*Review Article*

# The Place of PET to Assess New Therapeutic Effectiveness in Neurodegenerative Diseases

**Anne-Claire Dupont** [ID]**,**[1,2] **Bérenger Largeau** [ID]**,**[2] **Denis Guilloteau,**[1,3,4] **Maria Joao Santiago Ribeiro,**[1,4,5] **and Nicolas Arlicot**[1,2,4]

[1]*UMR 1253, iBrain, Université de Tours, Inserm, Tours, France*
[2]*CHRU de Tours, Unité de Radiopharmacie, Tours, France*
[3]*CHRU de Tours, Service de Médecine Nucléaire in vitro, Tours, France*
[4]*INSERM CIC 1415, University Hospital, Tours, France*
[5]*CHRU de Tours, Service de Médecine Nucléaire in vivo, Tours, France*

Correspondence should be addressed to Anne-Claire Dupont; ac.dupont@chu-tours.fr

In vivo exploration of neurodegenerative diseases by positron emission tomography (PET) imaging has matured over the last 20 years, using dedicated radiopharmaceuticals targeting cellular metabolism, neurotransmission, neuroinflammation, or abnormal protein aggregates (beta-amyloid and intracellular microtubule inclusions containing hyperphosphorylated tau). The ability of PET to characterize biological processes at the cellular and molecular levels enables early detection and identification of molecular mechanisms associated with disease progression, by providing accurate, reliable, and longitudinally reproducible quantitative biomarkers. Thus, PET imaging has become a relevant imaging method for monitoring response to therapy, approved as an outcome measure in bioclinical trials. The aim of this paper is to review and discuss the current inputs of PET in the assessment of therapeutic effectiveness in neurodegenerative diseases connected by common pathophysiological mechanisms, including Parkinson's disease, Huntington's disease, dementia, amyotrophic lateral sclerosis, multiple sclerosis, and also in psychiatric disorders. We also discuss opportunities for PET imaging to drive more personalized neuroprotective and therapeutic strategies, taking into account individual variability, within the growing framework of precision medicine.

## 1. Background

Neurodegenerative diseases (NDDs) are highly morbid hereditary and sporadic conditions characterized by progressive nervous system dysfunction and, ultimately, the loss of neurons. This heterogeneous group of disorders, including Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), is increasingly affecting the elderly worldwide, with a number of patients expected to double every 20 years [1]. Since these are progressive and irreversible disorders, early detection and differentiation of the disease are primordial for possible therapeutic intervention. Despite different initial clinical manifestations, many studies suggest that overlapping pathophysiologic processes may be involved in various forms of NDD, such as deposition of proteins with altered physicochemical properties in the human brain. Indeed, NDDs are thought to share a common pathogenesis mechanism, the aggregation and deposition of misfolded proteins not only in neurons but also in glial cells, which leads to progressive central nervous system impairments [2]. Thus, NDDs are classified according to current concepts of NDD based on clinical presentation, anatomical regions and cell types affected, and altered proteins involved in the pathogenetic process [3]. Basically, concerning correlation between anatomical involvement and NDD, it is well admitted that hippocampus, entorhinal cortex, or also limbic system are mainly involved in cognitive decline symptoms, whereas basal ganglia, thalamus, motor cortical areas, or cerebellar cortex are more involved in movement disorders. Amyloid-$\beta$ (A$\beta$) and

$\tau$-protein aggregates in Alzheimer disease, as well as other forms of aggregates such as the $\alpha$-synuclein aggregates (or Lewy bodies) found in Parkinson disease and dementia with Lewy bodies are among most proteins associated with the majority of NDDs. Concomitantly, microglial activation has also been linked with degenerative brain diseases by releasing proinflammatory cytokines including interleukin- (IL-) $1\beta$, IL-6, and tumor necrosis factor- (TNF-) $\alpha$, leading to neuronal damage and loss [4]. These common physiopathological processes suggest that these pathologies contribute to the development of other features of neurodegeneration such as neuronal and synaptic dysfunction in the central nervous system.

## 2. Current PET Imaging of Neurodegenerative Diseases

An early detection of the onset of NDD is pivotal as it can provide a chance for an early treatment that may prevent further progression of the disease. Over the past two decades, the traditional view of NDD, such as AD or PD, as purely clinical entity has been changed to one as a clinicobiological entity. A definite diagnosis has thus far been possible only by histopathologic postmortem assessment of brain tissue. Nevertheless, an important gap between the onset of symptoms and neuropathology in NDD is widely recognized. Hence, it has become increasingly possible to identify in vivo evidence of the specific neuropathology of NDD by use of validated biomarkers. Principal requirements for a good biomarker are preciseness, reliability, and capacity to distinguish healthy and pathological tissues. Among these, numerous neuroimaging biomarkers, being correlated with the NDD physiopathological process, have been introduced into the core diagnosis pathway. Positron emission tomography (PET) is a nuclear medicine imaging technique used to noninvasively assess various biological functions at the molecular level, by tracking a chemical compound of biological significance, called radiopharmaceutical, labeled with short-lived positron emitter radionuclide. In NDD, PET allows noninvasive evaluation of not only regional cerebral metabolism or perfusion but also the change of neurotransmission and presence of abnormal protein such as amyloid-$\beta$. $^{18}$F-FDG PET is a well-established radiopharmaceutical to measure regional glucose metabolism indicating neuronal function. In different forms of neurodegenerative dementias, specific patterns of neuronal dysfunction have been described [5]. Besides, dopamine transporter and vesicular monoamine transporter imaging are useful in the diagnosis and evaluation of Parkinson disease progression, providing information about the integrity of presynaptic striatal dopaminergic neurons. More recently, PET tracers for molecular imaging of A$\beta$ have improved early diagnosis by targeting the amyloid deposition. Cholinergic and microglial imaging can be also useful in the early diagnosis of dementia and improve understanding of insights into pathophysiology of neurodegenerative diseases.

Therefore, the ability of molecular imaging to identify and quantify cerebral pathology has significant implications for early detection and differential diagnosis in NDD.

## 3. PET Neuroimaging Interest for Therapeutic Effectiveness Assessment

Molecular PET neuroimaging is a sensitive technique able to identify subtle molecular changes in the brain even before structural changes are present. Thus, one of the most important short-term roles of PET neuroimaging could be in the clinical evaluation and validation of new treatments of NDD, such as antiamyloid therapies in AD, which have entered in human trials (e.g., passive immunization, $\gamma$-secretase, and $\beta$-secretase inhibitors). Without a surrogate biomarker to assess the efficacy of these therapeutic agents on their intended central nervous system target, one cannot properly interpret the outcome of a therapeutic trial. All the more so as the assessment of clinical symptoms may therefore not represent an ideal tool for follow-up and therapy monitoring in NDD, it could have an important symptomatic overlap between NDD themselves. The ability of PET to not only provide spatial localization of metabolic changes but also to accurately and consistently quantify their distribution proved valuable for applications in assessment of drug effectiveness. Indeed, the great strength provided by functional and molecular PET approach allows visualizing numerous of the physiopathological pathways involved in NDD. The development of PET radioligands for the in vivo neuroimaging has been the focus of intense research efforts in recent years and most of the pathophysiologic processes involved in NDD mentioned above such as neuroinflammation, neurotransmission or misfolded protein aggregation, could to date be explored. Furthermore, the capacity to obtain quantitative information with PET tracer uptake in the brain could be relevant for the follow-up evaluation in therapy monitoring. The availability of plenty of PET tracers validated in humans (both on pharmacokinetic or dosimetry fields) provides exciting opportunities for the discovery, validation, and development of novel therapeutics in NDD. The new drug candidates may be radiolabeled in order to reflect, for instance, the biodistribution or the blood-brain barrier passage. But PET can especially be used to study the synthesis and release of neurotransmitters and the availability of neurotransmitter receptors. The growing epidemics of NDD such as AD, PD, or ALS have increased the need for new treatments, and their development is conditioned by first, the choice and the knowledge about the target and second, by the optimization of their validation in vivo. Known to be an important tool in both research and clinical care, PET neuroimaging approach in the therapeutic evaluation and optimization in NDD is discussed in this manuscript.

