HHS Public Access

Author manuscript

Lancet Neurol. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

Lancet Neurol. 2020 November ; 19(11): 940–950. doi:10.1016/S1474-4422(20)30346-X.

PET Imaging of Neuroinflammation in Neurological Disorders

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Summary

A growing need exists for reliable in vivo measurement of neuroinflammation to better characterize the inflammatory processes underlying various diseases and to inform the development of novel therapeutics that target deleterious glial activity. Positron emission tomography (PET) is well suited to quantify neuroinflammation and has the potential to discriminate components of the neuroimmune response. However, PET imaging is not currently used to measure neuroinflammation in clinical practice, in part because of the complexity of the brain's varied immune responses and the technical challenges associated with reliable quantification. Despite these challenges, PET studies have consistently identified associations between neuroimmune response and pathophysiology in Alzheimer's disease and chronic traumatic encephalopathy. Recently, positive results have been observed with second-generation radioligands as markers of immune response in immune-mediated diseases, such as multiple sclerosis and HIV-related cognitive impairment, as well as in neurodegenerative disorders, epilepsy, and stroke. A small but growing number of studies have similarly suggested that PET imaging of neuroinflammation could play a role in drug discovery. However, interpreting

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Author Contributions

All authors contributed equally to the literature search, generation of figures, writing, and revision of this manuscript. All authors approved the final version of the paper.

Declaration of Interests

Disclosures

All authors have no conflict of interest to disclose, financial or otherwise.

Search Strategies and Selection Criteria

References for this review were identified by searching PubMed between 2015 and 2020 and by further examining the reference lists from relevant articles. Combinations of the following search terms were used: "PET", "TSPO", "translocator protein", "peripheral benzodiazepine receptor", "inflammation PET", "microglia PET", "Alzheimer's disease", "progressive supranuclear palsy", "corticobasal degeneration", "dementia", "Huntington's disease", "multiple sclerosis", "TBI", "CTE", "HIV", "HAND", "epilepsy", "stroke", "Parkinson's disease", "dementia with Lewy bodies," and "amyotrophic lateral sclerosis". There were no language restrictions. Only references published within the last five years were included, except for key or landmark studies in the field. In addition, we limited disorders to those for which there was at least one positive study using a second-generation TSPO radioligand. The final reference list was generated on the basis of relevance to the theme of this review.

neuroinflammation PET studies remains somewhat controversial because of limited understanding regarding the cellular mechanisms that underlie changes in PET signal. Future studies are needed to improve our knowledge of how immune response contributes to neurological disease and how it might be therapeutically modified.

1.0 Introduction

Recent discovery of glial-expressed risk variants associated with neurodegenerative diseases[1], coupled with increasing evidence supporting neuroimmune modulation as a strategy for drug development, underscore the critical need for reliable in vivo measurement of neuroinflammation, which would enable research into the neuroimmune mechanisms that contribute to neurological disease and inform clinical trial design. Due to its ability to measure select proteins at low concentrations, positron emission tomography (PET) is particularly well-suited to quantify neuroinflammation and has the potential to discriminate components of the neuroimmune response (Figure 1). However, obstacles to reliable PET measurement of neuroinflammation include misperceptions and limitations regarding 18 kDa translocator protein (TSPO; the most common neuroinflammatory target), such as high nonspecific binding and sensitivity to a genetic polymorphism that affects binding affinity of early TSPO radioligands, as well as a paucity of non-TSPO targets with validated radioligands. In addition, the only validated non-TSPO target in recent use is the astrocyte-expressed protein monoamine oxidase B (MAO-B), which has its own limitations (e.g., expression by neurons).

Fortunately, there are several reasons for optimism. First, combining TSPO PET with other biomarkers has provided insights into the temporal and spatial relationships between neuroinflammation and the canonical pathologies underlying brain disorders such as Alzheimer's disease. Second, tissue studies have begun to clarify the meaning of increased TSPO PET signal in certain diseases. Third, improved TSPO radioligands, particularly [^{11}C]ER176, have overcome some of the major disadvantages of earlier tracers. Finally, novel non-TSPO targets are under investigation, and several radioligands are in various stages of early development.

This review provides a critical assessment of the role of PET imaging of neuroinflammation in neurological disorders. Rather than provide an exhaustive, historical list of all published PET studies, the review only discusses disorders for which at least one positive study was conducted using a second-generation TSPO radioligand. These include multiple sclerosis (MS), HIV-associated cognitive impairment, Alzheimer's disease (AD), frontotemporal dementia, chronic traumatic encephalopathy (CTE), Huntington's disease, amyotrophic lateral sclerosis, epilepsy, and stroke. Other disorders such as corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies were excluded because they have not yet been studied with second-generation TSPO radioligands. In addition, only negative studies using second-generation radioligands in Parkinson's disease (PD) have been published; however, the possible role of TSPO PET in drug discovery for PD is discussed. Disorders are discussed based on similarities in terms of proposed relatedness to

neuroinflammatory response. Classic immune-related disorders are discussed first, followed by neurodegenerative disorders, and then epilepsy and stroke.

2.0 Overcoming obstacles to identifying neuroinflammation using PET imaging

In our experience, the major obstacles to reliable PET measurement of neuroinflammation include misperceptions regarding TSPO as a biomarker, the limitations associated with early TSPO radioligands, and the paucity of non-TSPO targets with validated radioligands. Fortunately, recent multimodal imaging and tissue studies have increased our understanding of the meaning of the TSPO PET signal, and radioligand development has improved the ability to measure TSPO in vivo.

