

Review

# Positron Emission Tomography Molecular Imaging of the Major Neurodegenerative Disorders: Overview and Pictorial Essay, from a Nuclear Medicine Center's Perspective

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## Abstract

Computed tomography (CT) and magnetic resonance imaging (MRI) provide key structural information on brain pathophysiology. Positron emission tomography (PET) measures metabolism in the living brain; it plays an important role in molecular neuroimaging and is rapidly expanding its field of application to the study of neurodegenerative diseases. Different PET radiopharmaceuticals allow *in vivo* characterization and quantization of biological processes at the molecular and cellular levels, from which many neurodegenerative diseases develop. In addition, hybrid imaging tools such as PET/CT and PET/MRI support the utility of PET, enabling the anatomical mapping of functional data. In this overview, we describe the most commonly used PET tracers in the diagnostic work-up of patients with Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases. We also briefly discuss the pathophysiological processes of tracer uptake in the brain, detailing their specific cellular pathways in clinical cases. This overview is limited to imaging agents already applied in human subjects, with particular emphasis on those tracers used in our department.

**Keywords:** PET; amyloid imaging; tau protein; molecular imaging; neurodegenerative diseases; [<sup>18</sup>F]FDOPA; [<sup>18</sup>F]FDG; MRI

## 1. Introduction

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and Lewy body dementia (LBD), are often associated with pronounced protein deposition in the brain. Although NDs determine different clinical conditions with a different clinical onset, they share some features, such as neuro-inflammation, the breakdown of molecular cleaning pathways, and selected or generalized loss of neurons [1]. Certain neurodegenerative diseases are also linked to intracellular or extracellular macro-aggregates in selected brain structures, which are represented by amyloid-beta ( $A\beta$ ) for AD, tau ( $\tau$ ) protein in AD and other types of dementia,  $\alpha$ -synuclein in PD and LBD, and Creutzfeldt-Jacob disease, which is a prion-linked neurodegenerative disorder [2].  $A\beta$  is essential in signal regulation, neuronal metabolism, and intracellular delivery of metabolites [3], and the  $\tau$  protein is involved in cellular stability, in particular of axonal microtubules [4]. Both proteins aggregate and precipitate in the white and/or grey matter, in the form of fibrillary structures or as oligomers [5]. Naturally, some risk factors promote the development of clinical onset. Aging, genetic factors, brain vascular

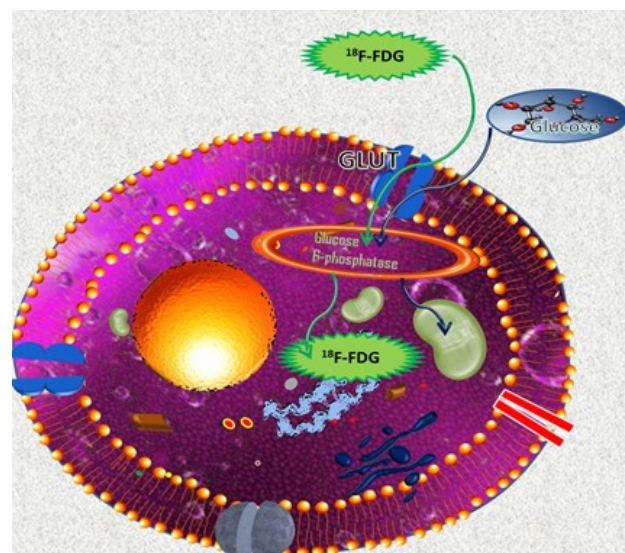
damage, and lifestyle (alcohol consumption and obesity) can be underlying determinants in both non-cognitive and cognitive symptoms of NDs. On the other hand, in several patients, the leading cause of the disease seems to be unclear; in some of these patients the role of infectious agents is under study [6]. The main aim of neuroimaging in the management of patients with NDs is to identify the underlying disease. In this field, contrast-enhanced computed tomography (CT) of the brain is useful for the preliminary evaluation of brain anatomy and to identify structural abnormalities. Ventricular enlargement, vascular lesions, and brain atrophy are significant findings that can be assessed using CT in ND patients. However, these are common, non-specific features of NDs and other brain disorders, such as aging, epilepsy, vascular damage, and infectious diseases [7]. The main advantage of the CT is that it is widely available, although the diagnostic accuracy can be suboptimal, due to the low soft tissue contrast. Magnetic resonance imaging (MRI) is the gold standard imaging technique for the characterization of brain morphology and visualization of functional processes. Due to the high soft tissue contrast and the possibility of a multi-planar brain evaluation, MRI morphological sequences also enable brain lesions and/or vascular damage to be diagnosed [8].



MRI can also reveal patterns of neurodegeneration such as atrophy of the temporal and parietal regions in AD or atrophy of the frontotemporal lobes in frontotemporal dementia (FTD) [9]. However, these patterns are generally detectable in the advanced stages of the disease; other NDs are not associated with brain atrophy [10]. Ventricular enlargement is generally considered as a further non-specific finding. Shape analysis of the brain ventricles may show that markers, such as ventricular perimeters, can be adequately extrapolated from MR morphological imaging to differentiate AD from healthy controls [11]. In the last few decades, functional MRI (fMRI) has become a valid tool for the detection of alterations in the hippocampus in selected AD patients. In several studies, it has been demonstrated that fMRI can help in the detection of altered connectivity and hippocampal co-activation in AD patients [12,13], while arterial spin labeling (ASL) has shown promising results in the depiction of brain metabolism and perfusion [14]. ASL-MRI and oxygen-15 labeled water ( $[^{15}\text{O}]\text{H}_2\text{O}$ ) positron emission tomography (PET) measurements of the regional cerebral blood flow (CBF) are strictly correlated across different perfusion states. In fact, as is ASL-MRI,  $[^{15}\text{O}]\text{H}_2\text{O}$  is a useful PET tracer for assessing regional cerebral blood flow in both white and grey matter [15]. However, these techniques still need to be improved and validated. The main goal in the examination of ND patients is an early and specific diagnosis, in order to select patients who could potentially benefit from therapies (such as PD patients) and who could be enrolled in experimental treatment programs. In the past two decades, novel radiopharmaceuticals developed for PET imaging of the brain have enabled the diagnosis and monitoring of several NDs concurrently. Novel PET tracers have been used to show the molecular abnormalities at the basis of the ND under study [1], which is essential for early diagnosis and for investigating potential pharmacological treatments. The aim of this review is to summarize the information on the most widely used radiopharmaceuticals for the diagnosis and monitoring of NDs, from the perspective of nuclear physicians. Considering the large number of PET tracers investigated in human studies and animal models, this overview focuses only on those which, to the best of our knowledge, are the main radiopharmaceuticals used for PET imaging of NDs in humans.