## 4. PET Imaging to Assess Therapeutic Effectiveness

*4.1. Glucose Metabolism Imaging.* Since its first application in humans in 1979 (Table 1) [13], $^{18}$F-FDG PET improves our understanding of many brain disorders. Indeed, its ability to measure local glucose consumption in various structures of the brain allows to detect alterations in local cerebral metabolism. $^{18}$F-FDG uptake by the cortical and subcortical structures in the brain has the advantage to provide valuable

TABLE 1: Glucose metabolism imaging approach to assess therapeutic effectiveness.

| Disorder | Physiopathological approach | Radioligand | Population | Therapeutical class | Main findings | References |
|---|---|---|---|---|---|---|
| HD | Glucose metabolism | $^{18}$F-FDG | 11 riluzole-treated HD patients versus 12 untreated HD patients | Riluzole (benzothiazole) | Placebo-treated patients showed significantly greater proportional volume loss of grey matter and decrease in metabolic FDG uptake than patients treated with riluzole in all cortical areas ($p < 0.05$). | Squitieri et al. [6] |
| AD | Glucose metabolism | $^{18}$F-FDG | 6 months treatment pramipexole 20 mild-to-moderate AD, 15 completed all visits | Pramipexole (D2-family dopamine receptor agonist) | Broad regions where glucose uptake decreased suggesting a relative decrease in metabolism (consistent with regions of reduced metabolism in individuals with AD). Nonapparent effect of r-pramipexole on brain regional glucose uptake. | Benett et al. [7] |
| AD | Glucose metabolism | $^{18}$F-FDG | 12 months treatment rosiglitazone versus placebo in 80 mild-to-moderate AD patients | Rosiglitazone (PPAR agonist) | Rosiglitazone is associated with an early increase in whole brain glucose metabolism but not with any biological or clinical evidence for slowing progression over a 1 year follow up in the symptomatic stages of AD. | Tzimopoulou et al. [8] |
| PD | Glucose metabolism | $^{18}$F-FDG | 12 patients with advanced PD were assessed before and after 6 months of add-on apomorphine | Apomorphine | Significant metabolic changes were observed, with overall increases in the right fusiform gyrus and hippocampus, alongside a decrease in the left middle frontal gyrus. Consistent correlations between significant changes in clinical scores and metabolism were established. | Auffret et al. [9] |
| SCZ | Glucose metabolism | $^{18}$F-FDG | 18 neuroleptic-naïve first-episode schizophrenic patients | Olanzapine | Glucose metabolism in responders was significantly increased after treatment in the left precentral gyrus, left postcentral gyrus, and left paracentral lobule and significantly decreased in the left hypothalamus. | Yoshimuta et al. [10] |
| SCZ | Glucose metabolism | $^{18}$F-FDG | 30 never-previously medicated psychotic adolescents (ages 13–20) | Olanzapine or haloperidol | Individuals treated with olanzapine showed increased relative metabolic rates in the frontal lobe more than the occipital lobe while patients treated with haloperidol failed to show increase in frontal metabolic rates and did not show an anteroposterior gradient in medication response. | Buchsbaum et al. [11] |
| SCZ | Glucose metabolism | $^{18}$F-FDG | 17 schizophrenic patients previously treated with antipsychotics | Olanzapine | No significant regional metabolic changes were related to previous treatment with classical neuroleptics. | Molina et al. [12] |

AD, Alzheimer disease; FDG, fluorodeoxyglucose; HD, Huntington disease; PD, Parkinson disease; PPAR, peroxisome proliferator-activated receptor; SCZ, schizophrenia.

information before any morphological changes become discernible. Thus, ^{18}F-FDG PET is a well-established tool to identify disease-specific cerebral metabolic brain patterns in several neurodegenerative brain diseases at an early disease stage. In AD, the most prevalent neurodegenerative cause of dementia [14], ^{18}F-FDG is an effective modality for detecting functional brain changes since AD patients exhibit characteristic temporoparietal glucose hypometabolism. Furthermore, a correlation between the degree of hypometabolism and the severity of dementia has been reported during disease progression [15], in relation with neuronal cell loss and decreased synaptic activity. By assessing indirect functional effects of neurodegeneration, ^{18}F-FDG can be useful for early diagnosis and the differential diagnosis between AD and other various types of dementia like dementia with Lewy bodies, frontotemporal lobe dementia, and vascular dementia. Thus, it is widely recognized that ^{18}F-FDG holds a special place for the staging and assessment of AD. Unlike oncology field, where ^{18}F-FDG is routinely used for treatment evaluation and follow-up, ^{18}F-FDG has only been used sporadically in the past as a biomarker for predicting therapeutic response in AD. The first multicenter clinical trial in AD using ^{18}F-FDG measuring brain glucose metabolism as the primary outcome has been described by Tzimopoulou et al. in 2010 [8]. Brain glucose metabolism was studied at baseline and at three later time points (1, 6, and 12 months) after 12 months treatment with the peroxisome proliferator-activated receptor (PPAR) gamma agonist rosiglitazone versus placebo in 80 mild-to-moderate AD patients. Rosiglitazone has been shown to ameliorate insulin resistance in patients with type II diabetes mellitus [16] and seems to improve cognition in AD in preliminary studies [17] but that effect could be limited to APOE4 subjects [18]. No statistically significant difference indicated that active treatment decreased the progression of decline in brain glucose metabolism over a one-year follow-up in the symptomatic stages of AD. Nevertheless, while failing to demonstrate an effect of rosiglitazone on neurodegeneration, these results are consistent with Phase III clinical trials using rosiglitazone in AD [19, 20], which conclude that PET imaging biomarker like ^{18}F-FDG could provide good mechanistic tests for the evaluation of future therapeutic hypotheses. In 2016, in a safety and tolerability study of 6 months of pramipexole in 15 mild-to-moderate AD patients, Bennett et al. has used PET imaging to complete the study by examination of cognitive performance with ^{18}F-FDG tracer. In this small single-arm, open-label study, there was no apparent effect of pramipexole because a 3–6% brain glucose uptake decrease has been observed during the 6-month follow-up, consistent with regions of reduced metabolism in AD patients without treatment [7]. Contrary to the minor interest of ^{18}F-FDG in AD therapeutic assessment, a recent study has shown that apomorphine pump seems to be an interesting option for treating advanced PD patients in therapeutic impasse, thanks to a brain glucose metabolism study [9]. In 12 advanced PD patients, significant metabolic changes were observed, with overall increases in the right fusiform gyrus and hippocampus, alongside a decrease in the left middle frontal gyrus before and after 6 months of add-on apomorphine. Besides, consistent correlations between

significant changes in clinical scores, mainly assessed according to UPDRS (Unified Parkinson's Disease Rating Scale) and MDRS (Mattis Dementia Rating Scale), and metabolism were established. In the same way, metabolic (by ^{18}F-FDG-PET) and volumetric (by Magnetic Resonance Imaging-MRI) differences in the brain have been investigated to evaluate neuroprotective effects of riluzole in HD [21]. Riluzole interferes with glutamatergic neurotransmission, thereby reducing excitotoxicity and enhancing neurite formation in damaged motoneurons [22]. It also has been reported to inhibit voltage-gated sodium channels and to be neuroprotective by suppressing astrocytosis [23]. The 12 placebo-treated HD patients showed significantly greater proportional volume loss of grey matter and decrease in metabolic ^{18}F-FDG uptake than the 11 HD patients treated with riluzole in all cortical areas ($p < 0.05$). Not only brain glucose metabolism was preserved in patients receiving riluzole, but also a correlation between the progressive metabolic consumption with worsening clinical scores (UHDRS-I, Unified Huntington Disease Rating Scale) in placebo group was reported. These findings corroborate that antiglutamatergic drugs like riluzole could represent a neuroprotective strategy in HD and that ^{18}F-FDG-PET may be a valuable tool to assess brain markers of HD. Considered as a neurodegenerative or neurodevelopmental disorder, recent studies have shown the importance of treating schizophrenia, a chronic and severe mental disorder characterized by abnormal social behaviour and failure in assessing reality. Mostly, we distinguish positive (i.e. hallucinations, paranoid delusions, beliefs), negative (i.e. apathy, lack of emotion, and poor or nonexistent social functioning), and cognitive (disorganized thoughts, difficulty concentrating and/or following instructions, difficulty completing tasks, and memory problems) psychotic symptoms; and that is why many structural brain studies have correlated schizophrenia symptoms with reproducible structural brain abnormalities. For instance, progressive prefrontal grey matter atrophy is known to be more related to pronounced negative symptoms [24]. Cerebral metabolic studies with ^{18}F-FDG have an interest to define brain regions associated with treatment-related improvement of symptoms in schizophrenic patients. Thus, increased relative metabolic rate has been observed in the frontal lobe in 30 psychotic patients treated with olanzapine versus no medication subjects [11]. Such a difference has not been observed in 17 patients previously exposed to antipsychotics [12]. Linking to the interest to treat schizophrenia as soon as possible, Yoshimuta et al. have examined the effects of olanzapine and identified brain regions associated with a positive response in neuroleptic-naive first-episode schizophrenic (FES) patients [10]. Glucose metabolism in responders was significantly increased after treatment in the left precentral gyrus, left postcentral gyrus, and left paracentral lobule and significantly decreased in the left hypothalamus. These observations added to the positive correlation between the changes in "Positive and Negative Syndrome Scale" (PANSS) scores and metabolic changes before and after treatment reinforce the beneficial action of olanzapine in FES patients.

*4.2. Amyloid and Tau Imaging.* Currently, the only FDA-approved AD drugs such as donepezil, galantamine, or memantine act partially on the symptoms of AD, without treating the underlying causes of the disease (Table 2). A worldwide quest is under way to find new treatments to stop, slow, or even prevent AD. Many of the new drugs in development aim at modifying the disease process itself, by impacting one or more of its hallmarks, like extracellular plaque deposits of the $\beta$-amyloid peptide (A$\beta$). For this purpose, interest of immunotherapy has grown during the last decade: antibodies are attractive drugs as they can be made highly specific for their target and often confer a lower risk of side effects in a vulnerable patient population during long-term treatment as compared with small-molecule anti-A$\beta$ therapy. Thus, monoclonal antibodies have emerged to lower the beta-amyloid load in the brain, preventing the formation of plaques or even carrying excess beta-amyloid out of the brain. One of the earliest compounds evaluated for the treatment of AD was the bapineuzumab, a humanized N-terminal-specific anti-A$\beta$ monoclonal antibody. Several PET studies measuring A$\beta$ load have been performed for the clinical evaluation of this antibody, using radiopharmaceuticals developed from the chemical structure of histologic dyes. This noninvasive approach made it possible to track amyloid pathology longitudinally, following the disease progression.