Although widely used as an inflammatory biomarker, TSPO has important caveats that require consideration to avoid misinterpreting PET imaging results. First, while TSPO is predominantly expressed in brain by microglia,[2] expression by other cell types must be considered. TSPO was originally found in peripheral tissue,[3] and is also expressed in brain by astrocytes[4] and vascular endothelium.[5] Migration of peripheral myeloid cells into brain can also contribute to the TSPO signal.[6] Therefore, the relative contribution of TSPO radioligand binding by microglia versus other cells depends on the disease studied. For example, some,[7, 8] though not all,[9] autopsy studies have shown that microglia are the predominant TSPO-positive cells in the brain of individuals with AD. Similarly, TSPO in human MS lesions is mostly expressed in microglia but also in astrocytes, though to a lesser extent.[5] However, disease stage can, in some cases, also influence cellular expression of TSPO. For instance, in an experimental stroke models in rats, TSPO-expressing microglia were first found in the ischemic lesion; days later, TSPO-expressing astrocytes were found in the surrounding area.[10] In addition, the meaning of increased TSPO binding remains controversial, even within the proportion of signal due to microglia. Rodent studies found that increased TSPO expression signals a shift from resting to activated morphology in microglia, resulting in the widely held view that increased TSPO binding equates to microglial activation.[11] However, human tissue studies do not necessarily support this view. Pro-inflammatory conditions did not increase TSPO expression in a study using human microglia, suggesting that radioligand binding may reflect microglial density rather than microglial phenotype.[12] Furthermore, while human autopsy studies identified TSPO-expressing microglia proximal to neuritic plaques in the AD brain,[7, 8] one AD study demonstrated that area fraction of TSPO immunoreactivity did not correlate with that of microglial activation (defined as CD68 immunoreactivity).[9] In addition, while increased TSPO immunoreactivity was detected in brain and spinal cord tissue from individuals with MS, TSPO was found in both pro-inflammatory and anti-inflammatory microglia (defined by co-expression of CD40 or CD206, respectively).[5] Nevertheless, immunohistochemistry results do not always agree with PET results. TSPO antibodies attach to the C terminus of the target protein, while radioligands bind to its active site. Furthermore, autoradiography and PET represent the available number of binding sites, not just the total amount of protein, and both techniques are inherently more quantifiable than immunostaining. Therefore, while TSPO binding should not be broadly assumed to reflect the extent of microglial activation,

disease- and species-specific tissue studies should guide the interpretation of increased TSPO signal.

Another challenge intrinsic to TSPO PET is determining which radioligand to use, given the tracers available and their varying limitations. The prototypical radioligand [^{11}C]-(*R*)-PK11195 has low signal-to-noise ratio, which limits its ability to detect subtle changes in TSPO density.[13] While second-generation radioligands have improved ratios of specific-to-nonspecific binding, they are sensitive to a common polymorphism (rs6971) in the *TSPO* gene.[14] Individuals with two copies of the rare allele (low affinity binders) bind these radioligands with a lower affinity than those with two copies of the major allele (high affinity binders), and heterozygotes (mixed affinity binders) express both high and low binding sites in similar proportions. Thus, individuals with the same TSPO density but different genotypes will produce different PET signals. This obstacle has been addressed by performing *TSPO* genotyping prior to imaging (to exclude low affinity binders) and by including binding affinity as a statistical covariate.[15, 16] One study compared four carbon-11-labeled TSPO radioligands ([^{11}C]-(*R*)-PK11195, [^{11}C]PBR28, [^{11}C]DPA-713, and [^{11}C]ER176) and found that [^{11}C]DPA-713 had the greatest signal-to-noise ratio in human brain.[17] However, [^{11}C]ER176 also had a high signal-to-noise ratio, was least likely to generate brain-penetrant radiometabolites, and was sufficiently insensitive to the rs6971 polymorphism to allow reliable TSPO measurement in low affinity binders.[17] Thus, current evidence suggests that [^{11}C]ER176 is the best available TSPO radioligand. While [^{18}F]GE180 has been described as a “third-generation” TSPO radioligand, this tracer has unfavorable kinetics for human brain imaging due to low penetration into brain from the vascular compartment;[18] thus, we do not advise use of this tracer.

Another potential obstacle for TSPO PET is lack of a true reference region. TSPO is diffusely expressed throughout the brain, and accurate measurement of its density relies on kinetic modeling using the metabolite-corrected arterial input function (AIF). Different methods have attempted to circumvent the need for arterial sampling, including cluster sampling techniques[19] and the use of “pseudo-reference” regions.[20, 21] Although AIF-free methods inherently introduce bias, several such studies have detected increased TSPO in various neurological disorders, with colocalization to abnormalities in other biomarkers.[22, 23] In addition, AIF-free methods often reduce variance caused by inter-subject differences in physiological TSPO expression, thus improving power for statistical analysis.[21] Because binding behavior may differ among different radioligands and diseases, we recommend validating pseudo-reference methods against arterial sampling prior to their application. The diffuse nature of TSPO is less of an issue in focal disorders such as stroke, where contralateral tissue of the same volume can be used for comparison. However, Wallerian degeneration or diaschisis may affect regions distant to focal injury,[24] potentially influencing results.

Finally, although [^{11}C]ER176 has emerged as the preferred TSPO radioligand, TSPO appears to reflect a broad spectrum of immune responses; thus, more precise targeting of inflammatory mechanisms will require novel radioligands for novel biomarkers. The only non-TSPO radioligand in recent usage is [^{11}C]deuterium-L-deprenyl, a radioligand for MAO-B. However, while MAO-B is expressed by astrocytes, it is also expressed by

pyramidal neurons in AD brain,[25] and physiological signal in basal ganglia—due to its high dopamine turnover—may limit sensitivity to detect changes in this region.[26] Novel inflammatory targets include cyclooxygenase-1 (COX-1) and COX-2, colony stimulating factor 1 receptor (CSF1-R), and the P2X purinergic receptor 7 (P2X7R). To date, no radioligand for any of these targets has been fully validated in human disease although each shows promise for more precisely measuring neuroimmune response. Discussion of these emerging targets can be found in our companion review in *The Lancet Psychiatry*.[27] Table 1 summarizes the neuroinflammatory radioligand studies performed in humans in the last five years, noting those using non-TSPO radioligands, arterial sampling, or autopsy tissue, as well as studies in which neuroinflammation PET has been incorporated into clinical trials.