## 2. $[^{18}\text{F}]\text{FDG}$ PET

Glucose is the energy substrate of the brain. In all NDs, glucose consumption tends to deteriorate in selected neurons. The glucose analogue  $[^{18}\text{F}]\text{Fluorodeoxyglucose}$  ( $[^{18}\text{F}]\text{FDG}$ ) circulates in the blood, crosses the blood-brain barrier, and is highly metabolized in grey matter. In fact, after uptake and phosphorylation by hexokinase,  $[^{18}\text{F}]\text{FDG}$  becomes trapped in neurons, enabling the imaging and measurement of the cerebral metabolic rate of glucose (Fig. 1).



**Fig. 1. Glucose and  $[^{18}\text{F}]\text{FDG}$  cellular uptake.** Glucose and  $[^{18}\text{F}]\text{FDG}$  enter the cells via glucose transporter membrane proteins (GLUTs); subsequently, both are phosphorylated by glucose-6-phosphatase. Phosphorylated glucose can be further metabolized by the cells in mitochondria, while phosphorylated  $[^{18}\text{F}]\text{FDG}$  cannot be further metabolized and remains trapped in the cells. FDG, fluorodeoxyglucose.

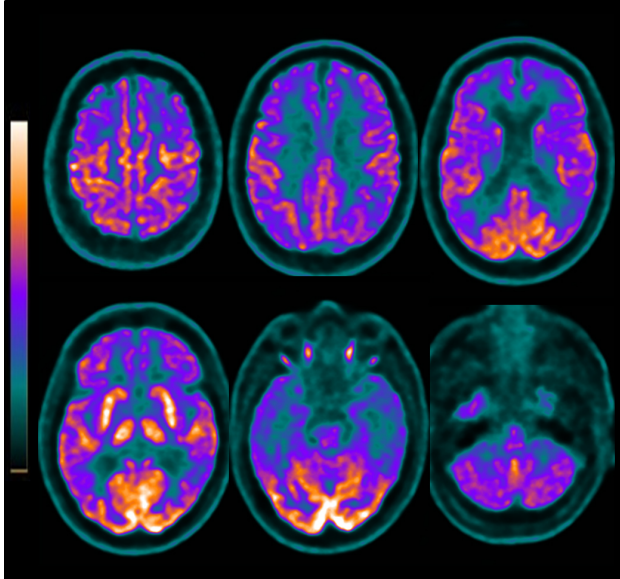
Preliminary studies on PET imaging have focused on brain metabolism and demonstrated that the level of cerebral glucose metabolism is a reliable measure of neuronal activity [16]. In line with the work of Sokoloff *et al.* [16], synaptic activity is directly proportional to neuronal glucose metabolism, as confirmed by several human resting and functional activation studies [17–19]. In healthy controls, the most intense  $[^{18}\text{F}]\text{FDG}$  uptake occurs in the subcortical putamen, caudate nucleus, and thalamus, followed by high uptake in the cortical gray matter. The globus pallidus typically demonstrates mild uptake, and the white matter shows low uptake. On the other hand, the precuneus and posterior cingulate, parietal and frontal lobes normally show the highest tracer uptake [20].

$[^{18}\text{F}]\text{FDG}$  PET of the brain thus enables whole brain glucose metabolism to be mapped, showing different pathological conditions such as epilepsy [21], brain tumors (high-grade gliomas) [22], and NDs [23]. The reduction of  $[^{18}\text{F}]\text{FDG}$  uptake in selected brain regions can also help clinicians to recognize NDs, which also helps to improve the differential diagnosis.

### 2.1 $[^{18}\text{F}]\text{FDG}$ PET in Dementia

The clinical application of  $[^{18}\text{F}]\text{FDG}$  PET concerns regional neocortical hypometabolism as a marker used to differentiate dementias, although regional patterns can overlap [24]. In AD, hypometabolism can appear before atrophy is detectable [25]. Notably, there is symmetrical hypometabolism in the temporal- parietal, posterior cingulate,

and medial temporal cortices (Fig. 2). Varying sensitivities and specificities for AD diagnosis have been reported. According to Smailagic *et al.* [26], the sensitivity and specificity in diagnosing AD are 76% and 82% respectively in a population with mild cognitive impairment (MCI).

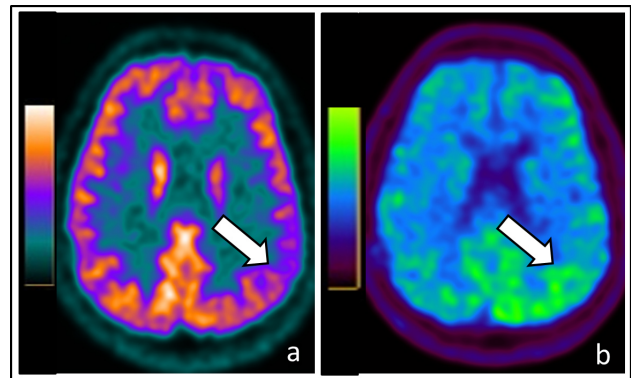


**Fig. 2.** [ $^{18}\text{F}$ ]Fluorodeoxyglucose and Alzheimer's disease. A 67-year-old female patient with a clinical diagnosis of Alzheimer's disease. Axial [ $^{18}\text{F}$ ]Fluorodeoxyglucose Positron Emission Tomography (PET) views show hypometabolism in frontal, parietal, and temporal regions.

However, due to the heterogeneity of examined patients, data on the diagnostic accuracy are often not available. Another study in 67 patients diagnosed with AD variants [25] demonstrated an overall good diagnostic performance of brain [ $^{18}\text{F}$ ]FDG PET in examining AD variant-specific patterns of brain hypometabolism. This was demonstrated as being highly consistent at the single-subject level and already evident in the prodromal stages, thus representing important markers of disease neurodegeneration, with a highly supportive diagnostic and prognostic role.

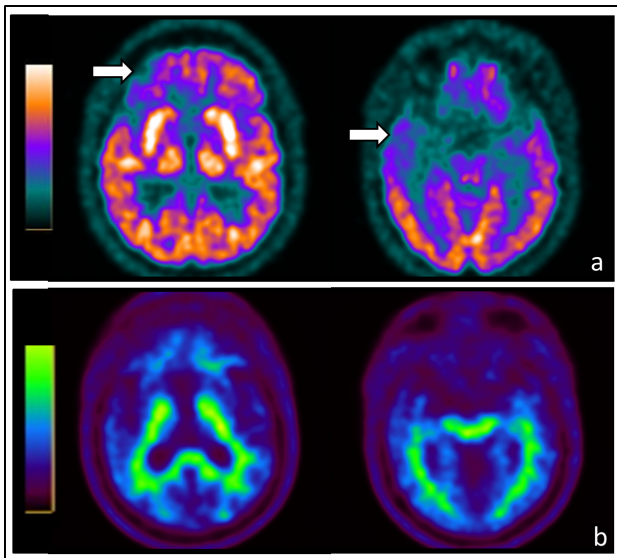
At pathological analysis, AD is linked to early neuronal loss and gliosis in the mesial-temporal cortex, and subsequent extension to other brain structures. Pathological hallmarks are represented by  $A\beta$  plaques and  $\tau$  proteins. The earliest changes in metabolism at PET imaging can be usually seen in the posterior cingulate gyrus [27]. However, the typical pattern of reduced tracer uptake generally concerns the posterior cingulate gyri, precuneus, posterior temporal lobes, and parietal lobes [28,29]. Metabolism impairment can be asymmetric between the two hemispheres, or unilateral. Hypometabolism in the frontal lobes may also be found in advanced AD patients. In NDs, sparing of the sensorimotor cortex may also be observed in an ad-