In a study conducted by Rinne et al. in 2010 in 28 AD patients, the amyloid load was found to be reduced in the brains of patients treated with bapineuzumab as compared with placebo, as measured by binding of ^{11}C-PIB to brain amyloid with PET [25]. In contrast, in a second Phase II study, bapineuzumab subcutaneous once monthly did not demonstrate a significant treatment difference over placebo on cerebral amyloid signal, assessed with ^{18}F-florbetapir at one year [26]. Then, two Phase III trials of bapineuzumab in mild-to-moderate AD, supported by Janssen Alzheimer Immunotherapy Research & Development and Pfizer Inc. confirmed this result since bapineuzumab failed to reach the clinical endpoint in Phase III, namely, the overall negative clinical findings [27, 28]. The other humanized anti-A$\beta$ monoclonal antibody that has been involved to large Phase III clinical trials is solanezumab, recognizing the central A$\beta$13–28 region [29]. Two large randomized double-blind controlled Phase III trials tested solanezumab as a potential treatment to slow the progression of mild-to-moderate AD, EXPEDITION 1 and EXPEDITION 2, with, respectively, 1012 and 1040 patients randomized to 400 mg of solanezumab or placebo every 4 weeks for 80 weeks [30]. Solanezumab failed to improve cognition or functional ability assessed with cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14) [31]. In both studies, a total of 169 patients and 97 in EXPEDITION 1 and 2, respectively, underwent baseline and follow-up [18]F-florbetapir-PET scanning. The composite SUVR for the anterior and posterior right and left cingulate, plus right and left frontal, lateral temporal, and parietal regions, combined and normalized to the whole cerebellum, did no change significantly in the solanezumab group or the placebo group in either study. Many other anti-A$\beta$ monoclonal antibodies are under development, and among them is the first fully

human antibody, the gantenerumab that also binds specifically to A$\beta$ plaques. The effect of up to 7 infusions of IV gantenerumab or placebo every 4 weeks on the A$\beta$ amyloid load as measured by ^{11}C-PiB has been studied in patients with mild-to-moderate AD in a preliminary PET study [32]. In 16 AD patients, the PET study has shown a dose-dependent reduction in brain A$\beta$ plaques, but again no consistent treatment effects on cognitive measures were noted. Ongoing Phase III trials on gantenerumab on prodromal or mild stage of AD may clarify whether any reduction in brain A$\beta$ deposits will successfully translate into clinical practice benefit at well-tolerated doses of gantenerumab [33]. Overall, to date, most of clinical trials trying to stop AD progression has led to reduce amyloid deposition but has little beneficial effect on cognitive improvement. Therefore, new approaches are being investigated, and a preliminary PET study has shown that benfotiamine significantly improved the cognitive abilities of 3 mild-to-moderate AD patients despite the progression of brain amyloid assessed by ^{11}C-PIB [30]. Benfotiamine is a synthetic thiamine derivative preventing abnormal glucose metabolism via multiple pathways [34]. It is so demonstrated in this study that the alteration of cognitive capability is independent of brain amyloid accumulation, which is consistent with previous results showing that the reduction of brain amyloid accumulation by antibodies has little effect on the cognitive ability and disease progression of AD patients. It will be necessary to validate these results by randomized, double-blinded, placebo-controlled clinical trials.

As $\beta$-amyloid peptide, aggregates of hyperphosphorylated tau protein known as neurofibrillary tangles (NFTs) are one of the hallmarks of AD and related disorders, called tauopathies. Aggregates of tau are prominent targets for novel therapeutics as well as for biomarkers for diagnostic in vivo imaging. While immunotherapy targeting A$\beta$ peptide gave poor results, tau-based immunotherapy clinical trials have recently emerged [35]. Promising results are expected from a new active vaccine, namely, AADvac1, targeting pathological tau protein in Alzheimer's disease [36]. In addition, the recent development of tau-specific PET tracers has allowed in vivo quantification of regional tau deposition and offers the opportunity to monitor the progression of tau pathology along with cognitive impairment. To our knowledge, any study with a tau PET tracer as a reliable outcome measure of drug efficacy assessment has been published yet. As explained by Okamura and Yanai [37], the methods to image analysis with tau PET tracer need to be optimized. Indeed, the variety of the different types of tau deposits is a crucial issue for the development in tau PET tracers. Recent data evidence the existence of off-target binding in areas of tau accumulation. Thus, a longitudinal observation of patients at baseline and post-selegiline (MAO-B inhibitor) ^{18}F-THK5351 PET scans has tested the hypothesis that a reduction of MAO-B availability also reduces ^{18}F-THK5351 uptake. In this study, Ng et al. reported that MAO-B was an ^{18}F-THK5351 off-target binding site; hence, the interpretation of PET images is confounded by the high MAO-B availability [38].

With the increasing interest in antitau therapies, tau PET tracers will certainly be a tool to assess the therapeutic effects

TABLE 2: Amyloid imaging approach to assess therapeutic effectiveness.

| Disorder | Physiopathological approach | Radioligand | Population | Therapeutical class | Main findings | References |
|---|---|---|---|---|---|---|
|  | Amyloid | $^{18}$F-florbetapir | 12 month study to determine long-term effects of monthly SC injections on 146 amyloid positive patients with mild to moderate AD (36 placebo versus 110 bapineuzumab 2 mg, 7 mg, 20 mg) | Bapineuzumab immunotherapy | Bapineuzumab did not demonstrate significant difference over placebo on GCA of 5 SUVR ROI: anterior cingulate, frontal cortex, lateral temporal cortex, parietal cortex, posterior cingulate/precuneus). Subgroup analysis based on disease severity: change in SUVR significant only in 7 mg/month group in patient with mild AD. | Brody et al. [26] |
|  | Amyloid | $^{11}$C-PiB | 78 weeks study on 28 patients with mild to moderate AD (8 placebo versus 20 Bapineuzumab IV 0.5 mg/kg, 10 mg/kg, 2.0 mg/kg) (7 placebo and 19 bapineuzumab included in PiB PET analysis) Patients with mild to moderate AD | Bapineuzumab immunotherapy | Estimated difference on cerebral retention ratio is significant between Bapineuzumab and placebo group. $^{11}$C-PiB PET seems to be useful in assessing the effects of potential AD treatments on cortical fibrillar amyloid-$\beta$ load in vivo. Change from baseline to week 78 for GCA SUVR was not statistically significant versus placebo in either study. | Rinne et al. [25] |
| AD | Amyloid | $^{11}$C-PiB | 2 substudies: ApoEε4 carriers (24 placebo versus 32 bapineuzumab IV 0.5 mg/kg) ApoEε4 non carriers (13 placebo versus 17 bapineuzumab IV 0,5 mg/kg) Patients with mild to moderate AD | Bapineuzumab immunotherapy | No significant treatment differences were seen in amyloid burden on PiB-PET. | Vandenberghe et al. [27] |
|  | Amyloid | $^{11}$C-PiB | PiB PET substudy: ApoE ε4 carriers: 75 Bapineuzumab IV versus 40 placebo; ApoE ε4 non-carriers: 22 Bapineuzumab IV versus 15 placebo Patients with mild-to-moderate AD receiving placebo or solanezumab IV 4 weeks for 18 months | Bapineuzumab immunotherapy | Significant differences in mean SUVR were only observed between bapineuzumab and placebo in the ApoE ε4 carrier study. | Salloway et al. [28] |
|  | Amyloid | $^{18}$F-florbetapir | Combining the 2 substudies, a total of 266 patients underwent PET examination at baseline and week 80 or early termination | Solanezumab immunotherapy | The composite SUVR for the anterior and posterior right and left cingulate, plus right and left frontal, lateral temporal, and parietal regions, combined and normalized to the whole cerebellum, did no change significantly in the solanezumab group or the placebo group in either study. | Doody et al. [29] |

of these new drugs acting on tau load in the brain. For that purpose, new tau PET tracers (i.e., ^{18}F-MK-6240 and ^{18}F-AM-PBB3) have recently been reported to have less off-target binding than their predecessors [39].