3.0. Neuroimmunological and infectious disorders

3.1 Multiple Sclerosis

Most PET studies quantifying neuroinflammation in MS have used TSPO as the PET target. Numerous studies have found increased TSPO expression in MRI-defined white matter lesions in individuals with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS).[28–31] The fact that white matter lesions, which are indistinguishable on MRI, have different patterns with TSPO PET suggests that TSPO PET can detect pathophysiological heterogeneity to which MRI is insensitive.[28, 29] As may be expected, the molecular changes detected by TSPO PET precede the structural changes detected by MRI.[31] In addition to the higher signal in lesions, non-lesional white matter in MS also shows greater TSPO signal than in age-matched controls.[28, 32, 33] This increase is associated with greater brain atrophy and worse disability.[20, 29, 34] Higher signal also predicts the appearance of new lesions, worsening brain atrophy, and a more severe trajectory of disability worsening over the subsequent 12 months.[20, 28] Increased signal in cortical grey matter has also been detected, which again correlates with disability and cognitive impairment.[32, 34] The effect of standard medications (including glatiramer acetate, fingolimod, and atalizumab) on TSPO signal has been assessed in a handful of studies, all of which have shown modest reductions in the signal in either lesional or non-lesional white matter.[35–38]

While previous neuropathology studies identified activated microglia as the source of TSPO in lesions,[8] a recent comprehensive assessment of post-mortem MS brain demonstrated that TSPO is not preferentially expressed on activated microglia but, rather, is found equally across all microglial phenotypes.[5] Furthermore, although microglia are the main contributors to TSPO signal in white matter lesions, a substantial contribution (~25%) is made from astrocytes and, to a lesser extent, endothelial cells.[5] It should also be noted that TSPO PET studies in MS participants relative to controls identified much smaller differences than might be expected from pathological investigations. This could be due to the relatively small size of the lesions or could reflect differences in the configuration of TSPO between in vitro and in vivo states.

3.2 HIV Cognitive Impairment

Cognitive impairment remains prevalent among individuals infected with human immunodeficiency virus (HIV), including those using effective antiretroviral therapy.[39, 40] Microglial activation and reactive astrocytosis are among the posited contributing factors to

cognitive impairment in HIV. One [^{11}C]-(*R*)-PK11195 PET study found higher regional binding in HIV^{+} participants (cognitively impaired and unimpaired) relative to uninfected controls, with the highest binding observed in those with HIV-associated dementia.[41] A second [^{11}C]-(*R*)-PK11195 PET study found higher binding in cognitively intact HIV^{+} participants compared to uninfected controls,[42] while a third study found no difference between HIV^{+} individuals (cognitively impaired or unimpaired) and controls.[43] For studies using the second-generation radiotracers [^{11}C]DPA-713[44] or [^{11}C]PBR28,[45] higher regional binding was found in virally-suppressed HIV^{+} individuals compared to uninfected controls. Those with HIV-associated dementia had higher [^{11}C]DPA-713 binding in frontal cortex,[44] and subsequent analyses using data from HIV^{+} individuals revealed inverse correlations between regional [^{11}C]DPA-713 binding and performance in particular cognitive domains.[46] In HIV^{+} individuals, [^{11}C]PBR28 PET also revealed region-specific (hippocampus, thalamus) associations between higher binding and lower performance in memory and verbal learning.[45] Inconsistencies between these studies may stem from differences between radioligands, clinical characteristics within patient and control groups, and analytic methods. Nevertheless, taken together the data suggest that TSPO may be regionally elevated and linked to domain-specific cognitive impairment in treated HIV.

4.0 Neurodegenerative disorders

4.1 Alzheimer's disease (AD)

Both human and preclinical PET studies have linked neuroinflammation with AD pathology. Most TSPO PET studies have shown increased binding in AD participants compared to controls, particularly in fronto-temporal regions, with more modest increases observed in neocortical regions in individuals with mild cognitive impairment (MCI) (see[47] for a meta-analysis). Presymptomatic carriers of autosomal dominant AD mutations[48] showed increased binding as assessed using [^{11}C]deuterium-L-deprenyl, a radioligand for MAO-B. While these studies suggest astrocytosis as a pathological entity in early-stage AD, MAO-B is also expressed by pyramidal neurons in AD brain.[25] Transgenic AD mouse studies found increased TSPO and MAO-B binding on PET, often confirmed with autoradiography.[49, 50]

The exact pathological stimulus for increased TSPO in AD remains unclear. Studies have observed increased TSPO binding in asymptomatic individuals with incidental amyloid positivity[23, 51] and in participants meeting clinical criteria for amnestic MCI or mild AD with absence of amyloid binding on PET.[23, 52] This suggests that TSPO may increase in response to both amyloid deposition and amyloid-independent neurodegeneration. Multimodal PET studies have looked for spatial correlations between TSPO binding and both amyloid plaque and neurofibrillary tau burden. Studies comparing TSPO and amyloid binding have been inconsistent, showing no correlation,[15, 53] positive correlations,[51, 54–56] and negative correlations.[57] Nevertheless, three of four studies found positive correlations between TSPO and tau binding.[22, 23, 54, 58] One study identified distinct patterns of TSPO binding in different clinical variants of AD,[59] similar to previously reported patterns of tau pathology[60] (Figure 2). Notably, both TSPO and tau binding were increased in younger AD participants than in older ones.[61, 62] Therefore, TSPO may have a stronger relationship with tau than with amyloid, at least during the clinical stages of AD.

Whether increased TSPO binding in the early stages of AD represents a beneficial or maladaptive glial response remains controversial. Cross-sectional studies in AD found that TSPO binding is associated with worse cognitive impairment.[15, 63] In addition, the first longitudinal TSPO PET studies in AD showed overall increased binding as the disease advanced.[61, 64] However, amyloid-positive individuals with MCI had greater [^{18}F]DPA-714 binding than individuals with AD, and greater [^{18}F]DPA-714 binding was associated with higher Mini-Mental State Exam (MMSE) score.[51] Another study found that six of eight individuals with MCI (four of whom were amyloid-negative) showed a mean *reduction* in [^{11}C]-(*R*)-PK11195 binding at follow-up.[65] The authors interpreted these results as evidence for a bimodal pattern of neuroimmune activation in AD, with a beneficial phase of glial behavior occurring prior to dementia onset followed by a detrimental phase of pro-inflammatory glial activity that worsened throughout the dementia stage.[66] In another study, [^{11}C]deuterium-L-deprenyl binding decreased over time in individuals with autosomal dominant AD, although no change was seen in individuals with sporadic MCI.[67] That MCI participants with higher [^{11}C]PBR28 binding had less cortical atrophy on MRI[68] supports the notion that TSPO-expressing microglia may have a beneficial effect early in AD. However, the results from that study could be interpreted another way, given that larger cortical volume is a marker of "brain reserve"—the ability to retain cognitive function despite increasing pathology.[69] In that context, MCI participants with less atrophy could be more resilient to the damaging effects of microglial and/or astrocyte activation, allowing a similar degree of cognitive impairment as those with more atrophy despite greater amounts of TSPO binding. Alternatively, inflammation-induced neuronal and glial swelling could result in increased cell volume, as posited by one [^{11}C]deuterium-L-deprenyl study showing that MAO-B binding was associated with greater cortical thickness.[70] The bimodal hypothesis of TSPO binding in AD progression has not been consistently supported in the literature, given that [^{18}F]DPA-714 binding was found to increase in both MCI and AD participants over time,[55] and several studies have observed a more or less linear increase in PBR28 binding across the clinical AD spectrum.[15, 21, 23]