vanced stage of the disease [30]. To improve diagnostic accuracy, some studies support the utility of the dual tracer brain PET with both [ $^{18}\text{F}$ ]FDG and amyloid tracers in the diagnostic workup of AD (Fig. 3), depending on the clinical presentation [23]. The commercial availability of hybrid PET/MRI scanners is also improving confidence in the management of NDs, by the added value of simultaneous morphological and functional evaluation of the brain. In the early stages of AD, with structural MRI it is very difficult to differentiate the signs of atrophy in the course of AD from those related to physiological brain aging [31]. In general, full-blown forms of atrophy are bilateral and symmetrical, prevailing in the temporal lobes and temporal-mesial structures, including *ex vacuo* enlargement of the ventricular and cerebrospinal fluid (CSF) spaces, and sparing of the primary sensorimotor cortex. Moreover, the evolution of atrophy in AD is more rapid than the atrophy occurring with normal aging. MRI in patients with AD can reveal increased amounts of white matter signal hyperintensity in the periventricular and deep white matter regions on T2-weighted and T2-fluid-attenuated inversion recovery (FLAIR) sequences.



**Fig. 3.** Dual tracer imaging. Axial brain [ $^{18}\text{F}$ ]FDG PET view in a 48-year-old male with *Mild Cognitive Impairment*, showing hypometabolism in the left parietal region (a). Corresponding axial [ $^{18}\text{F}$ ]Flutemetamol PET view (b) shows pathological amyloid burden in the same region.

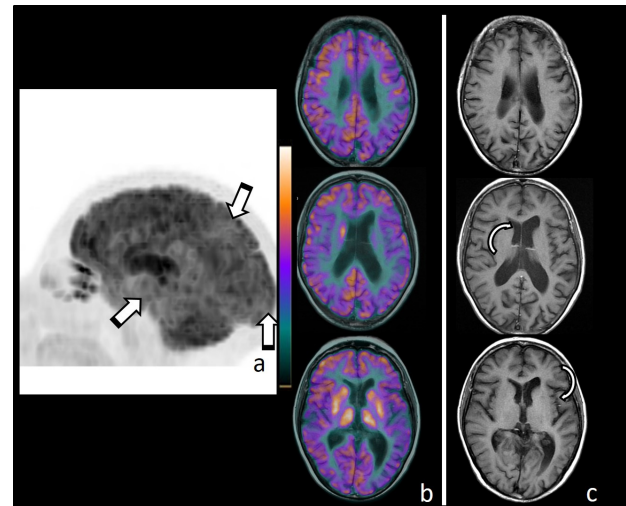
Volumetric software for quantifying hippocampal volumes can also be helpful [32]. The experience with fMRI has shown that there is impaired connectivity in the default mode network in AD [33]. Perfusion MRI with dynamic susceptibility contrast and ASL has demonstrated decreased CBF in bilateral temporal-parietal regions and the posterior cingulate, consistent with regional changes detected by PET or single photon emission computed tomography (SPECT) [34,35]. PET/MRI is therefore a hot topic in dementia research, with an emphasis on AD, thanks to the promising results of combining information from both the PET and MRI. In a typical brain PET/MRI study protocol, the MRI acquisition can take up to 60 minutes, while the PET scan



**Fig. 4. Dual tracer imaging of frontotemporal dementia.** In a 68-year-old male patient with clinical suspicion of frontotemporal dementia, [ $^{18}\text{F}$ ]FDG PET views show selected hypometabolism in the right frontal and temporal regions (a, arrows), confirming the diagnosis. Correlative [ $^{18}\text{F}$ ]Flutemetamol PET (b) supported clinical and imaging findings, excluding pathological amyloid burden in the brain.

can take 15 minutes. However, unlike PET/CT, the acquisition protocol is simultaneous, minimizing motion artifacts. Furthermore, hybrid PET/MRI corrects for the partial volume effect by improving the quantitative analysis of tracer activity on brain volume. MRI co-registered with PET can also provide valuable insights into the differential diagnosis of AD by combining structural and advanced functional techniques in a predefined multimodal protocol. PET/MRI facilitates the correlation of CBF, morpho-structural abnormalities with glucose metabolism, and amyloid plaque arrangement [36]. CBF derived from ASL has proven to be comparable with [ $^{18}\text{F}$ ]FDG PET in the differential diagnosis of AD, FTD, and dementia with Lewy bodies (DLB) [37,38]. In a PET/MRI study with functional sequences, in patients with AD, the intrinsic connectivity between the hippocampus and the precuneus was found to be significantly reduced and the glucose metabolism was reduced in the precuneus but was unchanged in the hippocampus [39]. All these features could improve confidence in diagnosing AD and managing such patients. However, it is important to consider that a comprehensive neuropsychological examination in a mixed sample of neurological patients should form the basis of the diagnostic workup of AD patients, while imaging could be of help in reaching the final diagnosis. On the other hand, decisions based on cognitive test results alone appear limited. The clinical impression based on anamnestic and clinical information obtained by the neuropsychological examiner plays a crucial role in the identification of AD patients in routine clinical practice. In FTD,

hypometabolic regions include the frontal and anterior temporal lobes, cingulate gyri, uncus, insula, basal ganglia, and medial thalamus. Hypometabolism is generally asymmetric (Fig. 4), with a sensitivity and specificity of 88% and 91%, respectively [11].