### 4.3. Neuroinflammation Imaging.

Initially discovered in Alzheimer's disease (AD), where activated microglia cells were found in postmortem nearby senile plaques (Table 3) [40], it is now clearly established that microglial activation and abnormal protein deposition take part in the process of neurodegenerative disorders such as AD, PD, ALS, and MS [4]. Thus, glial inflammation has heightened interest in the rapid discovery of neuroinflammation-targeted drugs [41]. Given the fact that anti-inflammatory drugs are able to suppress peripheral inflammation, many authors investigated their potential use for central nervous system (CNS) inflammation [42–44]. Nevertheless, only few clinical studies have evaluated, thanks to molecular imaging, and apart from clinical parameters, the ability of these drugs to reduce glial cell-propagated inflammation. In parallel, over the last 20 years, microglia PET imaging has successfully widened through the development of radiopharmaceuticals and the identification of several molecular targets of neuroinflammation. Among these targets, receptors including the translocator protein-18 kDa (TSPO) [45], cannabinoid receptor 2A [46], and adenosine receptor 2A [47, 48] and enzymes such as $\beta$-glucuronidase [49] have been targeted to evaluate the scope of microglia PET imaging in neurodegenerative disorders. To our knowledge, only TSPO PET imaging has been used to assess therapeutic efficacy in neurodegenerative disorders. Drugs evaluated in these studies include specific therapeutics which have already granted FDA licensure like interferon beta, [50] glatiramer acetate, [51] and fingolimod [52, 53] in MS, nonspecific drugs which exert anti-inflammatory effects, [54, 55] and new therapeutical class-targeting biochemical pathways involved in neurodegenerative disorder such as the hydrolysis of neuroprotective endocannabinoid [56] and oxidative stress [57]. Microglial activation plays a central role in maintaining the central chronic inflammation in MS [58]. MS is a chronic autoimmune disease of the CNS where the migration of myelin-reactive T-cells into the CNS is followed by microglial activation, recruitment of peripheral macrophages, and oligodendrocytes destruction [59]. Fingolimod blocks the egress of lymphocytes from secondary lymphoid tissues and thereby prevents their entry into the CNS [60]. In line with its mechanism of action, PET imaging showed that fingolimod reduced microglial activation [52, 53], especially in T2 lesion area [53]. Glatiramer acetate, a synthetic polypeptide resembling myelin basic protein, acts further downstream deceiving immune system and inducing immunomodulatory Th2 cells [61]. Ratchford et al. [51] provided proof of concept that microglia PET imaging with ^{11}C-PK11195 could also be a tool to assess disease-modifying drugs for relapsing-remitting multiple sclerosis (RRMS) efficacity. Indeed, radiopharmaceutical binding potential per unit volume was statistically decreased in the whole brain after one year of glatiramer acetate. This result supported the in vitro evidence of its mechanism of action in which an inhibition of transformation to an activated microglia form could be responsible for therapeutic effects [61]. In other neurodegenerative disorders, TSPO PET studies have not achieved convincing results. Indeed, authors reported no significant difference [57] in microglial activation or a slight decrease [56] in TSPO density and sometimes an increase in TSPO tracer binding after therapeutic challenge [55].

### 4.4. Neurotransmission Imaging.

During the past decades, numerous neurotransmitter systems have been identified and have been demonstrated to be directly involved in NDD. In vivo neuroimaging with PET using labeled ligands can visualize the various receptor and transporter systems and measure in quantitative terms their densities and binding and occupancy status (Table 4). The importance of PET in receptor-system-related drug research has increased tremendously in recent years.

One of the key monoamine neurotransmitters, the dopaminergic transmission plays a major role in neurological and psychiatric disorders such as PD, HD, and SCZ. Although mainly known to be involved in motor feature, dopamine is also involved in cognition and emotion. To investigate pre- and postsynaptic functions, PET tracers have been developed to measure dopamine synthesis and transport and postsynaptic receptors. For measuring dopamine synthesis, the most commonly used tracer is ^{18}F-DOPA, whereas for dopamine transport, several radiolabeled tropane analogs have been developed. For postsynaptic dopamine receptors, divided on five subtypes of receptors, ^{11}C-raclopride is the common tracer for D2/D3, whereas ^{18}F-fallypride is mainly used for the exploration of D2 [62]. In clinical practice, it is well admitted that the extent of dopaminergic neuronal loss in the substantia nigra in PD patients is measured in vivo using ^{18}F-DOPA considered as the gold-standard for monitoring the course of PD [63]. Unlike for other physiopathological pathways cited above as neuroinflammation or amyloid aggregation, dopamine molecular imaging has already widely been used for a long while to assess drug therapeutic effectiveness in PD essentially. Actually, it could be explained first by the fact that a treatment allowing restoration of dopamine neurotransmission is available for years for PD patients and second by direct dopaminergic transmission radiotracers availability. In 1990s, PET studies with ^{11}C-raclopride have demonstrated the downregulation of the striatal $D_2$ receptor binding in PD related to long-term treatment. Indeed, compared to the baseline, ^{11}C-raclopride binding was significantly decreased in the putamen and caudate nucleus in PD patients treated for 3–5 years with L-DOPA or lisuride, whereas no change was observed in D2 density 3–4 months posttreatment [64, 65]. More recently, ^{11}C-raclopride PET studies have evaluated the relationship between clinical improvement following a single oral dose of levodopa and drug-induced synaptic dopamine increases. A significant increase of striatal DA in both caudate and putamen after levodopa administration was correlated with the improvement of rigidity and bradykinesia, whereas

TABLE 3: Neuroinflammation imaging approach to assess therapeutic effectiveness.

| Disorder | Physiopathological approach | Radioligand | Population | Therapeutical class | Main findings | References |
|---|---|---|---|---|---|---|
| AD | Neuroinflammation TSPO | $^{18}$F-GE180 | Preclinical: transgenic APdE9 mice were treated with JZL184 ($n = 7$) or with vehicle ($n = 5$) | Monoacylglycerol lipase inhibitor: JZL184 40 mg/kg/d | In JZL184-treated mice, there was a very slight decreasing trend in tracer uptake in multiple brains areas compared to vehicle-treated APdE9 mice. | Pihlaja et al. [56] |
| MS | Neuroinflammation TSPO | $^{18}$F-GE180 | Preclinical: chronic focal EAE-like lesions were induced in rats via stereotactic intrastriatal injection of BCG and subsequent activation using an intradermal injection of BCG. Animals were then treated for 28 days with either fingolimod ($n = 5$) or vehicle ($n = 3$) | Selective immunosuppressant (S1P receptor antagonist): fingolimod 0.3 mg/kg/d | Treatment with fingolimod for 28 days resulted in a clear reduction in the binding of trace when compared with vehicle-treated animals. Quantification of the binding of the radiotracer revealed a significant reduction in the $BP_{ND}$ of $^{18}$F-GE180 after treatment with fingolimod. | Airas et al. [52] |
|  | Neuroinflammation TSPO | $^{11}$C-PK11195 | Clinical: 9 drug-naïve RRMS patients were scanned at baseline before initiating GA and again after 1 year of GA treatment | Immunomodulatory: GA 20 mg/d | Significantly decreased tracer $BP_{ND}$ per unit volume 3.17% in whole brain between baseline and 1 year and especially in supratentorial brain, infratentorial brain, cerebral white matter, cortical grey matter, thalamus and putamen. | Ratchord et al. [51] |
|  | Neuroinflammation TSPO | $^{18}$F-FEDAA1106 | Clinical: RRMS patients in acute relapse: 6 drug-naïve patients and 3 patients on interferon beta therapy versus 5 HC | Immunomodulatory: interferon beta | No significant difference of tracer $BP_{ND}$ or $V_T$ between the three groups: MS without treatment, MS with interferon beta therapy, and normal control. | Takano et al. [50] |
|  | Neuroinflammation TSPO | $^{11}$C-PK11195 | Clinical: 10 RRMS patients were scanned at baseline before initiating fingolimod and again after 6 months of treatment | Selective immunosuppressant | Tracer binding was reduced (−12.3%) in the T2 lesion area after 6 months of fingolimod treatment, but not in the areas of NAWM or grey matter. |  |
|  | Neuroinflammation TSPO | $^{11}$C-PK11195 | 7 patients were scanned 2 months following the treatment initiation | Selective immunosuppressant (S1P receptor antagonist): fingolimod | 5/7 patients showed a slight increase tracer DVR in NAWM during the first 2 months of fingolimod treatment. 6/7 patients showed a slight increase in cortical gray matter after 2 months. | Sucksdorff et al. [53] |
| MSA | Neuroinflammation TSPO | $^{11}$C-PK11195 | Clinical: 8 MSA-P patients: 3 with minocycline versus 5 in placebo arm. Two groups were followed up for 6 months | Tetracycline with anti-inflammatory effects: minocycline 200 mg/d | Compared to baseline, tracer $BP_{ND}$ decreased in caudate nucleus, thalamus, midbrain and cerebellum for 2/3 treated patients after 24 weeks of minocycline. In placebo group, tracer $BP_{ND}$ is increased in most regions after 6 months. | Dodel et al. [54] |
| PD | Neuroinflammation TSPO | $^{11}$C-PK11195 | Clinical: 5 PD patients were scanned before and after one month of celecoxib | COX-2 inhibitor: celecoxib 100 mg/d | Tracer binding potential and distribution volume after celecoxib treatment were slightly higher. There was no significant difference of changes of $V_T$ between the treatment groups. | Bartels et al. [55] |
|  | Neuroinflammation TSPO | $^{11}$C-PBR28 | Clinical: 24 PD patients: 18 with AZD3241 versus 6 in placebo arm. 16 PD patients in AZD3241 arm were followed-up for 8 weeks | Myeloperoxidase inhibitor: AZD3241 600 mg/12 h | AZD3241 significantly reduced $V_T$ in regions of the nigrostriatal pathway compared to baseline $V_T$ values at 4 weeks and at 8 weeks. | Jucaite et al. [57] |

AD, Alzheimer's disease; BCG, bacillus Calmette-Guérin; $BP_{ND}$, binding potential; DVR, distribution volume ratio; EAE, experimental autoimmune encephalitis; GA, glatiramer acetate; MS, multiple sclerosis; MSA, multiple system atrophy; NAWM, normal appearing white matter; PD, Parkinson's disease; RRMS, relapsing-remitting multiple sclerosis; S1P, sphingosine 1-phosphate; $V_T$, total distribution volume.