4.2. Frontotemporal dementia

PET studies have consistently observed increased TSPO binding in individuals with clinically-diagnosed frontotemporal dementia (FTD). Using a reference region method, the first study found that five FTD participants showed an average increase in [^{11}C]-(*R*)-PK11195 binding in left dorsolateral prefrontal cortex, right hippocampus, right parahippocampus, and bilateral putamen compared to eight controls.[71] An [^{11}C]PBR28 study that used arterial sampling found increased binding in four individuals with FTD and further confirmed the lack of comorbid AD pathology with amyloid PET (Figure 3).[72] While participants lacked genetic or neuropathological determination of underlying histopathology, the pattern of [^{11}C]PBR28 binding mirrored that of FDG hypometabolism. In both studies, the patients had varied clinical presentations and patterns of atrophy on MRI. In a larger study, the topographic pattern of [^{11}C]-(*R*)-PK11195 binding discriminated FTD subtypes from each other and from controls.[73] That study also found that, in autopsy tissue, the density of microglia, particularly in those with activated morphology, correlated with the extent of abnormal protein aggregation (phosphorylated tau or TAR DNA-binding protein 43).

4.3 Chronic Traumatic Encephalopathy

Chronic traumatic encephalopathy (CTE) is pathologically defined by deposits of phosphorylated tau in a perivascular distribution, particularly in the depths of cortical sulci.[74] CTE has been found in human brain following traumatic brain injury (TBI), including sports-related, repetitive concussion incurred through American football.[74, 75] Prolonged microglial activation after repeated TBI has been hypothesized to contribute to CTE.[76] Indeed, increased [^{11}C]-(*R*)-PK11195 or [^{11}C]PBR28 binding has been reported in the brains of TBI participants,[77, 78] even years after injury.[79] In addition, higher [^{11}C]DPA-713 binding was found in young NFL players in medial temporal cortex and supramarginal gyrus (Figure 4).[80] Relatively high levels of [^{11}C]DPA-713 binding were also observed in the supermarginal gyrus in a study of older players decades after their last NFL play.[81] Whole brain images included in each [^{11}C]DPA-713 PET study[80, 81] suggested widespread distribution of high TSPO beyond the examined regions of interest. However, the clinical implications of high TSPO signal in former NFL players remain elusive. No cognitive deficits were found in the cross-sectional population of active and recently former NFL players with high [^{11}C]DPA-713 binding.[80] Longitudinal investigation of the relationship between neuroimmune activation marked by high TSPO and TBI-associated behavioral decline is needed.

4.4. Huntington's Disease

The neurodegenerative disorder Huntington's disease (HD) is associated with increased gliosis and expression of glial fibrillary acidic protein (GFAP) and complement proteins, particularly in the striatum.[82] Increased pro-inflammatory cytokines are found in HD gene carriers.[83]

Early PET studies showed that asymptomatic gene carriers and HD participants had increased [^{11}C]-(*R*)-PK11195 binding.[84, 85] In a more recent study, pre-manifest HD carriers had greater [^{11}C]-(*R*)-PK11195 binding in cortical, basal ganglia, and thalamic brain regions;[86] radioligand binding in somatosensory cortex also correlated with plasma concentrations of interleukin-1β (IL-1β), IL-6, IL-8, and tumor necrosis factor (TNF)-α. Second-generation TSPO radioligands have shown similar results. For instance, one study found that HD participants had greater [^{11}C]PBR28 binding in putamen and pallidum than controls (Figure 3);[87] however, arterial sampling was not performed, and only relative [^{11}C]PBR28 binding was reported (using whole brain as a reference region). While a similar approach has been used in [^{11}C]PBR28 studies of chronic pain[88] and amyotrophic lateral sclerosis (ALS),[89] this methodology has not been validated against a "gold-standard" kinetic modeling approach.

4.5 Amyotrophic Lateral Sclerosis

An [^{11}C]-(*R*)-PK11195 study first identified increased TSPO binding in motor cortex and associated brain regions of individuals with ALS,[90] and the finding has since been reproduced using second-generation TSPO radioligands. Interestingly, increased TSPO binding in motor cortex significantly correlated with severity of upper motor neuron symptoms with both [^{11}C]-(*R*)-PK11195 and [^{11}C]PBR28.[89, 90] Furthermore, studies using larger populations of individuals with either ALS or primary lateral sclerosis (PLS) reported

that increased [^{11}C]PBR28 binding in motor cortex also correlated with other MR image parameters such as diffusion tensor imaging and cortical thickness measured both cross-sectionally and longitudinally.[91–93] [^{18}F]DPA714 studies also found increased TSPO binding in the motor cortex, although these did not evaluate correlation with clinical severity.[94] As an extension of these findings, a therapeutic trial using [^{11}C]PBR28 PET as a biomarker of neuroinflammation was conducted in individuals with ALS, but the results identified no difference between pre- and post-treatment TSPO uptake, possibly due to low statistical power.[95] With regard to radioligands targeting other neuroinflammatory mediators than TSPO, a preliminary result with [^{11}C]JNJ717, a P2X7 radioligand, found no such increase in ALS participants.[96]

5.0 Epilepsy

Several PET studies targeting TSPO support the role of neuroinflammation in epileptogenesis or ictogenesis, although most of these studies were based on small sample sizes. Initial case reports with [^{11}C]-(*R*)-PK11195 PET imaging demonstrated a focal increase of TSPO uptake co-localized with the seizure focus;[97, 98] a subsequent study revealed that this uptake had even greater intensity and spatial extent in post-seizure status (~36 hours) compared to the seizure-free period, perhaps due to transient seizure-induced inflammation.[99]

In more extensive studies conducted with second-generation TSPO radioligands, [^{11}C]PBR28 uptake was found to be higher ipsilateral to the seizure focus in 16 participants with unilateral temporal lobe epilepsy (TLE).[100] Using full quantitation of TSPO binding, the same group demonstrated that [^{11}C]PBR28 binding was higher in TLE participants than healthy controls for all ipsilateral as well as some contralateral temporal regions.[101] When the same evaluation was done in participants with neocortical seizure foci, nine of 11 participants had significant asymmetry in seizure foci, although the absolute binding levels in patients did not significantly differ from those in healthy controls.[102]

PET imaging of neuroinflammation in epilepsy has thus far investigated pathophysiology without correlating it with clinical severity or prognosis, suggesting that additional studies with full quantitative methods are needed before clinical application.