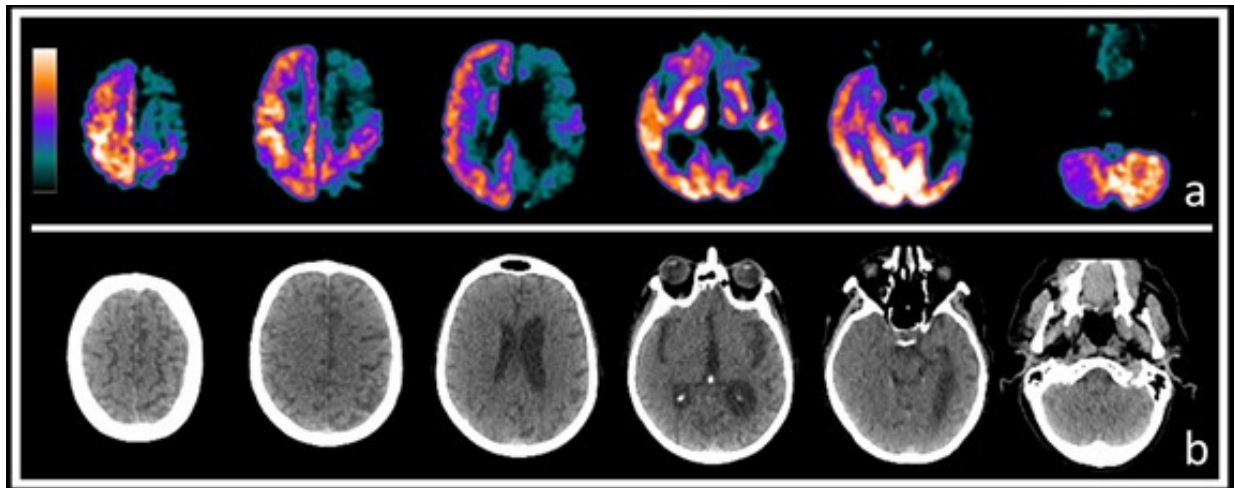


**Fig. 5. PET/MRI and Lewy Body Dementia (LBD).** A 60-year-old woman with clinical suspicion of LBD dementia (cognitive impairment, parkinsonism, and visual hallucinations), examined by PET/MRI with [ $^{18}\text{F}$ ]FDG: PET maximum-intensity projection (a) shows diffuse hypometabolism in the brain, particularly in parietal and temporal regions and in the occipital lobes, as evident in correlative axial PET/MRI views. (b) MRI displayed mild ventricular enlargement and mild diffuse atrophy (c).

Brain [ $^{18}\text{F}$ ]FDG PET is therefore the method of choice in the diagnosis of such disease, since the hallmark MRI feature is frontal and temporal lobe atrophy, with relative preservation of the posterior areas, which may be detectable only in the advanced stage [40]. Also in this clinical setting, interesting indications are provided by fMRI. In FTD patients, MRI with ASL sequences can detect the following: frontotemporal hypoperfusion compared with cognitively normal subjects with sparing of the parietal and occipital brain regions; greater perfusion in the parietal lobe compared with AD; absence of anatomical abnormalities underlying the areas of hypoperfusion; and decreased perfusion in the frontal cortex correlated with cognitive impairment, thus ASL-MRI can estimate the severity of FTD [41].

[ $^{18}\text{F}$ ]FDG PET/MRI imaging may thus reveal a strict relationship between hypoperfusion and hypometabolism; however, the areas of hypometabolism are more extensive than the hypoperfused areas [42]. Similarly to AD, relative sparing of the sensory-motor cortex is usually found.

Among dementias, Lewy Body Dementia (LBD) is the second most common ND in patients over 65 years of age. The classic clinical triad includes fluctuating levels of cognitive arousal, parkinsonism, and visual hallucinations. The



**Fig. 6. PET imaging of cortico-basal degeneration.** A 59-year-old man was examined for clinical suspicion of corticobasal degeneration by [ $^{18}\text{F}$ ]FDG PET/CT of the brain. Axial PET views (a) clearly show severe asymmetrical left hemisphere hypometabolism and reduction in uptake in the right cerebellar hemisphere (crossed cerebellar diaschisis). Correlative CT (b) supported the diagnosis by showing ipsilateral ventricular enlargement and atrophy.

pattern of glucose metabolism impairment on [ $^{18}\text{F}$ ]FDG PET is usually represented by bilateral parietal and posterior temporal deficit of tracer uptake and hypometabolism in the posterior cingulate gyrus [24]. Early diagnosis of DLB has been challenging, particularly in the context of differentiation with Parkinson's disease-related dementia and other forms, such as AD and rapidly progressive dementia. In fact, unlike other types of dementia, impairment of glucose metabolism of the occipital lobes is not uncommon (Fig. 5), which is an imaging feature congruent with the clinical diagnosis of LBD [24]. Another feature suggestive of early diagnosis of LBD is the relative preservation of amygdala metabolism, recently defined by Pillai *et al.* [43] as the amygdala sign. Functional MRI, especially on hybrid scanners, could improve the diagnosis by highlighting a lack of connectivity between cortical regions [44].

FTD is a neurodegenerative disorder presenting with degeneration of the frontal and temporal lobes. No approved pharmacological interventions for FTD are available [45]. Patients often present social impairment and disinhibited, impulsive behavior [46]. In patients with FTD, a significant association between higher levels of education and lower brain glucose metabolism is seen, supporting the cognitive reserve hypothesis—defined as the ability to maintain cognitive functions relatively well at a given level of pathology—as reported in a recent paper by Beyer *et al.* [47]. Although no pharmacological treatment is available for FTD, a precise diagnosis is needed to rule out psychiatric disorders that are characterized by disinhibition and cognitive impairment [48].

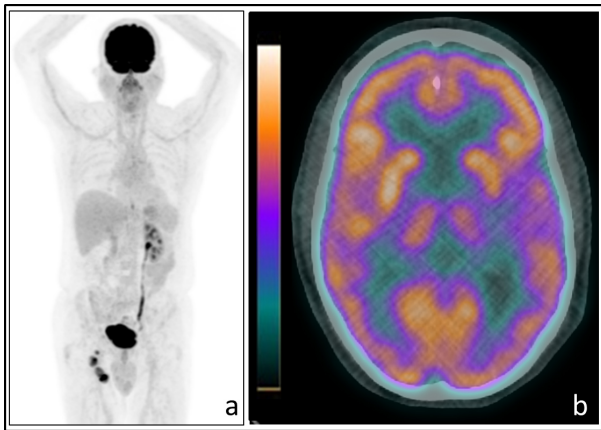
MRI is also able to overcome the limitations of PET imaging, by improving temporal and soft tissue contrast and motion artifacts, and reducing patient exposure to radiation. In our opinion, PET/MRI will play a predominant role in the

evaluation of ND patients. However, the current availability of hybrid PET/MRI scanners is currently insufficient to replace conventional PET/CT imaging.

A multimodal approach should, however, be combined with clinical examinations. The use of novel PET radiopharmaceuticals, such as  $A\beta$  and  $\tau$  tracers, could further aid towards an in-depth understanding of this highly disabling disease [49]. On this topic, structural MRI does not seem to be useful since the MRI findings of DLB are nonspecific. Brain MRI studies have demonstrated variable volume loss of white and cortical matter with relative preservation of the hippocampus [50]. Compared with AD-related forms of atrophy, most studies have reported that patients with dementia DLB had less severe temporal atrophy [51,52]. However, an association between hypometabolism and hypoperfusion correlating with [ $^{18}\text{F}$ ]FDG PET studies and ASL in MRI has been demonstrated [53].