TABLE 4: Neurotransmission imaging approach to assess therapeutic effectiveness.

| Disorder | Physiopathological approach | Radioligand | Population | Therapeutical class | Main findings | References |
|---|---|---|---|---|---|---|
| | Dopamine neurotransmission | $^{11}$C-raclopride | 18 previously untreated PD patients and 14 healthy volunteer subjects | Levodopa/lisuride | 3 to 4 months' oral therapy with LD or lisuride does not change striatal dopamine D2-receptor density in PD patients. | Antonini et al. [64] |
| | Dopamine neurotransmission | $^{11}$C-raclopride | 9 patients with PD at an early drug-naive stage and 3–5 years later and 10 healthy controls in the same age range | Levodopa/lisuride | After 3–5 years, binding was significantly reduced in the putamen ($p < 0.03$) and caudate nucleus ($p < 0.03$) compared with baseline. These results indicate long-term downregulation of striatal dopamine D2 receptor binding in PD. | Antonini et al. [65] |
| | Dopamine neurotransmission | $^{11}$C-raclopride | 16 advanced PD patients | Levodopa | Following LD, mean caudate and putamen $^{11}$C-raclopride BPs were significantly lower versus baseline, consistent with increased synaptic DA. A two-scan RAC PET study has reported, in advanced PD cases that, improvement in bradykinesia and rigidity scores following oral DA medication administration were significantly correlated with reductions in RAC binding suggesting an effect of increased DA on the striatal D2 receptors. | Pavese et al. [66] |
| PD | Dopamine neurotransmission | $^{18}$F-6-fluorodopa | 67 patients with IP, 52 with fluctuations and 15 with a stable response to LD | Levodopa | A 28% decrease in presynaptic terminal function in the putamen of PD patients with a fluctuating response to LD compared to the stable responders. | de la Fuente-Fernández et al. [68] |
| | Dopamine neurotransmission | $^{18}$F-6-fluorodopa | 9 patients with PD followed for 10 to 72 months after human embryonic mesencephalic tissue | Human embryonic mesencephalic tissue | $^{18}$F-6-DOPA uptake increases in the striatum following the transplantation. | Wenning et al. [67] |
| | Dopamine neurotransmission | $^{18}$F-6-fluorodopa | 40 patients with PD | Transplantation of human embryonic dopamine neurons | Among younger patients (60 years old or younger), standardized tests of PD revealed significant improvement in the transplantation group as compared with the sham-surgery group when patients were tested in the morning before receiving medication. | Freed et al. [70] |
| | Dopamine neurotransmission | $^{18}$F-6-fluorodopa | 34 patients with advanced PD | Fetal nigral transplantation | Striatal $^{18}$F-6-DOPA uptake was significantly increased after transplantation in both groups and robust survival of dopamine neurons was observed at postmortem examination. | Olanow et al. [71] |

TABLE 4: Continued.

| Disorder | Physiopathological approach | Radioligand | Population | Therapeutical class | Main findings | References |
|---|---|---|---|---|---|---|
| AD | MAO-B inhibition dopamine neurotransmission | $^{11}$C-L-deprenyl-D2 $^{11}$C-PMP | 10 AD patients versus 6 elderly control subjects | Sembragiline MAO-B inhibitor | This PET study confirmed that daily treatment of at least 1 mg sembragiline resulted in near-maximal inhibition of brain MAO-B enzyme in patients with AD. In the galantamine group, there was significant inhibition of AChE activity in all four cortical regions (frontal, parietal, parietotemporal, temporal). | Sturm et al. [74] |
| | Acetylcholine neurotransmission | $^{11}$C-nicotine | 18 subjects (12 galantamine versus 6 placebo) with mild to moderate AD (14 completed 12 months study) | Galantamine | The placebo group did not show any significant inhibition compared with baseline. A positive correlation was observed between changes in the average cortical $^{11}$C nicotine binding and plasma galantamine concentrations. | Kadir et al. [75] |
| PD | Serotonin neurotransmission | $^{11}$C-DASB | 2 PD patients who had shown recovery of motor function after intrastriatal fetal ventral mesencephalic tissue transplantation but experienced off-phase GIDs | Neural transplantation Buspirone 5-HT$_{1A}$ receptor agonist | It was found excessive serotoninergic innervation in the grafted putamen in one patient and putamen and caudate nucleus in second patient. Buspirone in low repeated dose markedly attenuated dyskinesia severity in both transplanted patients. | Politis et al. [73] |
| SCZ | GABA neurotransmission | $^{11}$C-flumazenil | 17 off-medication SCZ patients versus 22 HC | Tiagabine IGAT1 | $^{11}$C-flumazenil $V_T$ was significantly increased across all cortical brain regions in the healthy comparison group but not in the schizophrenia group. | Frankle et al. [72] |
| | GABA neurotransmission | $^{11}$C-Ro15-4513 | 12 healthy male completed the Tiagabine challenge study | Tiagabine IGAT1 | Tiagabine administration produced significant reductions in hippocampal, parahippocampal, amygdala, and anterior cingulate synaptic α1 $^{11}$C-Ro15-4513 binding, and a trend significance reduction in the nucleus accumbens. | Stokes et al. [76] |

AChE, acetylcholinesterase; AD, Alzheimer disease; BP, binding potential; DA, dopamine; EC, elderly control; GIDs, graft-induced dyskinesia; HC, healthy comparison; MAO-B, monoamine oxydase type B; IP, idiopathic parkinsonism; LD, levodopa; PET, positron emission tomography; RAC, $^{11}$C-raclopride; SCZ, schizophrenia; $V_T$, tissue distribution volume.

tremor and axial symptoms are not found to be related to this striatal synaptic dopamine level [66]. This last study indicates that pathways other than nigrostriatal pathway may be implicated in the pathogenesis of parkinsonian tremor and axial features and so other treatments are expected. In parallel, dopaminergic system molecular imaging has broadly been investigated in levodopa-induced dyskinesias (LID) field [67]. LIDs are associated with increased and fluctuating synaptic dopamine levels following levodopa administration [68]. Finally, dopamine in vivo imaging has extensively been used to assess safety after neural transplantation [69–73].

Finally, PET imaging in clinical transplantation trials can provide additional valuable information alongside clinical observations. Although being used in almost ever case in PD study, dopamine transmission in vivo imaging has measured brain MAO-B inhibition in patients with AD and elderly controls after oral administration of sembragiline [74]. In order to assist in dose selection of the Phase 2 sembragiline study in patients with moderate AD, Sturm et al. had to determine the relationship between exposure to Sembragiline and the inhibition of MAO-B enzyme activity in the brain, thanks to $^{11}$C-L-Deprenyl-D2.

In addition to the dopamine neurotransmission, radioligands have been developed to target cholinergic, serotoninergic, or gabaergic transmissions. Thanks to two cholinergic system tracers ($^{11}$C-PMP and $^{11}$C-nicotine), we can see the acetylcholinesterase inhibition by the galantamine up to 12 months in 18 mild AD patients [75]. The inhibitory $\gamma$-aminobutyric acid (GABA) is known to be involved in a number of neuropsychiatric disorders including schizophrenia, and that is why, the tiagabine effect, which increases synaptic GABA, has been investigated with $^{11}$C-Ro15-4513 in 12 male participants to show its potential involvement in schizophrenia. Tiagabine produced significant reductions in hippocampal, parahippocampal, amygdala, and anterior cingulate synaptic tracer binding, suggesting that acute increases in endogenous synaptic GABA are detectable in the living human brain using $^{11}$C-Ro15-4513 PET [76]. Then, an in vivo impairment in GABA transmission in schizophrenia has been recently demonstrated with $^{11}$C-flumazenil after administration of tiagabine, in 17 off-medication patients with schizophrenia and 22 healthy comparison subjects [77]. Finally, anectodal evidence suggests that serotonine PET imaging could also be interesting to assess buspirone efficacy in PD [73].

## 5. Discussion

As PET has become increasingly available and as the range of available brain radioligands continues to expand, the use of PET neuroimaging has increased in drug development assessment in recent years. To date, the neurotransmitter system which has been most widely studied in humans is the dopaminergic system, mainly explored in movement disorders notably, thanks to $^{18}$F-DOPA or even $^{11}$C-raclopride. These dopaminergic relevant biomarkers allowed to improve our knowledge about why PD patients develop daily fluctuations in mobility and troublesome involuntary movements after several years of dopamine replacement therapy. In vivo dopamine imaging could also help to improve PD patient selection in future clinical trials by selecting those with better predicted outcomes. Another physiopathological approach has surged recently with the development of PET amyloid radioligands. Developed and approved for clinical use as important diagnosis and prognostic biomarkers for AD or mild cognitive impairment (MCI) patients, amyloid tracers are also being used to evaluate therapeutic interventions. Thus far, clinical trials of promising treatment for AD have failed to significantly stop the disease progression [78]. Surprisingly, while almost all research effort has been focused on antiamyloid therapy for AD, a recent PET study shows that the alteration of cognitive capability is independent of brain amyloid accumulation, and thus, also other physiopathological ways have to be explored to try to reduce AD progression [30].

