Current radiotracers to image neurodegenerative diseases

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Abstract

The term of neurodegenerative diseases covers a heterogeneous group of disorders that are distinguished by progressive degeneration of the structure and function of the nervous system such as dementias, movement disorders, motor neuron disorders, as well as some prion disorders. In recent years, a paradigm shift started for the diagnosis of neurodegenerative diseases, for which successively clinical testing is supplemented by biomarker information. In research scenarios, it was even proposed recently to substitute the current syndromic by a biological definition of Alzheimer's diseases. PET examinations with various radiotracers play an important role in providing non-invasive biomarkers and co-morbidity information in neurodegeneration. Information on co-morbidity, e.g. Aβ plaques and Lewy-bodies or Aβ plaques in patients with aphasia or the absence of Aβ plaques in clinical AD patients are of interest to expand our knowledge about the pathogenesis of different phenotypically defined neurodegenerative diseases. Moreover, this information is also important in therapeutic trials targeting histopathological abnormalities.

The aim of this review is to present an overview of the currently available radiotracers for imaging neurodegenerative diseases in research and in routine clinical settings. In this context, we also provide a short summary of the most frequent neurodegenerative diseases from a nuclear medicine point of view, their clinical and pathophysiological as well as nuclear imaging characteristics, and the resulting need for new radiotracers.

Keywords: Alzheimer’s disease, Parkinsonian syndromes, Primary progressive aphasia, Frontotemporal dementia, PET, SPECT, ß-amyloid, Tau, Cholinergic system, Dopaminergic system

Introduction

It is well recognized that increased life expectancy results in an increased frequency of neurodegenerative diseases. In the last two to three decades, the development of new diagnostic and therapeutic methods has been intensified in neurodegenerative diseases. Molecular radiopharmaceutical-based neuroimaging is a growing field and provides several new diagnostic methods to investigate and characterize neurodegenerative diseases during life. This review summarizes the facts for the most frequent neurodegenerative diseases from a nuclear medicine point of view. Furthermore, the review provides information on approved radiotracers and ongoing research activities in the...
development of new radiotracers for imaging neurodegenerative diseases as well as a short passage about the need for novel radiotracers.

Neurodegenerative diseases – important histopathological and clinical facts

Alzheimer’s disease (AD)

Alzheimer’s disease (AD) is the most common neurodegenerative disease causing dementia in the elderly. Histopathological characteristics of this disease are a progressive accumulation of β-amyloid (Aβ) plaques and hyperphosphorylated neurofibrillary tau protein (tau). However, only approximately 50% of the patients have solely Alzheimer’s pathology. Many patients show additional pathologic changes related to other neurodegenerative diseases in autopsy studies (Alzheimer’s Association report 2018 - https://www.sciencedirect.com/science/article/pii/S1552526018300414). Along with the typical clinical features like memory impairment, especially in the semantic and episodic domain and the executive dysfunction (McKhann et al. 2011), atypical variants of AD exist. As such, posterior cortical atrophy (PCA) and logopenic variant primary progressive aphasia (lvPPA) are labeled as atypical AD, since the histopathological changes (i.e. Aβ and tau accumulation) in these neurodegenerative diseases determine the “typical” AD features, although the distributional pattern of the pathologic changes seems to be different (Crutch et al. 2012; Harris and Jones 2014). However, in both PCA and lvPPA a significant minority of cases showed other underlying pathologies than AD, e.g. Lewy bodies, transactive response DNA binding protein of about 43 kDa (TAR DNA-binding protein 43, TDP-43) proteinopathies, “pure” tauopathy or cerebrovascular disease (Crutch et al. 2012; Harris and Jones 2014) (Table 1). The core clinical features of patients with PCA are caused by a decline in visual processing and other posterior cognitive functions, e.g. space and/or object perception deficits, simultanagnosia or constructional dyspraxia (Crutch et al. 2017). The core clinical features of lvPPA are impaired single-word retrieval in spontaneous speech and naming as well as impaired repetition of sentences and phrases (Harris and Jones 2014).