## 2.2 [ $^{18}\text{F}$ ]FDG PET in Parkinson's Disease and Parkinsonism

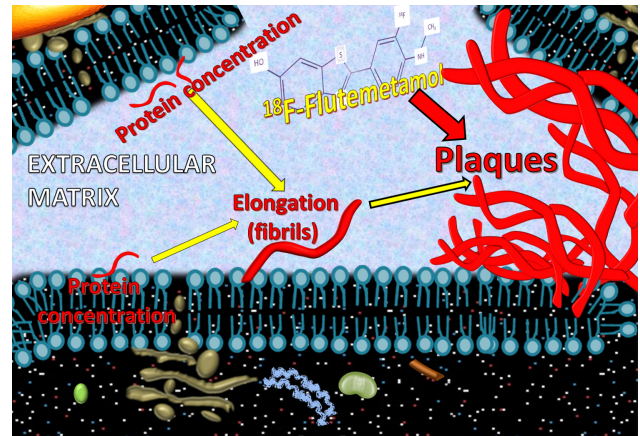
[ $^{18}\text{F}$ ]FDG PET is useful in the management of patients with cognitive impairment; however, it cannot easily detect the reduction in metabolism in the striatum, due to its high rate of normal distribution in healthy brain structures. [ $^{18}\text{F}$ ]FDG PET can thus only support the diagnosis of PD, by characterizing specific uptake patterns when the clinical diagnosis of parkinsonism or PD is unclear [54,55]. Thus, in line with available data, brain [ $^{18}\text{F}$ ]FDG PET may play a limited role in the diagnosis of parkinsonism [56,57], with the emphasis on the diagnosis of the dementia complex associated with PD, which occurs in a significant minority of PD patients. Eggers *et al.* [58] examined a cohort of 64 PD patients, with both akinetic-rigid and tremor-dominant features, using [ $^{18}\text{F}$ ]fluoro-L-phenylalanine ([ $^{18}\text{F}$ ]FDOPA)



**Fig. 7. Brain vascular injury.** A 57-year-old man with Hodgkin's lymphoma was examined by whole-body PET (a), showing pathological  $[^{18}\text{F}]$ FDG uptake in right inguinal lymphadenopathies. Axial PET/CT detail of the basicranium (b) shows focal hypometabolism in the left putamen, due to deep brain infarct, as confirmed during patient anamnesis.

and  $[^{18}\text{F}]$ FDG PET of the brain. They showed a clear difference between the two subgroups of patients in the ventral striatum, reporting a significantly lower neuronal glucose metabolism within the ventral striatum for akinetic-rigid patients compared with those with tremor-dominant symptomatology. These studies could provide significant information on the pathogenesis of PD and its complex molecular mechanisms [59]. However, despite the widespread use of  $[^{18}\text{F}]$ FDG PET in clinical practice and extensive research, there is still very limited evidence for the use of  $[^{18}\text{F}]$ FDG PET in PD patients. According to the majority of researchers,  $[^{18}\text{F}]$ FDG PET is a clinically useful imaging biomarker only for idiopathic PD and atypical parkinsonism or parkinsonian syndromes associated with dementia [60]. The potential impact of  $[^{18}\text{F}]$ FDG PET in this aforementioned clinical setting could be of special interest, by highlighting the different patterns of hypometabolism in selected brain regions. Corticobasal degeneration (CBD) is a form of neuronal degeneration, a dementia involving the loss of cognitive functions as well as movement and vision. The loss of neurons in this disease is generally asymmetrical or unilateral (Fig. 6), concerning only one brain hemisphere [61]. For this reason,  $[^{18}\text{F}]$ FDG may be a reliable marker of disease, helping to easily identify the disease location and extension.

In the early stages of CBD, MRI generally does not reveal any changes. As the disease progresses, asymmetric cortical atrophy involving the frontal-parietal lobes, corpus callosum, and ipsilateral cerebellar peduncle may become evident. FLAIR sequences can show hyperintensity of white matter tissue signal in the atrophic frontoparietal sulci [62]. The putamen and globus pallidum may appear hypointense on T2-weighted images. Volume in the basal ganglia and hippocampus, unlike in AD, is conserved [63,64].



**Fig. 8. Uptake of amyloid PET tracers in relation to the deposition of  $A\beta$  plaques in the brain.**

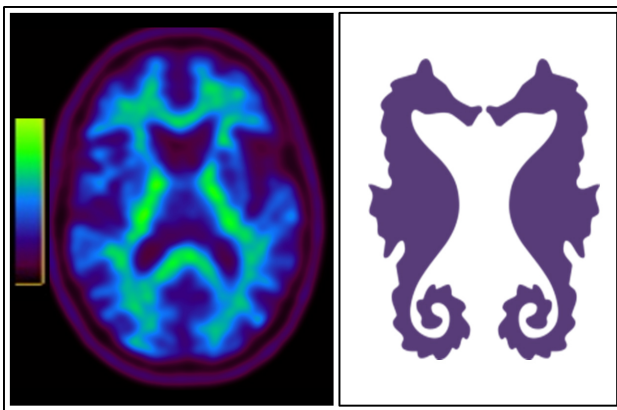
There are similar concerns regarding progressive supranuclear palsy (PSP) and multiple-system atrophy (MSA). PSP patients generally show hypometabolism in the medial and dorsolateral prefrontal cortex, caudate, thalamus, and upper brainstem. MSA patients have a hypometabolic striatum and cerebellum [65–67]. Positive brain  $[^{18}\text{F}]$ FDG PET findings in such patients could also represent a gatekeeper for subsequent PET imaging with  $\tau$  protein tracers, in order to improve the diagnosis, as one study recently demonstrated [68]. In this latter study performed on 117 patients with parkinsonian syndromes,  $[^{18}\text{F}]$ FDG PET was found to be very useful in clinical routine evaluation of suspected dementia related to parkinsonian syndromes, with a satisfactory differential diagnosis in two thirds of patients. One third of patients would have potentially profited from further evaluation by more specific tracers. In the future, the radiomics signature with metabolic, structural, and metabolic information provided by hybrid  $[^{18}\text{F}]$ FDG PET/MRI should hopefully be diagnostically effective in distinguishing between PD and MSA, as reported by Hu *et al.* [69] who examined 90 patients. A possible role for  $[^{18}\text{F}]$ FDG PET imaging may be also hypothesized in identifying those patients with post-ischemic vascular lacunae causing tremor (Fig. 7), thus excluding NDs [70], or rare neurological conditions involving a movement disorder [71,72].