6.0 Stroke

Studies using [^{11}C]-(*R*)-PK11195 in acute ischemic stroke observed widespread TSPO binding at the primary infarct site and in the peri-infarct lesions.[103] During the chronic phase, increased TSPO binding also involved sites distant from the primary stroke lesion, perhaps as a result of Wallerian degeneration of neuronal tracts.[103, 104] One case report found increased binding in a subacute lacunar infarction as assessed via [^{11}C]PBR28.[105] Using [^{11}C]vinpocetine, a radioligand that binds with moderate affinity to TSPO but has favorable brain penetration, another study also demonstrated increased TSPO binding in the peri-stroke region for several weeks after ischemic stroke.[106] An [^{18}F]DPA714 study in nine individuals with recent ischemic stroke found co-localized uptake within areas of ischemic

infarction as well as extension beyond the region corresponding to blood-brain barrier damage.[107]

In contrast to such well-reproduced findings in acute or subacute ischemic stroke, hemorrhagic stroke has rarely been investigated with PET imaging of neuroinflammation. One [^{11}C]-(*R*)-PK11195 study reported low uptake in hematomas, with two of five participants showing widespread increases in TSPO binding in the perihematomal region compared to the contralateral hemisphere.[108] However, it remains unknown whether these peri-lesional or distant increases of TSPO are associated with any favorable or unfavorable clinical outcomes.

7.0 Neuroinflammation PET in drug development

Although TSPO PET does not have an established clinical application, evidence supports potential use in drug development. First, TSPO density may predict treatment response in some instances. For example, greater TSPO binding in major depressive episodes was associated with greater reduction of symptoms after treatment with celecoxib,[109] suggesting that TSPO PET may play a potential role in participant stratification, similar to how amyloid PET is currently employed to select participants for AD trials. Second, TSPO has served as a surrogate biomarker in proof-of-concept studies, although some results have been difficult to interpret. For instance, while minocycline treatment led to reduced [^{11}C]PBR28 binding in individuals with brain trauma, it also increased plasma concentrations of neurofilament light chains, raising the question of whether reduced TSPO signal is necessarily beneficial.[78] In another example, after treatment with a myeloperoxidase inhibitor, individuals with PD showed mean reductions in [^{11}C]PBR28 binding in nigro-striatal regions, with a 13·2–15·7% decrease in distribution volume (V_T) from baseline.[110] However, similar decreases were found in all other measured brain regions, indicating a global effect on TSPO binding and raising the question of whether the treatment resulted in a change in microglial (or astrocyte) function or just depletion of TSPO protein. Notably, despite three well-designed studies using [^{11}C]PBR28 or [^{18}F]FEPPA, no second-generation TSPO study has shown increased binding in individuals with PD.[111–113] Conversely, the same myeloperoxidase inhibitor failed to reduce [^{11}C]PBR28 binding in individuals with multiple system atrophy (MSA)[114]. Phase 3 studies are needed to determine whether these changes in TSPO binding equate to clinical efficacy. Emerging non-TSPO biomarkers are also expected to be useful in evaluating novel treatments, particularly those targeting the same protein as the radioligand. For example, CSF1R radioligands could be used for target engagement studies of CSF1R antagonists.

8.0 Conclusions and future directions

While neuroinflammatory PET has largely been limited to targeting TSPO, this imaging modality has far-reaching potential. Although emerging non-TSPO radioligands may soon allow more precise investigation of the mechanisms underlying specific immune response, for the time being TSPO PET remains the most extensively studied method for spatial measurement of neuroinflammation.

In neurology, the most consistent TSPO imaging results have arguably been in: 1) AD, where inflammation may more closely reflect the distribution of tau than of amyloid and where neuroinflammation may have a meaningful—though not necessarily linear—relationship to disease progression; and 2) CTE, where five of five studies of recent or remote TBI found elevated TSPO levels. Yet, discrepancies in the TSPO literature remain, the most striking being in MS, in which a prominent in vitro TSPO signal is nevertheless much less able to be imaged. This and other in vitro/in vivo discrepancies for TSPO could reflect disruption of the in vivo multimeric complex during tissue preparation, as occurs for other multimeric complexes. This phenomenon could be present in other disorders and could explain the subtle genotype effect on in vivo binding to peripheral organs seen with [^{11}C]-(*R*)-PK11195 and [^{11}C]ER176 despite these two radioligands having similar in vitro affinity between high and low affinity binders.[115, 116]

As noted above, TSPO PET has potential for drug development in select instances. For instance, TSPO binding changes over time in AD, is modifiable by minocycline and myeloperoxidase inhibition, predicts response to COX inhibition during major depressive episodes, and is increased in presymptomatic HD mutation carriers. Thus, this imaging modality may have important clinical applications in determining which individuals are most likely to respond to novel drugs and which stage of disease is optimal for treatment.

Overall, our view is that this is a promising time for neuroinflammation PET, in that improved TSPO radioligands may be used as broad markers of immune response. Depending on their success, emerging biomarkers may allow more precise targeting of specific proteins involved in immune response; these could be used alone or in combination to delineate the mechanisms underlying neurological disease. Finally, neuroinflammation PET may be most useful in the context of clinical trials, in terms of both predicting and monitoring response to treatment in early drug discovery.