Thus, it may be of interest to provide perspectives on new targets for which PET tracers are currently under development and which are also considered relevant for therapeutic management of NDD:

(i) Purinergic ion channel receptors, and especially P2X7 receptor (P2X7R), are known to be overexpressed in activated microglia in animal models of neurodegenerative diseases, such as AD [79], ALS [80], or HD [81], and might be a promising target to assess therapeutics, especially since the GSK1482160, a strong P2X7R antagonist, has been evaluated in Phase 1 clinical study by GSK company [82]. Labeled with carbon-11, $^{11}$C-GSK1482160 is a promising radioligand for neuroinflammation PET imaging, and one would think that this P2X7R antagonist could be an excellent candidate for a theranostic approach.

(ii) Regarding the protein accumulation, three major types of aggregated hyperphosphorylated proteins (amyloid-beta, tau, and alpha-synuclein ($\alpha$-syn)) are involved in the pathogenesis of a variety of neurodegenerative diseases, referred to as proteinopathies. Indeed, PD, Lewy body dementia, and multisystem atrophy are part of a family called synucleinopathies. We have described the importance of amyloid-beta and tau tracers and the criticality of developing selective PET tracers for each type of aggregate above, in order to assess their relative contribution in pathogenesis. $\alpha$-Syn appears undoubtedly to be an excellent target for PET radiotracer development for PD and other synucleinopathies. $\alpha$-Synuclein inclusions (Lewy bodies) appear before dopaminergic changes, (i.e., premotor PD) so imaging $\alpha$-syn could better predict premotor PD [83]. While success in the development of selective $\alpha$-syn PET imaging agents has not been realized yet, $\alpha$-syn radiotracer could be a potentially useful surrogate marker in clinical trials. Work is ongoing in multiple laboratories throughout the world, and AC Immune and Biogen companies have identified two lead compounds designed to selectively bind to $\alpha$-syn aggregates.

(iii) As mentioned earlier, numerous neurotransmitter systems have been identified and allowed to assess

therapeutics. Among them, the cholinergic system could be of interest for the follow-up of NDD and their treatment. Degeneration of cholinergic neurons is well described in pathophysiology of AD and is associated in several reports with a significant loss of $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$-nAChRs) in the cortex and hippocampus of patients. $\alpha 7$-nAChR mediates various brain functions and represents an important target for drug discovery. In clinical trials with selective $\alpha 7$ agonists, activation of the receptor improved cognitive performance in patients with schizophrenia [84]. The recently developed $^{18}$F-ASEM, a highly $\alpha 7$-nAChR specific and selective radiotracer for brain PET, opens new horizons for studying $\alpha 7$-nAChRs in the living human brain.

Finally, PET imaging in NDD therapeutic development assessment can lead to (i) the study of the role and density of receptor involved, (ii) the study of the mechanism of action of therapeutic drug, and (iii) the optimization of new treatment development by reducing costs and the time required for new drug development.

Nevertheless, the expansion of PET imaging as a reliable biomarker for in vivo treatment evaluation faces the critical lack of effective treatment for NDD patients, especially for AD. Concurrently, new potential applications of these radiotracers initially developed for central application have shown their interest in the field of personalized medicine in numerous peripheral diseases, including cancer. $^{18}$F-DOPA illustrates this concept since it is a well-known excellent tracer for imaging neuroendocrine tumors (NETs), including pheochromocytoma, extraadrenal paraganglioma, medullary thyroid carcinoma, gastro-entero-pancreatic (GEP), or NE tumors (reviewed in [85]). In NET, $^{18}$F-DOPA may be particularly useful in patients with negative $^{68}$Ga-somatostatin analogs. More recently, TSPO PET imaging has been shown to assume a promising involvement in the development of diagnostic strategies in cancer. More recently, TSPO has been introduced as a possible molecular target for peripheral sterile inflammatory diseases PET imaging, making this protein a potential biomarker with the aim of addressing disease heterogeneity, assisting in patient stratification, and contributing to predicting treatment response [86–88]. Finally, amyloid tracers such as $^{18}$F-florbetapir or $^{11}$C-PIB may be promising PET radiotracers for imaging amyloid deposit in cardiac amyloidosis [89, 90], considering that they also exhibit specific affinity for myocardial amyloid fibers.

It would be consider that this field of investigation will grow up in the context of personalized and/or stratified medicine.

## 6. Conclusion

This paper has reviewed findings from PET neuroimaging studies which have contributed to assess efficacy of drugs in NDD. In the last decades, molecular imaging with PET led to the progress in the development of new drugs, thanks to multiple molecular probes imaging biological, functional, and pathological conditions of NDD. Brain PET imaging allows a multiple approach of the disease by assessing several physiopathological pathways like neuroinflammation, neurotransmission, or protein aggregation in the disease. This multiple approach allows to assess drug efficacy from different perspectives and forms the link between clinical and physiopathological conditions. Complementary to the recent concept called "theranostics" referring to the use of molecular targeting vectors labeled either with diagnostic or therapeutic radionuclides for diagnosis and therapy, respectively, brain PET imaging seems to be a relevant and attractive tool in SNC drug development that could help in therapeutic decision-making within the growing framework of precision medicine.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Acknowledgments

## References

[1] C. Reitz and R. Mayeux, "Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers," *Biochemical Pharmacology*, vol. 88, no. 4, pp. 640–651, 2014.

[2] A. Drzezga, H. Barthel, S. Minoshima, and O. Sabri, "Potential clinical applications of PET/MR imaging in neurodegenerative diseases," *Journal of Nuclear Medicine*, vol. 55, no. 2, pp. 47S–55S, 2014.

[3] G. Kovacs and H. Budka, "Current concepts of neuropathological diagnostics in practice: neurodegenerative diseases," *Clinical Neuropathology*, vol. 29, no. 9, pp. 271–288, 2010.

[4] W. W. Che, X. Zhang, and W. J Huang, "Role of neuroinflammation in neurodegenerative diseases (review)," *Molecular Medicine Reports*, vol. 13, no. 4, pp. 3391–3396, 2016.

[5] K. Herholz, "FDG PET and differential diagnosis of dementia," *Alzheimer Disease and Associated Disorders*, vol. 9, no. 1, pp. 6–16, 1995.

[6] F. Squitieri, S. Orobello, M. Cannella et al., "Riluzole protects Huntington disease patients from brain glucose hypometabolism and grey matter volume loss and increases production of neurotrophins," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 36, no. 7, pp. 1113–1120, 2009.

[7] J. Bennett, J. Burns, P. Welch, and R. Bothwell, "Safety and tolerability of R(+) pramipexole in mild-to-moderate Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 49, no. 4, pp. 1179–1187, 2016.

[8] S. Tzimopoulou, V. J. Cunningham, T. E. Nichols et al., "A multicenter randomized proof-of-concept clinical trial applying [18F] FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 22, no. 4, pp. 1241–1256, 2010.

[9] M. Auffret, F. Le Jeune, A. Maurus et al., "Apomorphine pump in advanced Parkinson's disease: effects on motor and nonmotor symptoms with brain metabolism correlations," *Journal of the Neurological Sciences*, vol. 372, pp. 279–287, 2017.

[10] H. Yoshimuta, M. Nakamura, E. Kanda et al., "The effects of olanzapine treatment on brain regional glucose metabolism in neuroleptic-naive first-episode schizophrenic patients," *Human Psychopharmacology: Clinical and Experimental*, vol. 31, no. 6, pp. 419–426, 2016.

[11] M. S. Buchsbaum, M. M. Haznedar, J. Aronowitz et al., "FDG-PET in never-previously medicated psychotic adolescents treated with olanzapine or haloperidol," *Schizophrenia Research*, vol. 94, no. 1–3, pp. 293–305, 2007.

[12] V. Molina, J. D. Gispert, S. Reig et al., "Olanzapine-induced cerebral metabolic changes related to symptom improvement in schizophrenia," *International Clinical Psychopharmacology*, vol. 20, no. 1, pp. 13–18, 2005.

[13] M. Reivich, D. Kuhl, A. Wolf et al., "The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man," *Circulation Research*, vol. 44, no. 1, pp. 127–137, 1979.

[14] L. Picanço, P. Ozela, M. F. Brito Brito et al., "Alzheimer's disease: A review from the pathophysiology to diagnosis, new perspectives for pharmacological treatment," *Current Medicinal Chemistry*, vol. 23, no. 999, p. 1, 2016.

[15] Y. F. Tai, "Applications of positron emission tomography (PET) in neurology," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 75, pp. 669–676, 2004.

[16] J. M. Lehmann, L. B. Moore, T. A. Smith-Oliver, W. O. Wilkison, T. M. Willson, and S. A. Kliewer, "An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma)," *Journal of Biological Chemistry*, vol. 270, no. 22, pp. 12953–12956, 1995.