### 3. Amyloid Imaging

AD is the most common neurodegenerative disease causing dementia in the elderly. Histopathology defines this disease as linked to the accumulation  $A\beta$  plaques and hyperphosphorylated neurofibrillary  $\tau$  protein. Thus, the  $A\beta$  plaques are the pathognomonic signs of AD, and their appearance in the brain is an early event in the pathogenesis. The first amyloid tracer was the Pittsburgh compound, used to image brain amyloid plaques. This tracer is labeled with  $^{11}\text{C}$ ; the short half-life decay of the nuclide does not support its use in routine clinical applica-

tions [73]. Three fluorinated types of amyloid radiopharmaceuticals are therefore currently employed for PET/CT and PET/MRI: [ $^{18}\text{F}$ ]Florbetapir, [ $^{18}\text{F}$ ]Flutemetamol (Fig. 8), and [ $^{18}\text{F}$ ]Florbetaben [74,75].

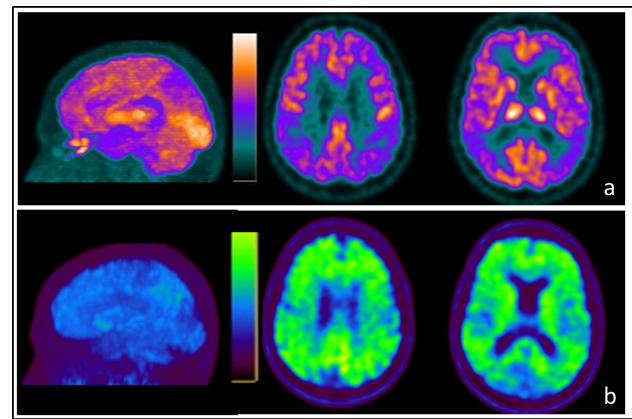
All fluorinated types of amyloid radiopharmaceuticals have demonstrated a high diagnostic accuracy (sensitivity 88–96%, specificity 80–100%) in the detection of A $\beta$  plaques, in comparison with postmortem data [76–78]. Imaging A $\beta$  plaques with fluorinated-tracer PET is therefore becoming the most useful tool aimed at the *in vivo* detection of brain plaque density and increasing the diagnostic accuracy in cognitively impaired patients. Negative PET scans of patients with amyloid tracers generally show physiological distribution of the radiopharmaceutical in the white matter, particularly evident in the axial slices of the basicranium, which has been defined as the “sign of the seahorses” (Fig. 9).



**Fig. 9. Amyloid imaging.** A 48-year-old woman with mild cognitive impairment was examined by [ $^{18}\text{F}$ ]Flutemetamol PET. The scan did not show pathological tracer uptake; axial PET view of the basicranium shows physiological tracer distribution in the white matter (*sign of the seahorses*).

In positive patients, amyloid accumulation is detected by a high tracer uptake in parietal cortices, temporal lobes, and the anterior and posterior cingulates. Some variability can be observed among patients, in particular in the case of MCI, while the involvement of frontal lobes usually occurs in advanced stages of the disease [79]. This variability led to the development of a particular dual phase PET, on a single day or in separate imaging sessions, including imaging of the brain with both [ $^{18}\text{F}$ ]FDG and an amyloid tracer (Fig. 10), in order to assess the glucose metabolism of the cortex and possible amyloid burden [80,81].

However, despite the overall good diagnostic accuracy, the validation processes are still incomplete, and the real impact on clinical outcome and cost-effectiveness needs to be assessed [82]. Future blood biomarkers will probably play an important screening role in AD, selecting patients who would benefit from more expensive and in-



**Fig. 10. Dual tracer imaging of Alzheimer's Disease.** [ $^{18}\text{F}$ ]FDG and [ $^{18}\text{F}$ ]Flutemetamol PET scans in a 61-year-old man examined due to clinical suspicion of Alzheimer's disease. [ $^{18}\text{F}$ ]FDG 3D-PET and axial PET (a) show severe hypometabolism in the parietal and temporal cortex, bilaterally, congruent with the clinical diagnosis. [ $^{18}\text{F}$ ]Flutemetamol 3D-PET and correlative axial images (b) confirm the diagnosis, showing a pathological amyloid burden in the parietal, temporal, and frontal lobes, in both hemispheres.

vasive testing such as the amyloid PET [79]. In selected patients with cognitive impairment, current evidence suggests that amyloid imaging provides diagnostic clarity and significantly changes clinical management, while reducing the overall number of investigations. The advent of amyloid tracers in the PET imaging of dementia is encouraging studies on asymptomatic/paucisymptomatic patients who could benefit from new clinical prevention trials, particularly using monoclonal antibodies [83].

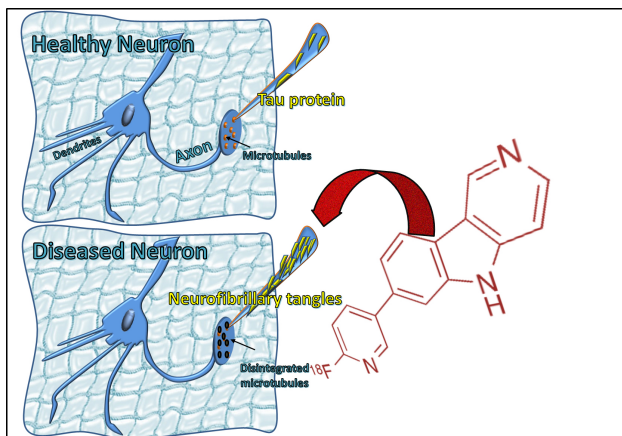
## 4. Tau Imaging

The amyloidic, intracellular nature of neurofibrillary tangles is at the root of synaptic dysfunction and degeneration occurring in several types of dementia [84].

### 4.1 Tau Imaging in AD

AD accounts for the vast majority of tauopathies according to data from Braak *et al.* [85]. For this reason, most studies on PET with  $\tau$  protein radiopharmaceuticals have been carried out on AD. Deposits of  $\tau$  protein generally begin in the entorhinal cortex, moving to the inferolateral temporal cortex and medial parietal lobe, finally, being detected in the cortex (Fig. 11).

Age-related tracer accumulation can therefore be observed in the medial temporal lobe, while high levels of tracer enhancement may be detected in cortical areas, such as the posterior cingulate, inferior lateral temporal regions, and also frontal and parietal regions [86]. The cortical deposition of the  $\tau$  protein is generally associated with dementia and AD [87,88] and can be documented by  $\tau$  protein tracers such as [ $^{18}\text{F}$ ]Flortaucipir [89]. [ $^{18}\text{F}$ ]Flortaucipir has been most frequently reported as physiologically enhanced in the



**Fig. 11. PET imaging with  $\tau$  tracers.** The PET  $\tau$  tracers present high *in vivo* affinity with neuronal neurofibrillary tangles.

basal ganglia, substantia nigra, choroid plexus, meninges, and vessels, as off-target binding. The recent approval by the Food and Drug Administration of this novel PET  $\tau$  protein agent marks a step forward in the field of AD research and creates opportunities for second-generation  $\tau$  protein tracers to advance PET imaging into the clinic [90].