Acknowledgments

Funding and Role of Funding Source

This study was partly funded by the Intramural Research Program of the National Institute of Mental Health, National Institutes of Health (ZIAMH002852) (to MJK, IDH, and RBI). WCK and JMC received funding from the National Institutes of Health (K23AG052633 to WCK and R01NS100847 to JMC). DRO received funding from the Medical Research Council (MR/N008219/1). These institutions had no further role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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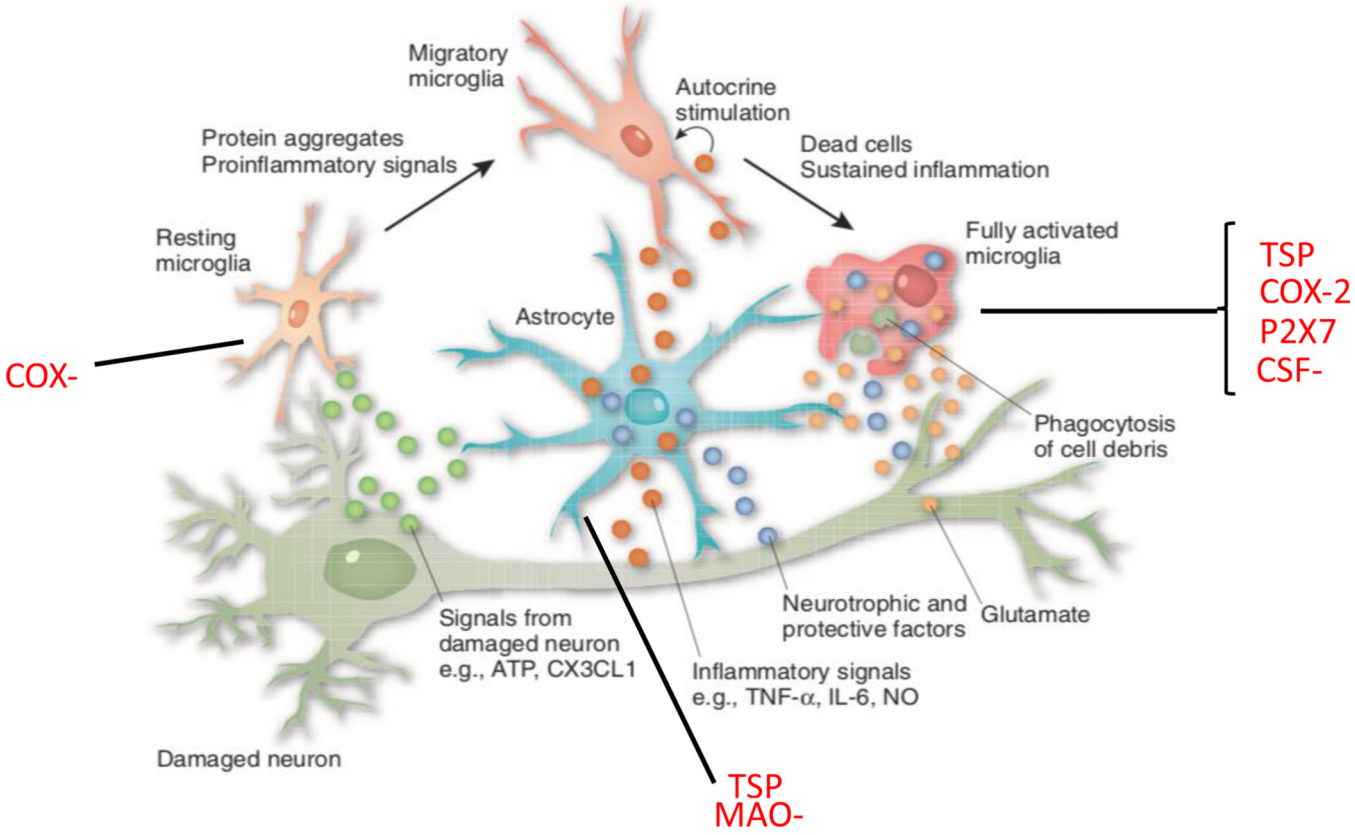

Figure 1. Neuroinflammation

Relationship between neurons and glial cells (microglia and astrocytes). Microglia become activated in response to several immunological signals, including from cytokines and aggregated proteins. This activation may be either protective or toxic for the surrounding glial cells and neurons. Proteins expressed by glial cells are established and proposed targets for positron emission tomography (PET) imaging to quantify neuroinflammation (red text). Abbreviations: ATP: adenosine triphosphate; CX3CL1: CX3C chemokine ligand 1; TNF-alpha: tumor necrosis factor alpha; IL-6: interleukin-6; NO: nitric oxide; TSPO: 18 kDa translocator protein; COX: cyclooxygenase; P2X7R: P2X purinergic receptor 7; CSF-1R: colony stimulating factor 1 receptor; MAO-B: monoamine oxidase B.
Modified with permission from.[128]