Frontotemporal lobar degeneration (FTLD)

FTLD is a potpourri of clinically, histopathologically and genetically different disorders that become united due to predominant pathological involvement of the frontal and temporal brain regions. Three distinct clinical phenotypes of FTLD are recognized including a behavior/dysexecutive syndrome - the behavioral variant of frontotemporal dementia (bvFTD); language disorders - the primary progressive aphasia (PPA): semantic variant (svPPA) and non-fluent/agrammatic variant (nfvPPA); and motor disorders (amyotrophic lateral sclerosis, corticobasal and progressive supranuclear palsy syndromes).

In general, an individual FTLD disorder can be ascribed to different histopathologies such as tauopathy (FTLD-tau), TDP-43 proteinopathy (FTLD-TDP-43) and the FET protein family that consists of Fused in sarcoma, Ewing sarcoma and TATA-binding protein associated factor 15 proteinopathy (FTLD-FET) (Table 1). Here, some histopathology is more often seen in one than in another FTLD disorder (Harris and Jones 2014; Bang et al. 2015; Mackenzie and Neumann 2016). Thus, more than 70% of the patients with svPPA have TDP-43 proteinopathy. Over 50% of patients with nfvPPA
have FTLD-tau, approximately 20% show TDP-43 proteinopathy (Harris and Jones 2014). Almost half of the patients with bvFTD have FTLD-tau (Pressman and Miller 2014) and more than 25% TDP-43 pathology (Bang et al. 2015). Of interest, tauopathies can be differentiated in at least 5 subtypes according to their molecular subtype (Mackenzie and Neumann 2016).

**Parkinsonian syndromes**

In Parkinson’s disease (PD), a degeneration of the nigrostriatal system occurs causing a reduction of the neurotransmitter dopamine. Degeneration of dopaminergic neurons in the substantia nigra pars compacta is an inherent neuropathological sign of PD. Histologically, most patients suffering from PD exhibit intracellular accumulation of protein inclusions mainly constituted of α-synuclein (Lewy bodies). However, some patients with specific genetic forms of PD do not have Lewy body pathology and it
remains unclear how Lewy bodies and neuronal loss are connected to each other. The typical clinical criteria of PD consist of symptoms such as bradykinesia, rigidity or resting tremor as cardinal motor manifestations (Postuma et al. 2015). Important supportive criteria include response to dopamine replacement, unilateral onset, olfactory dysfunction and REM sleep behavior disorder (Berg et al. 2013; Postuma et al. 2015). Corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and multisystem atrophy (MSA) are classified as atypical parkinsonisms. Histopathologically, CBD and PSP belong to primary tauopathies while MSA, DLB and PD are characterized by a pathologic accumulation of α-synuclein protein (α-synucleinopathies). The clinical presentation of CBD can be subdivided into 4 phenotypes: corticobasal syndrome, behavior spatial syndrome, nfvPPA and PSP (Armstrong et al. 2013) demonstrating that the accuracy to diagnose CBD ante-mortem is still limited.

Clinical core features of PSP are akinetic-rigid syndrome, postural instability or falls and supranuclear ophthalmoplegia (Bensimon et al. 2009). The most recent version of PSP criteria published by the Movement Disorder Society includes eleven clinical phenotypes of PSP (Ali and Josephs 2018). Overall, the clinical diagnoses of post-mortem validated PSP cases were correctly established only in 19% of cases at the first clinical visit, and in 71% of cases over the course of the disease (Respondek et al. 2013). Furthermore, an average of 24% of post-mortem histopathologically diagnosed cases of MSA, PD and CBD were, ante-mortem, falsely diagnosed as PSP (Respondek et al. 2013). Also, the occurrence of concomitant AD (in approximately 36%) or PD (in approximately 20%) pathologies in PSP patients is remarkable (Dugger et al. 2014).