Several studies have confirmed that the association between  $\tau$  protein accumulation and cognitive impairment is stronger than that known for  $A\beta$  tracers. In AD patients, a close relationship has been shown between  $\tau$  protein PET results and the patterns of cortical hypometabolism on [ $^{18}\text{F}$ ]FDG PET, despite a significant interindividual difference in the distribution of  $\tau$  protein pathology across the brain [91]. The anti- $\tau$  protein therapy landscape is rapidly evolving, with multiple ongoing trials on the post-translational modification of  $\tau$  protein, immunotherapy, and inhibitors of  $\tau$  protein aggregation, targeting the production of  $\tau$  protein and the reduction in intracellular  $\tau$  protein levels [92].

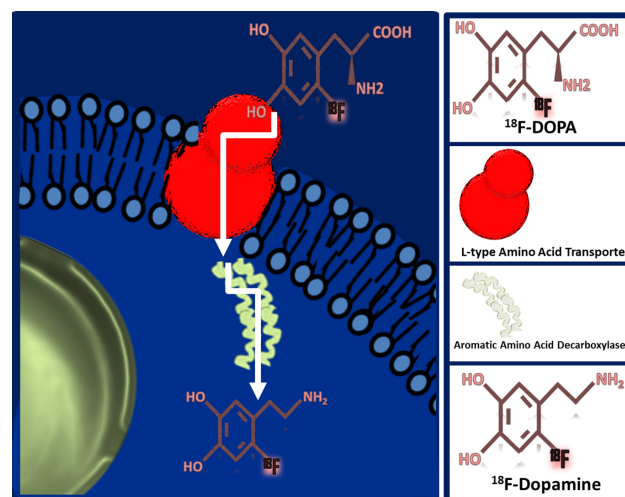
#### 4.2 Tau Imaging in Other Types of Dementia

Moderate uptake  $\tau$  protein tracers can be observed on PET imaging of DLB [92]. In addition, patients with PD dementia complex show an increased  $\tau$  protein burden [93], confirming a multifactorial process in the development of cognitive impairment in this significant minority of PD patients, involving  $\alpha$ -synuclein,  $\tau$  protein deposition, and  $A\beta$  deposition. However, [ $^{18}\text{F}$ ]Flortaucipir is useful in differentiating between AD dementia and non-AD neurodegenerative disorders, based on different thresholds applied to the medial-basal and lateral temporal cortex tracer uptake [84].

### 5. [ $^{18}\text{F}$ ]FDOPA

[ $^{18}\text{F}$ ]-fluoro-L-phenylalanine ([ $^{18}\text{F}$ ]FDOPA) is the precursor of L-DiOxyPhenylAlanine (L-DOPA) of levodopamine, and follows the same metabolic pathway *in*

*vivo*. [ $^{18}\text{F}$ ]FDOPA penetrate the cells carried by the L-type amino acid transporters 1 and 2. These transporters are involved in the permeability to the blood-brain barrier of the tracer. Subsequently, this radiopharmaceutical is converted into [ $^{18}\text{F}$ ]Fluorodopamine by the amino acid decarboxylase in central nervous system (Fig. 12). In the brain, faint uptake is normally registered in the cortex and white matter. The target tissue is only represented by the basal ganglia, thus enabling the identification of cellular damage in the caudate and putamen nuclei.

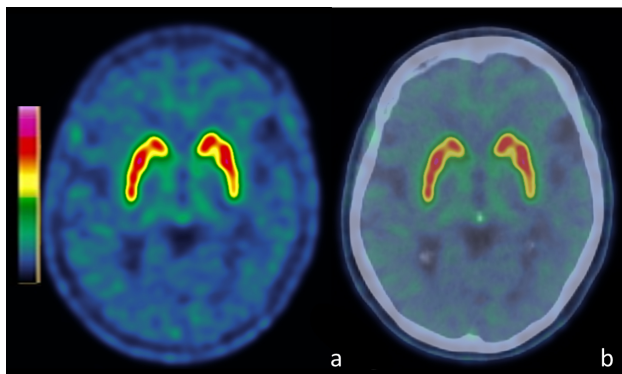


**Fig. 12. Intracellular uptake of [ $^{18}\text{F}$ ]FDOPA in the brain.**

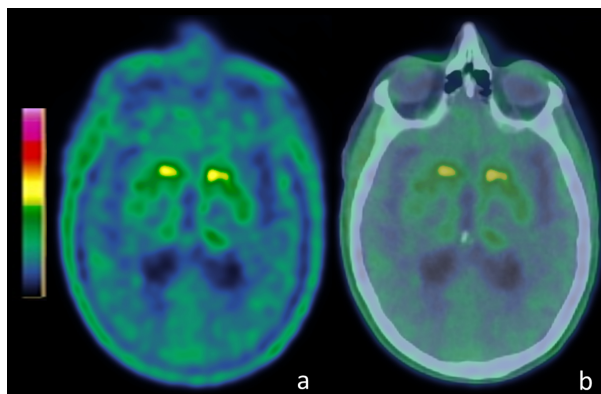
SPECT imaging with cocaine analogues is used to study the integrity of dopaminergic neurons in PD patients [94]. Several studies have demonstrated the lack of [ $^{18}\text{F}$ ]FDOPA uptake in the striatum of PD patients [95] compared with healthy controls (Fig. 13). Other studies have supported the potential of [ $^{18}\text{F}$ ]FDOPA in the early diagnosis of early stage of PD and in the differential diagnosis of essential tremor [96] (Fig. 14), demonstrating that on the contralateral to symptoms side the striatal uptake is decreased more than the other side [97].

The mean annual rate of decreased [ $^{18}\text{F}$ ]FDOPA accumulation in PD patients has been reported to be 8–12% in the putamen, and 4–6% in the caudate; on the other hand, in healthy volunteers this value is less than 1% in both structures [98]. Following Braak's hypothesis [85], tracer uptake is lower in the putamen than in the caudate nuclei, thus indicating the earlier involvement of the putamens in the natural progression of the disease. Conversely, a lack of [ $^{18}\text{F}$ ]FDOPA uptake in the striatum may also be identified in juvenile PD, due to the rapid loss of striatal neurons [99]. The most important goal in PET imaging of the striatum with [ $^{18}\text{F}$ ]FDOPA is probably the differential diagnosis with other parkinsonian syndromes, such as PSP, MSA and CBD. In fact, only PD patients adequately respond to anti-Parkinson drug therapy. Otsuka *et al.* [100] preliminarily investigated the [ $^{18}\text{F}$ ]FDOPA uptake in 10 patients with





**Fig. 13. Physiological  $^{18}\text{F}$ FDOPA bio-distribution.** Normal distribution of  $^{18}\text{F}$ FDOPA in the striatum on PET (a) and PET/CT (b) axial details of the basicranium, in a 56-year-old man examined for essential tremor and suspicion of Parkinson's disease.