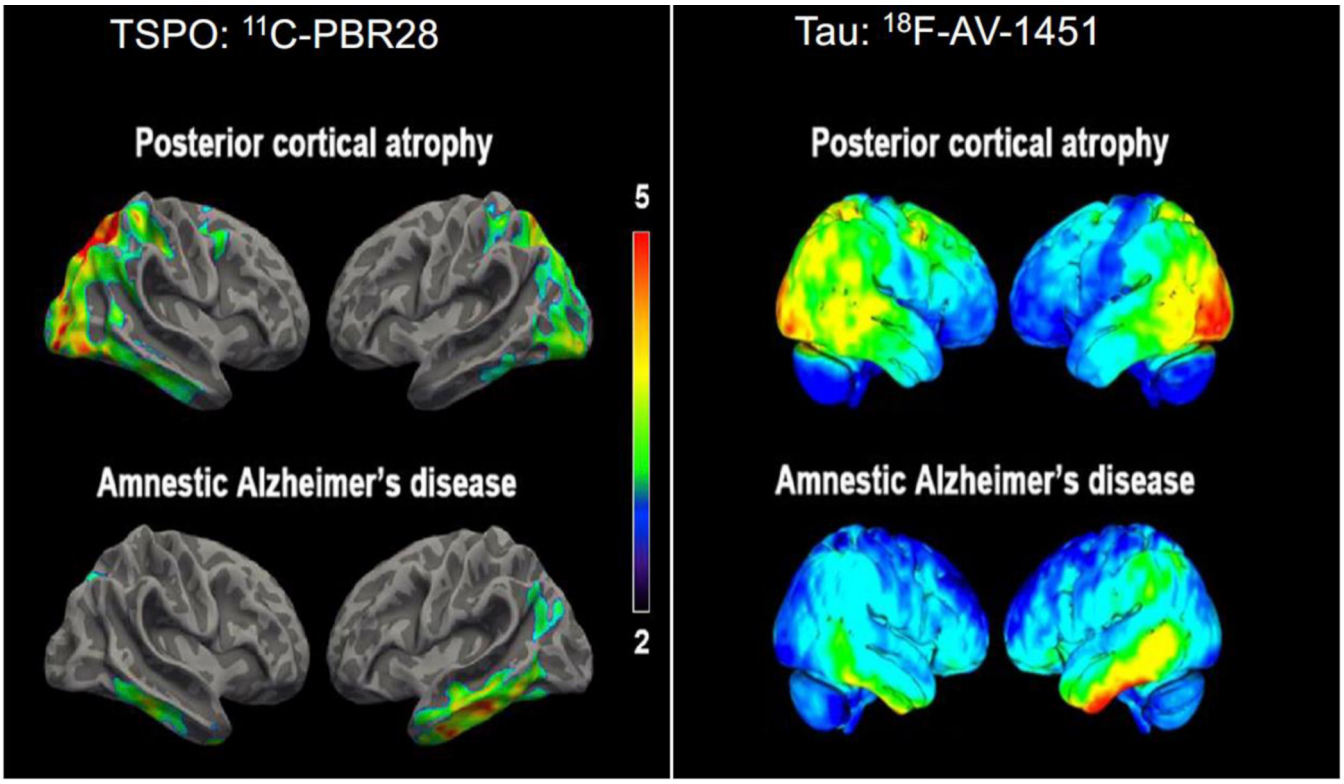

Figure 2. TSPO and tau imaging: Alzheimer's Disease (AD) versus Posterior Cortical Atrophy (PCA).

Topographical distribution of translocator protein (TSPO) resembles that of tau pathology in different clinical subtypes of Alzheimer's disease (AD). Left panel: Surface-based projection maps showing differences in [^{11}C]PBR28 binding (measured as standardized uptake value ratio (SUVR), cerebellar reference) between individuals with AD and age-matched controls for posterior cortical atrophy (PCA, a visual variant of AD, top) and typical amnestic presentation of AD (bottom). Contrast threshold is $P < 0.05$ after family-wise correction for multiple comparisons and *TSPO* genotype, age, and education as covariates. Color bars denote T-values. Right panel: Single-subject PET SUVR images from a separate study in which [^{18}F]AV-1451 was used to label neurofibrillary tau deposits. Representative participants with PCA (top) or amnestic AD (bottom) are shown. [^{11}C]PBR28 images adapted from[59] and [^{18}F]AV-1451 images adapted from.[60] The [^{18}F]AV-1451 images are printed and adapted by permission of Oxford University Press on behalf of the Guarantors of *Brain*. OUP and the Guarantors of *Brain* are not responsible or in any way liable for the accuracy of the adaptation.

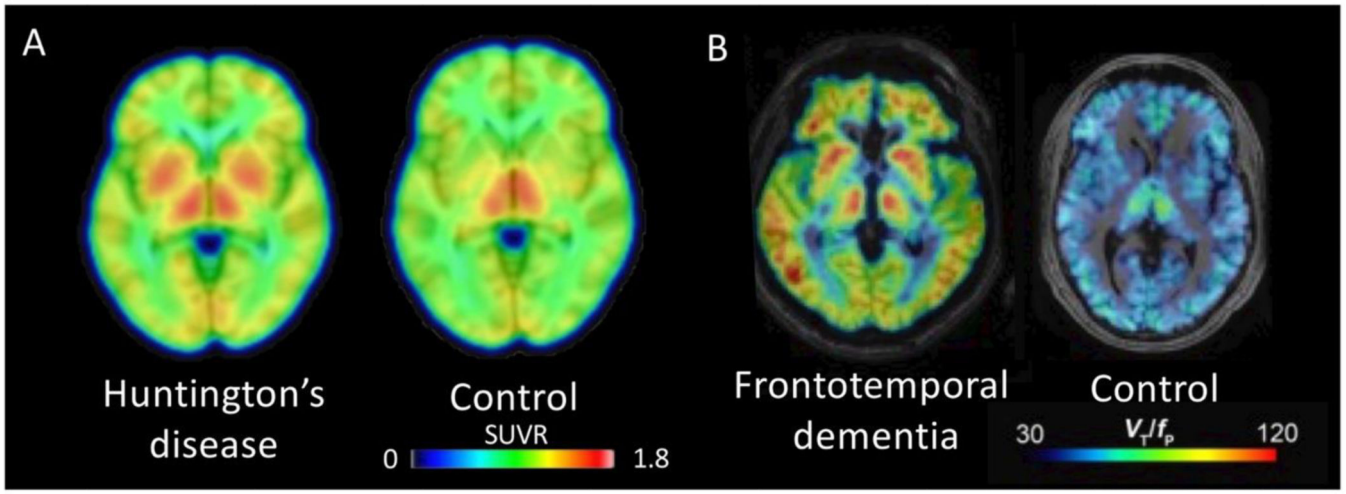

Figure 3. TSPO imaging in Huntington's Disease (HD) and Frontotemporal Dementia (FTD)

(A) Averaged [^{11}C]PBR28 PET images from three controls and seven individuals with Huntington's disease (HD). PET images represent standardized uptake value ratio (SUVR; normalized to whole brain activity) using images acquired 60–90 minutes post-injection. Increased binding in bilateral basal ganglia was found in the HD participants. (B) Representative [^{11}C]PBR28 PET images from an individual with frontotemporal dementia (FTD) and an age-matched control, both high affinity binders. Images represent total distribution volume, corrected for free fraction of radioligand in plasma (V_T/f_P). Increased binding was most notable in frontal and temporal lobes. Adapted from.[72, 87] Reprinted with permission from,[87] copyright 2018 American Chemical Society.