[17] G. S. Watson, B. A. Cholerton, M. A. Reger et al., "Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study," *American Journal of Geriatric Psychiatry*, vol. 13, no. 11, pp. 950–958, 2005.

[18] M. E. Risner, A. M. Saunders, J. F. B. Altman et al., "Rosiglitazone in Alzheimer's Disease Study Group Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease," *Pharmacogenomics Journal*, vol. 6, no. 4, pp. 246–254, 2006.

[19] M. Gold, C. Alderton, M. Zvartau-Hind et al., "Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study," *Dementia and Geriatric Cognitive Disorders*, vol. 30, no. 2, pp. 131–146, 2010.

[20] C. Harrington, S. Sawchak, C. Chiang et al., "Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies," *Current Alzheimer Research*, vol. 8, no. 5, pp. 592–606, 2011.

[21] F. Squitieri, A. Ciammola, C. Colonnese, and A. Ciarmiello, "Neuroprotective effects of riluzole in Huntington's disease," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 35, no. 1, pp. 221-222, 2008.

[22] A. Bergerot, P. J. Shortland, P. Anand, S. P. Hunt, and T. Carlstedt, "Co-treatment with riluzole and GDNF is necessary for functional recovery after ventral root avulsion injury," *Experimental Neurology*, vol. 187, no. 2, pp. 359–366, 2004.

[23] M. Carbone, S. Duty, and M. Rattray, "Riluzole elevates GLT-1 activity and levels in striatal astrocytes," *Neurochemistry International*, vol. 60, no. 1, pp. 31–38, 2012.

[24] D. H. Mathalon, E. V. Sullivan, K. O. Lim, and A. Pfefferbaum, "Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study," *Archives of General Psychiatry*, vol. 58, no. 2, pp. 148–157, 2001.

[25] J. O. Rinne, D. J. Brooks, M. N. Rossor et al., "11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study," *The Lancet Neurology*, vol. 9, pp. 363–372, 2010.

[26] M. Brody, E. Liu, J. Di et al., "A phase II, randomized, double-blind, placebo-controlled study of safety, pharmacokinetics, and biomarker results of subcutaneous bapineuzumab in patients with mild to moderate Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 54, no. 4, pp. 1509–1519, 2016.

[27] R. Vandenberghe, J. O. Rinne, M. Boada et al., "Bapineuzumab 3000 and 3001 clinical study investigators bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials," *Alzheimer's Research and Therapy*, vol. 8, no. 1, p. 18, 2016.

[28] S. Salloway, R. Sperling, N. C. Fox et al., "Bapineuzumab 301 and 302 clinical trial investigators two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease," *New England Journal of Medicine*, vol. 370, no. 4, pp. 322–333, 2014.

[29] B. P. Imbimbo, S. Ottonello, V. Frisardi et al., "Solanezumab for the treatment of mild-to-moderate Alzheimer's disease," *Expert Review of Clinical Immunology*, vol. 8, no. 2, pp. 135–149, 2012.

[30] X. Pan, Z. Chen, G. Fei et al., "Long-term cognitive improvement after benfotiamine administration in patients with Alzheimer's disease," *Neuroscience Bulletin*, vol. 32, no. 6, pp. 591–596, 2016.

[31] R. S. Doody, M. Farlow, and P. S. Aisen, "Alzheimer's disease cooperative study data analysis and publication committee phase 3 trials of solanezumab and bapineuzumab for Alzheimer's disease," *New England Journal of Medicine*, vol. 370, no. 15, p. 1460, 2014.

[32] S. Ostrowitzki, D. Deptula, L. Thurfjell et al., "Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab," *Archives of Neurology*, vol. 69, pp. 198–207, 2012.

[33] F. Panza, V. Solfrizzi, B. P. Imbimbo et al., "Efficacy and safety studies of gantenerumab in patients with Alzheimer's disease," *Expert Review of Neurotherapeutics*, vol. 14, no. 9, pp. 973–986, 2014.

[34] H. P. Hammes, X. Du, D. Edelstein et al., "Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy," *Nature Medicine*, vol. 9, no. 3, pp. 294–299, 2003.

[35] E. Giacobini and G. Gold, "Alzheimer disease therapy–moving from amyloid-$\beta$ to tau," *Nature Reviews Neurology*, vol. 9, no. 12, pp. 677–686, 2013.

[36] P. Novak, R. Schmidt, E. Kontsekova et al., "Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial," *The Lancet Neurology*, vol. 16, no. 2, pp. 123–134, 2017.

[37] N. Okamura and K. Yanai, "Brain imaging: applications of tau PET imaging," *Nature Reviews Neurology*, vol. 13, no. 4, pp. 197-198, 2017.

[38] K. P. Ng, T. A. Pascoal, S. Mathotaarachchi et al., "Monoamine oxidase B inhibitor, selegiline, reduces (18)F-THK5351 uptake in the human brain," *Alzheimer's Research and Therapy*, vol. 9, p. 25, 2017.

[39] B. Hall, E. Mak, S. Cervenka, F. I. Aigbirhio, J. B. Rowe, and J. T. O'Brien, "In vivo tau PET imaging in dementia:

pathophysiology, radiotracer quantification, and a systematic review of clinical findings," *Ageing Research Reviews*, vol. 36, pp. 50–63, 2017.

[40] S. Haga, K. Akai, and T. Ishii, "Demonstration of microglial cells in and around senile (neuritic) plaques in the Alzheimer brain. An immunohistochemical study using a novel monoclonal antibody," *Acta Neuropathologica*, vol. 77, no. 6, pp. 569–575, 1989.

[41] J. M. Craft, D. M. Watterson, and L. J. Van Eldik, "Neuro-inflammation: a potential therapeutic target," *Expert Opinion on Therapeutic Targets*, vol. 9, no. 5, pp. 887–900, 2005.

[42] J. Butchart, L. Brook, V. Hopkins et al., "Etanercept in Alzheimer disease: a randomized, placebo-controlled, double-blind, phase 2 trial," *Neurology*, vol. 84, no. 23, pp. 2161–2168, 2015.

[43] R. S. Turner, R. G. Thomas, S. Craft et al., "Alzheimer's disease cooperative study a randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease," *Neurology*, vol. 85, no. 16, pp. 1383–1391, 2015.

[44] M. E. Cudkowicz, J. M. Shefner, D. A. Schoenfeld et al., "Trial of celecoxib in amyotrophic lateral sclerosis," *Annals of Neurology*, vol. 60, no. 1, pp. 22–31, 2006.

[45] A. C. Dupont, B. Largeau, M. J. Santiago Ribeiro, D. Guilloteau, C. Tronel, and N. Arlicot, "Translocator protein-18 kDa (TSPO) Positron Emission Tomography (PET) imaging and its clinical impact in neurodegenerative diseases," *International Journal of Molecular Sciences*, vol. 18, no. 4, p. 785, 2017.

[46] R. Slavik, U. Grether, A. Müller Herde et al., "Discovery of a high affinity and selective pyridine analog as a potential positron emission tomography imaging agent for cannabinoid type 2 receptor," *Journal of Medicinal Chemistry*, vol. 58, no. 10, pp. 4266–4277, 2015.

[47] M. Mishina, K. Ishiwata, M. Naganawa et al., "Adenosine A(2A) receptors measured with [C]TMSX PET in the striata of Parkinson's disease patients," *PLoS One*, vol. 6, no. 2, article e17338, 2011.

[48] E. Rissanen, J. R. Virta, T. Paavilainen et al., "Adenosine A2A receptors in secondary progressive multiple sclerosis: a [(11)C]TMSX brain PET study," *Journal of Cerebral Blood Flow and Metabolism*, vol. 33, no. 9, pp. 1394–1401, 2013.

[49] I. F. Antunes, J. Doorduin, H. J. Haisma et al., "18F-FEAnGA for PET of β-glucuronidase activity in neuroinflammation," *Journal of Nuclear Medicine*, vol. 53, no. 3, pp. 451–458, 2012.

[50] A. Takano, F. Piehl, J. Hillert et al., "In vivo TSPO imaging in patients with multiple sclerosis: a brain PET study with [18F]FEDAA1106," *EJNMMI Research*, vol. 3, no. 1, p. 30, 2013.

[51] J. N. Ratchford, C. J. Endres, D. A. Hammoud et al., "Decreased microglial activation in MS patients treated with glatiramer acetate," *Journal of Neurology*, vol. 259, no. 6, pp. 1199–1205, 2012.

[52] L. Airas, A. M. Dickens, P. Elo et al., "In vivo PET imaging demonstrates diminished microglial activation after fingolimod treatment in an animal model of multiple sclerosis," *Journal of Nuclear Medicine*, vol. 56, no. 2, pp. 305–310, 2015.

[53] M. Sucksdorff, E. Rissanen, J. Tuisku et al., "Evaluation of the effect of fingolimod treatment on microglial activation using serial PET imaging in multiple sclerosis," *Journal of Nuclear Medicine*, vol. 58, no. 10, pp. 1646–1651, 2017.

[54] R. Dodel, A. Spottke, A. Gerhard et al., "Minocycline 1-year therapy in multiple-system-atrophy: effect on clinical symptoms and [(11)C] (R)-PK11195 PET (MEMSA-trial)," *Movement Disorders*, vol. 25, no. 1, pp. 97–107, 2010.