**Fig. 14.  $^{18}\text{F}$ FDOPA and Parkinson's Disease.**  $^{18}\text{F}$ FDOPA axial PET (a) and PET/CT (b) details of the basicranium, in a 60-year-old man evaluated for Parkinson's disease in an advanced clinical stage, showing severe bilateral reduction in tracer uptake in the putamen nuclei and moderate-to-severe reduction in uptake in both caudate nuclei.

MSA and eight patients with PD. The  $^{18}\text{F}$ FDOPA accumulation was lower by a similar amount in the putamen of both groups, while there was a greater reduction in uptake in the caudate in MSA patients. These findings have been confirmed elsewhere. A greater reduction in uptake in the caudate of PSP and CBD patients in comparison with PD patients has been reported [101,102]. However, the overlap between these populations was too great for a meaningful differentiation.

Concerning the clinical implications of Braak's hypothesis [85], which considers that the earliest signs of PD, such as hyposmia, sleep disorders and constipation may precede the motor features of the disease by several years, some researchers have increasingly focused on the non-motor symptoms in order to detect early PD and to slow or stop its progression. Scherfler *et al.* [103] found a signifi-

cant association in PD patients between the reduction in uptake in the striatum and in the olfactory tract, suggesting another criterion to distinguish between PD and other movement disorders. SPECT imaging with cocaine analogues is widely used in the management of PD patients [104] and is the main reference standard for evaluating the diagnostic performance of  $^{18}\text{F}$ FDOPA PET in the management of movement disorders. The literature demonstrates a good correlation between striatal  $^{18}\text{F}$ FDOPA uptake and striatal  $^{123}\text{I}$ -ioflupane uptake, with similar values of sensitivity and specificity in PD patients [105,106]. In addition, better reproducibility of  $^{18}\text{F}$ FDOPA PET imaging has been noted, due to the shorter half-life of the tracer, the shorter time of the investigation, and the better resolution power of the PET scanner. In a recent study, the possible role of  $^{18}\text{F}$ FDOPA in the imaging of the nigrostriatal pathway and sympathetic cardiac innervation was also proposed. This approach is important as quantification of myocardial  $^{18}\text{F}$ FDOPA uptake may help in differentiating patients with and without Parkinson's [107].

## 6. Translocator Protein Radiopharmaceuticals

Translocator protein (TSPO) is a mitochondrial outer membrane 18 kDa protein, located at contact sites between the outer and inner mitochondrial membrane, initially known for taking up benzodiazepine in peripheral tissues [108]. Its functions, including cholesterol transport and steroid hormone synthesis, mitochondrial respiration, permeability pore opening, apoptosis, and proliferation, are still being investigated. Steroidogenic tissues, such as glandular and secretory, are particularly abundant in TSPO, while the brain and liver express low levels of TSPO [109]. A non-mitochondrial localization has been reported [110,111], for instance in red blood cells, endoplasmic reticulum, and nuclear membranes of erythroblasts, although its role has yet to be determined.

TSPO is a channel with five alpha transmembrane helices, able to form homodimers and a multimeric complex including the voltage-dependent anion channel 1 (VDAC1) [112], the ATPase family AAA domain-containing protein 3 (ATAD3), and the inner mitochondrial membrane cytochrome P450 side-chain cleavage enzyme (CYP11A1), a signal transduction complex involved in intracellular  $\text{Ca}^{++}$  pathways [113].

In the healthy central nervous system, TSPO is expressed at a low baseline level, not homogeneously, in several brain regions including the cerebellum and choroid plexus, with the ependyma of the ventricular system showing higher TSPO staining levels. Moreover, TSPO levels are higher in white matter than in gray matter. Astrocytes and microglia do not display constitutive TSPO expression, while endothelial cells and the pericytes of blood vessels do [113]. TSPO may be overexpressed in activated microglia and upregulated in astrocytes in the central nervous

system, due to ischemic damage or neurodegenerative diseases such as AD, PD, and multiple sclerosis [114–116]; therefore, TSPO is a biomarker of neuroinflammation and related diseases. In particular, abnormal protein aggregate accumulation, typically found in neurodegenerative disorders, triggers the brain immune response through upregulation of TSPO on activated microglia.

First and second generation TSPO ligands [117–119] have been developed for PET imaging of neuroinflammation, labeled with either  $^{11}\text{C}$  or, lately,  $^{18}\text{F}$ , in an attempt to overcome the short half-life of  $^{11}\text{C}$ , the low brain uptake and penetration of the intact blood-brain barrier [120,121], and with binding affinity to TSPO suitable to PET imaging. Both first- (e.g., [ $^{11}\text{C}$ ]PK11195) and second-generation (e.g., [ $^{11}\text{C}$ ]PBR28n and [ $^{18}\text{F}$ ]DPA714) tracers correlate well with amyloid and  $\tau$  protein PET imaging [119,122], linking the presence of beta fibrils and tangles to neuroinflammation in both MCI and AD. At the pre-symptomatic stage, neuroinflammation is associated with amyloid imaging in a subgroup of patients [123], interestingly at a very early stage of neuroinflammation. In FTD, which comprises different clinical syndromes, TSPO PET is positive in frontal and temporal lobes in the behavioral variant, in the temporal pole in semantic dementia, and in the premotor cortex in non-fluent primary progressive aphasia, correlating neuroinflammation to the location of pathology [119]. However, the results are not uniform in PD patients.

## 7. Conclusions

The molecular imaging of NDs provided by PET imaging enables the *in vivo* evaluation of specific molecular pathways with novel radiopharmaceuticals for personalized patient care. [ $^{18}\text{F}$ ]FDG still remains the standard among tracers, due to its intrinsic molecular properties. As an analogue of glucose, this tracer can clearly identify cortical and subcortical functional changes in patients with cognitive impairment and/or movement disorders. Amyloid tracers are becoming a reference tool in the clinical management of dementia, due to the high specificity. Potential added value could be provided in the future imaging of the  $\tau$  protein, in order to explore multiple physiopathological features of the diseases under study. In selected patients with movement disorders, [ $^{18}\text{F}$ ]FDOPA still plays an effective role in the assessment and monitoring of the disease over time.

## Author Contributions

FC designed the paper, and wrote the text. ML wrote the hybrid imaging section, made figures, figure legends, and bibliographic research. AC, MR, and LT made bibliographic research on tau, translocator protein and amyloid imaging. AB conducted bibliographic research on [ $^{18}\text{F}$ ]FDOPA and [ $^{18}\text{F}$ ]Fluorodeoxyglucose imaging. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All au-

thors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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