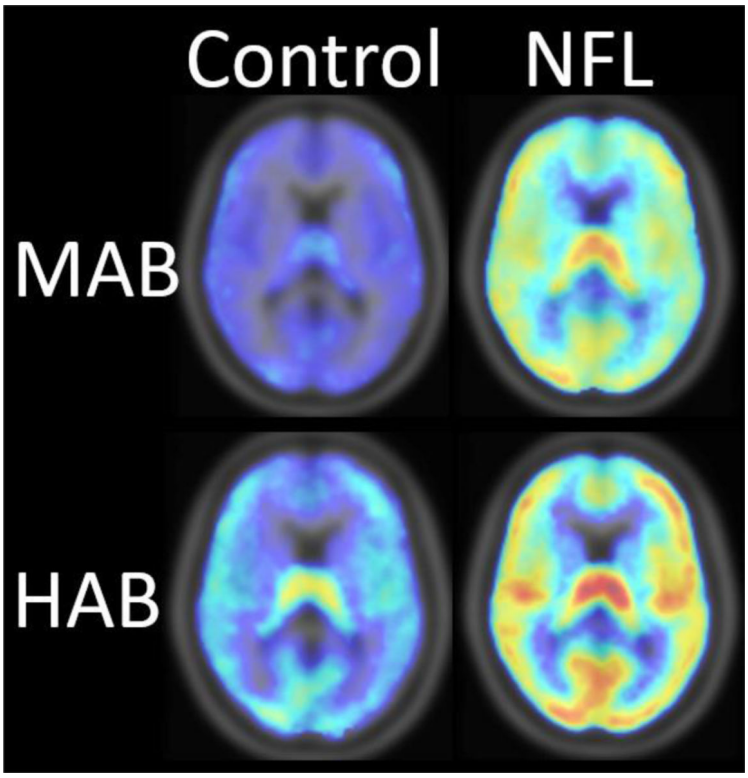

Figure 4. TSPO imaging of Chronic Traumatic Encephalopathy (CTE)

Compared to demographically- and genotype-matched controls, binding of [^{11}C]DPA-713 in gray matter was 53% higher in the brains of former National Football League (NFL) players with the mixed affinity binding (MAB) genotype and 34% higher in NFL players with the high affinity binding (HAB) genotype. Comparative mean [^{11}C]DPA-713 binding [total distribution volume (V_T)] is displayed for individuals with the MAB genotype (upper panel, six controls, five NFL players) and those with the HAB genotype (lower panel, five controls, seven NFL players). Adapted from.[80]

Table 1.

Human studies using neuroinflammatory radioligands 2015–2020

Disorder	Radioligands used	Studies using absolute quantification	Autopsy studies	Use in clinical trials[†]	Key findings
Multiple sclerosis	• [^{11}C]-(*R*)-PK11195 • [^{11}C]PBR28 • [^{18}F]PBR-111	• [^{18}F]GE-180[117, 118] • [^{18}F]DPA-714[119] • [^{11}C]PBR28[120]	—	• [^{11}C]-(*R*)-PK11195[35, 37, 38]	• TSPO decreased after disease modifying treatment[35, 37, 38] • TSPO predicts new lesions[20, 28]
HIV-associated cognitive impairment	• [^{11}C]-(*R*)-PK11195 • [^{11}C]PBR28 • [^{11}C]DPA-713	• [^{11}C]PBR28[45] • [^{11}C]DPA-713[46]	—	—	• Regional TSPO binding associated with domain-specific cognitive impairment[40, 45]
Alzheimer's disease	• [^{11}C]-(*R*)-PK11195 • [^{11}C]PBR28 • [^{18}F]FEPPA • [^{11}C]DAA1106 • [^{18}F]DPA-714 • [^{11}C]DPA-713 • [^{11}C]deuterium-L-deprenyl [*]	• [^{11}C]PBR28[21, 59, 121, 122] • [^{18}F]FEPPA[63, 123, 124] • [^{18}F]DPA-714 [**][125]	• [^{11}C]-(*R*)-PK11195[126]	—	• MAO-B increased in presymptomatic AD[48] • TSPO increased in amyloid-positive controls[23, 51] • TSPO correlates with tau pathology[22, 23, 54]
Frontotemporal dementia	• [^{11}C]-(*R*)-PK11195 • [^{11}C]PBR28	• [^{11}C]PBR28[72]	• [^{11}C]-(*R*)-PK11195[73]	—	• Patterns of TSPO binding discriminate FTD subtypes[73]
Chronic traumatic encephalopathy / traumatic brain injury	• [^{11}C]PBR28 • [^{11}C]DPA-713	• [^{11}C]PBR28[78] • [^{11}C]DPA-713[80, 81]	—	• [^{11}C]PBR28[78]	TSPO increased in medial temporal cortex and supramarginal gyrus in active and former NFL players[80, 81]
Huntington's disease	• [^{11}C]-(*R*)-PK11195 • [^{11}C]PBR28	—	—	—	• TSPO increased in presymptomatic mutation carriers[86]
Amyotrophic lateral sclerosis	• [^{11}C]PBR28 • [^{18}F]DPA-714 • [^{11}C]deuterium-L-deprenyl [*] • [11C]JNJ717 [*]	• [^{18}F]DPA-714[96] • [^{11}C]JNJ717 [*][96] • [^{11}C]PBR28[127]	• [^{18}F]DPA-714[96] • [^{11}C]JNJ717 [*][96]	• [^{11}C]PBR28[95]	• TSPO correlates with changes in white matter integrity and cortical atrophy[91–93]
Epilepsy	• [^{11}C]-(*R*)-PK11195 • [^{11}C]PBR28 • [^{11}C]DPA-713	• [^{11}C]PBR28[101, 102] • [^{11}C]DPA-713[101, 102]	—	—	• TSPO increased ipsilateral to seizure foci in temporal lobe epilepsy[101, 102]
Stroke[≠]	• [^{11}C]-(*R*)-PK11195	—	—	—	• TSPO increased around hematoma in two-fifths of patients with acute intracerebral hemorrhage[108]

[*] non-TSPO radioligand; binds to monoamine oxidase B (MAO-B), a proposed marker of astrocytosis.

[**] Second-generation TSPO radioligand study where *TSPO* genotype correction was not performed.

[†] Jucaite and colleagues[110] found reduced [^{11}C]PBR28 binding in individuals with Parkinson's disease after treatment with a novel myeloperoxidase inhibitor; however, PET studies published after 2015 using either [^{11}C]PBR28 or [^{18}F]FEPPA[111, 112] failed to show increased TSPO in individuals with Parkinson's disease.[113]

Lancet Neurol. Author manuscript; available in PMC 2021 November 01.

‡Studies published prior to 2015 using second-generation TSPO radioligands showed positive results in participants with stroke[105–107].