regions of ten ALS patients, six of which had a bulbar presentation [21]. In another study, ten ALS patients showed increased [^{11}C]PBR28 binding in their precentral gyrus [128]. When the cohort was stratified (limb onset vs. bulbar), the seven patients with limb-onset weakness were found to account for the increased binding. Also, [^{11}C]PBR28 binding in the precentral gyrus correlated with upper motor neuron burden score and negatively correlated with functional status.

The [^{18}F]DPA-714 study used a cluster-based approach to derive a reference region (similar to many [^{11}C](*R*)-PK11195 studies). The [^{11}C]PBR28 study normalized the uptake in precentral gyrus over a 60–90-min scan duration to the total brain uptake. Therefore, a global upregulation of activated microglia will reduce the effect size observed between the groups. Similarly, global downregulation of TSPO among ALS patients could result in erroneously elevated outcome measures among this group. Although reduction of TSPO can be deemed unlikely in ALS, the tendency to omit acquisition of arterial blood data obstructs clear interpretation of the results. To our knowledge, no studies targeting MAO-B, COX-1, or AA in ALS have been performed.

Conclusion

Evidence suggests that neuroimmune activation, defined as activation of microglia and astrocytes, occurs in a number of neurodegenerative diseases. Such responses do not necessarily reflect a primary role of these glial responses in pathogenesis or even a negative role as a downstream effect. However, increased densities of TSPO and MAO-B and, to some extent,

turnover of AA appear to be valid markers of these responses, and measuring these biomarkers with PET is possible with several available radioligands. Continued use of PET to quantify neuroinflammation, particularly in longitudinal studies, promises to clarify the role of neuroimmune activation in the pathophysiology of several neurodegenerative diseases and the utility of improved anti-inflammatory treatments.

Compliance with Ethical Standards

Conflict of Interest Martin Schain and William Charles Kreisl declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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