[55] A. L. Bartels, A. T. M. Willemsen, J. Doorduin, E. F. J. de Vries, R. A. Dierckx, and K. L. Leenders, "[11C]-PK11195 PET: quantification of neuroinflammation and a monitor of anti-inflammatory treatment in Parkinson's disease?," *Parkinsonism and Related Disorders*, vol. 16, no. 1, pp. 57–59, 2010.

[56] R. Pihlaja, J. Takkinen, O. Eskola et al., "Monoacylglycerol lipase inhibitor JZL184 reduces neuroinflammatory response in APdE9 mice and in adult mouse glial cells," *Journal of Neuroinflammation*, vol. 12, no. 1, p. 81, 2015.

[57] A. Jucaite, P. Svenningsson, J. O. Rinne et al., "Effect of the myeloperoxidase inhibitor AZD3241 on microglia: a PET study in Parkinson's disease," *Brain*, vol. 138, no. 9, pp. 2687–2700, 2015.

[58] Z. Gao and S. E. Tsirka, "Animal models of MS reveal multiple roles of microglia in disease pathogenesis," *Neurology Research International*, vol. 2011, Article ID 383087, 9 pages, 2011.

[59] A. O. Dulamea, "Role of oligodendrocyte dysfunction in demyelination, remyelination and neurodegeneration in multiple sclerosis," *Advances in Experimental Medicine and Biology*, vol. 958, pp. 91–127, 2017.

[60] M. Matloubian, C. G. Lo, G. Cinamon et al., "Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1," *Nature*, vol. 427, no. 6972, pp. 355–360, 2004.

[61] T. Ziemssen and W. Schrempf, "Glatiramer acetate: mechanisms of action in multiple sclerosis," *International Review of Neurobiology*, vol. 79, pp. 537–570, 2007.

[62] P. H. Elsinga, K. Hatano, and K. Ishiwata, "PET tracers for imaging of the dopaminergic system," *Current Medicinal Chemistry*, vol. 13, no. 18, pp. 2139–2153, 2006.

[63] A. Antonini and R. DeNotaris, "PET and SPECT functional imaging in Parkinson's disease," *Sleep Medicine*, vol. 5, no. 2, pp. 201–206, 2004.

[64] A. Antonini, J. Schwarz, W. H. Oertel, H. F. Beer, U. D. Madeja, and K. L. Leenders, "[11C]raclopride and positron emission tomography in previously untreated patients with Parkinson's disease: influence of L-dopa and lisuride therapy on striatal dopamine D2-receptors," *Neurology*, vol. 44, no. 7, pp. 1325–1329, 1994.

[65] A. Antonini, J. Schwarz, W. H. Oertel, O. Pogarell, and K. L. Leenders, "Long-term changes of striatal dopamine D2 receptors in patients with Parkinson's disease: a study with positron emission tomography and [11C]raclopride," *Movement Disorders*, vol. 12, no. 1, pp. 33–38, 1997.

[66] N. Pavese, A. H. Evans, Y. F. Tai et al., "Clinical correlates of levodopa-induced dopamine release in Parkinson disease: a PET study," *Neurology*, vol. 67, no. 9, pp. 1612–1617, 2006.

[67] F. Niccolini, L. Rocchi, and M. Politis, "Molecular imaging of levodopa-induced dyskinesias," *Cellular and Molecular Life Sciences*, vol. 72, no. 11, pp. 2107–2117, 2015.

[68] R. de la Fuente-Fernández, P. K. Pal, F. J. Vingerhoets et al., "Evidence for impaired presynaptic dopamine function in parkinsonian patients with motor fluctuations," *Journal of Neural Transmission*, vol. 107, no. 1, pp. 49–57, 2000.

[69] G. K. Wenning, P. Odin, P. Morrish et al., "Short- and long-term survival and function of unilateral intrastriatal dopaminergic grafts in Parkinson's disease," *Annals of Neurology*, vol. 42, no. 1, pp. 95–107, 1997.

[70] C. R. Freed, P. E. Greene, R. E. Breeze et al., "Transplantation of embryonic dopamine neurons for severe Parkinson's disease," *New England Journal of Medicine*, vol. 344, no. 10, pp. 710–719, 2001.

[71] C. W. Olanow, C. G. Goetz, J. H. Kordower et al., "A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease," *Annals of Neurology*, vol. 54, no. 3, pp. 403–414, 2003.

[72] M. Politis and P. Piccini, "In vivo imaging of the integration and function of nigral grafts in clinical trials," *Progress in Brain Research*, vol. 200, pp. 199–220, 2012.

[73] M. Politis and P. Piccini, "Brain imaging after neural transplantation," *Progress in Brain Research*, vol. 184, pp. 193–203, 2010.

[74] S. Sturm, A. Forsberg, S. Nave et al., "Positron emission tomography measurement of brain MAO-B inhibition in patients with Alzheimer's disease and elderly controls after oral administration of sembragiline," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 44, no. 3, pp. 382–391, 2017.

[75] A. Kadir, T. Darreh-Shori, O. Almkvist et al., "PET imaging of the in vivo brain acetylcholinesterase activity and nicotine binding in galantamine-treated patients with AD," *Neurobiology of Aging*, vol. 29, no. 8, pp. 1204–1217, 2008.

[76] P. R. A. Stokes, J. F. Myers, N. J. Kalk et al., "Acute increases in synaptic GABA detectable in the living human brain: a [11C] Ro15-4513 PET study," *Neuroimage*, vol. 99, pp. 158–165, 2014.

[77] W. G. Frankle, R. Y. Cho, K. M. Prasad et al., "In vivo measurement of GABA transmission in healthy subjects and schizophrenia patients," *American Journal of Psychiatry*, vol. 172, no. 11, pp. 1148–1159, 2015.

[78] A. Mallik, A. Drzezga, and S. Minoshima, "Clinical amyloid imaging," *Seminars in Nuclear Medicine*, vol. 47, no. 1, pp. 31–43, 2017.

[79] L. K. Parvathenani, S. Tertyshnikova, and C. R. Greco, "P2X7 mediates superoxide production in primary microglia and is up-regulated in a transgenic mouse model of Alzheimer's disease," *Journal of Biological Chemistry*, vol. 278, no. 15, pp. 13309–13317, 2003.

[80] Y. Yiangou, P. Facer, and P. Durrenberger, "COX-2, CB2 and P2X7-immunoreactivities are increased in activated microglial cells/macrophages of multiple sclerosis and amyotrophic lateral sclerosis spinal cord," *BMC Neurology*, vol. 6, no. 1, p. 12, 2006.

[81] M. Díaz-Hernández, M. Díez-Zaera, and J. Sánchez-Nogueiro, "Altered P2X7-receptor level and function in mouse models of Huntington's disease and therapeutic efficacy of antagonist administration," *FASEB Journal*, vol. 23, no. 6, pp. 1893–1906, 2009.

[82] Z. Ali, B. Laurijssens, and T. Ostenfeld, "Pharmacokinetic and pharmacodynamic profiling of a P2X7 receptor allosteric modulator GSK1482160 in healthy human subjects," *British Journal of Clinical Pharmacology*, vol. 75, no. 1, pp. 197–207, 2013.

[83] D. W. Dickson, H. Braak, and J. E. Duda, "Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria," *The Lancet Neurology*, vol. 8, no. 12, pp. 1150–1157, 2009.

[84] D. F. Wong, H. Kuwabara, and A. G. Horti, "PET Brain imaging of $\alpha$7-nAChR with [$^{18}$F]ASEM: reproducibility, occupancy, receptor density, and changes in schizophrenia," *International Journal of Neuropsychopharmacology*, 2018, In press.

[85] S. Balogova, J. N. Talbot, and V. Nataf, "18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 40, no. 6, pp. 943–966, 2013.

[86] M. N. Tantawy, H. Charles Manning, and T. E. Peterson, "Translocator protein PET imaging in a preclinical prostate cancer model," *Molecular Imaging and Biology*, vol. 20, no. 2, pp. 200–204, 2017.

[87] B. Zinnhardt, H. Pigeon, and B. Thézé, "Combined PET imaging of the inflammatory tumor microenvironment identifies margins of unique radiotracer uptake," *Cancer Research*, vol. 77, no. 8, pp. 1831–1841, 2017.

[88] A. R. Awde, R. Boisgard, and B. Thézé, "The translocator protein radioligand 18F-DPA-714 monitors antitumor effect of erufosine in a rat 9L intracranial glioma model," *Journal of Nuclear Medicine*, vol. 54, no. 12, pp. 2125–2131, 2013.

[89] S. Dorbala, D. Vangala, and J. Semer, "Imaging cardiac amyloidosis: a pilot study using 18F-florbetapir positron emission tomography," *Imaging Cardiac Amyloidosis*, vol. 41, no. 9, pp. 1652–1662, 2014.

[90] B. Pilebro, S. Arvidsson, and P. Lindqvist, "Positron emission tomography (PET) utilizing Pittsburgh compound B (PIB) for detection of amyloid heart deposits in hereditary transthyretin amyloidosis (ATTR)," *Journal of Nuclear Cardiology*, vol. 25, no. 1, pp. 240–248, 2016.