Histopathologic characteristics of MSA are inclusions of misfolded α-synuclein in oligodendrocytes (Jellinger 2014). According to the clinical presentation, MSA is usually subdivided into a parkinsonian subtype (MSA-P) and a cerebellar subtype (MSA-C). For the clinical phenotype, autonomic failure is a core symptom which must be present to establish the diagnosis of MSA (Gilman et al. 2008).

**Lewy body dementia pathologies**

Dementia with Lewy-bodies (DLB) is an α-synucleinopathy, characterized by widespread accumulation of Lewy bodies and Lewy neurites in the brain-stem, limbic system and cortical areas (Braak and Braak 2000) and a higher percentage of DLB compared to PD patients with dementia (PDD) show Aβ deposits in histopathological examinations. Consequently, approximately 80% of DLB patients have a positive Aβ PET scan (Drzezga 2010) (Table 1) indicating a significant overlap between AD and DLB, which is reflected in the clinical presentation of the patients. Only 50% of patients with DLB pathology show the typical symptoms of DLB (McKeith et al. 2016). Core clinical features are fluctuating cognition, recurrent visual hallucinations, rapid eye movement (REM) sleep behaviour disorder and parkinsonism (McKeith et al. 2017). However, “the likelihood that the observed neuropathology explains the DLB clinical syndrome is directly related to the severity of Lewy-related pathology, and inversely related to the severity of concurrent AD-type pathology” (McKeith et al. 2005).

More than 75% of PDD patients develop in the long term clinical course of the disease (Aarsland et al. 2003). PDD is characterized by an intracellular accumulation of α-synuclein (Lewy bodies). Approximately 15% of PDD patients show
cerebral β-amyloid plaques (Lucero et al. 2015; Edison et al. 2008). Due to an overlap of clinical and morphological features there is a continuous debate (Friedman 2018) of whether DLB and PDD are the same disease with different phenotypic representation of Lewy body disease spectrum.

**Huntington’s disease (HD)**

HD is an autosomal-dominant neurodegenerative disease caused by a single gene mutation (Kim and Fung 2014) i.e. a CAG repeat expansion in exon 1 of the huntingtin gene (MacDonald et al. 1993). This repeated CAG expression results in an abnormal toxic protein which is named Huntingtin. This protein is expressed in all brain cells and disturbs protein degradation as well as several other cellular processes, e.g. mitochondrial function, axonal trafficking or peripheral immune regulation (Kim and Fung 2014). The cerebral accumulation of hyperphosphorylated tau aggregates seems to be a further histopathological characteristic besides the accumulation of the mutated Huntingtin protein (Vuono et al. 2015). From the clinical perspective, HD is characterized by progressive motor symptoms, cognitive decline and neuropsychiatric disturbances (Kim and Fung 2014).

**Role of PET imaging in neurodegenerative diseases**

Currently, the classification of neurodegenerative diseases is in permanent change and progress. Predominantly, phenotypical definitions are increasingly substituted – at least in research settings- by classifications which include biomarkers for the underlying pathophysiological process and thus lead to a more biological definition of neurodegenerative diseases (Jack et al. 2018).

This development is of great significance for nuclear medicine, as molecular imaging using PET tracers can provide biomarker information, e.g. [$^{18}$F]FDG as a biomarker of neuronal injury or AB PET as a biomarker of AD pathology (Barthel et al. 2015). Table 2 summarizes all radiotracers mentioned in the review with abbreviation and chemical definition.

**Molecular imaging of neurodegeneration**

**[$^{18}$F]FDG PET**

Glucose is the energy supplier of the brain. In all neurodegenerative diseases, impairment of neuronal function and therefore reduced energy metabolism occur. [$^{18}$F]FDG (Fig. 1) as a marker for neuronal injury can be used to detect this impairment, and it is well known that different neurodegenerative diseases show distinct patterns of reduced [$^{18}$F]FDG uptake (Hellwig et al. 2012; Barthel et al. 2015) (Table 3). However, the hypometabolic patterns of some neurodegenerative disorders overlap. Due to its broad availability and sufficient diagnostic accuracy, [$^{18}$F]FDG is currently the widely used radiotracer in imaging of neurodegenerative diseases in clinical routine.

**Synaptic density PET**

In neurodegenerative diseases as well as in a variety of other neurological and psychiatric diseases, a reduction of synaptic density occurs during the course of disease (Feng et al. 2009; van Vliet et al. 2009; DeKosky and Scheff 1990; Hamos et
| Abbreviation | Chemical Structure |
|--------------|-------------------|
| $[^{11}C]$-A-582941 | 2-$[^{11}C]$methyl-5-[6-phenylpyridazine-3-yl]octahydropyrrole(3,4-c)pyrrole |
| $[^{11}C]$-A-844606 | 2-([6-$[^{11}C]$methyl-1,3,3a,4,6,6a-hexahydropyrrole(3,4-c)pyrrole-5-yl]-4a,9a-di-hydroxanthen-9-one |
| $[^{11}C]$AZD2184 | 2-(6-$[^{11}C]$methylaminopyridin-3-yl)-1,3-benzothiazol-6-ol |
| $[^{11}C]$CHIBA-1001 | (4-$[^{11}C]$methylphenyl)-1,4 diazabicyclo[3.2.2]nonane-4-carboxamide |
| $[^{11}C]$cocaine | methyl(3R)-3-(benzoyloxy)-8-$[^{11}C]$methyl-8-azabicyclo[3.2.1]octan-2-carboxylate |
| $[^{11}C]$DA1106 | N-(5-fluoro-2-phenoxyphenyl)-N-(5-methoxy-2-$[^{11}C]$methoxyphenyl)acetamide |
| $[^{11}C]$JNJ7777120 | 1-[5-chloro-1H-indol-2-yl]carbonyl-4-$[^{11}C]$methylpiperazine |
| $[^{11}C]$KTP-ME | 2-(3-benzoyl-phenyl)-propionic acid-4-$[^{11}C]$methylster |
| $[^{11}C]$methylenidate | $[^{11}C]$methylphenyl-piperidin-2-yl-acetic-acid |
| $[^{11}C]$MP4A | N-$[^{11}C]$methylpiperidin-4-yl acetate |
| $[^{11}C]$NS14492 | 4-[5-$[^{11}C]$methyl-1H-pyrrol-2-yl]-1,3,4-oxadiazol-2-yl]-1,4-diazabicyclo[3.2.2]nonane |
| $[^{11}C]$PBB3 | 2-(1E,3E)-4-$[^{11}C]$methylaminopyridin-3-yl)-1,3-benzothiazol-6-ol |
| $[^{11}C]$PBR-28 | N-(2-$[^{11}C]$methylphenyl)acetamide |
| $[^{11}C]$PiB | 2-[4-(1-$[^{11}C]$methylaminophenyl)-1,3-benzothiazol-6-ol |
| $[^{11}C]$PK-11195 | N-sec-Butyl-1-(2-chlorophenyl)-N-$[^{11}C]$methyl-3-isoquinolinecarboxamide |
| $[^{11}C]$ PMP | (1-$[^{11}C]$methyl-piperidin-4-yl)propionate |
| $[^{11}C]$raclopride | 3,5-dichloro-N-[[25S]-1-ethylpyrrolidin-2-yl]-2-hydroxy-6-$[^{11}C]$methoxybenzamide |
| $[^{11}C]$UCB-J | (R)-1-(3-$[^{11}C]$methylpyridin-4-yl)methyl-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one |
| $[^{18}F]$A-85380 | 2-([18F]fluoro-3-(2S)-azetidinyl)ethoxy)pyridine |
| $[^{18}F]$AV-133 | 3-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-6-[18F]fluoranyldibenzo[b,d]thiophene 5,5-dioxide |
| $[^{18}F]$AV-1451 | 7-[18F]fluoranyldipyrindin-3-yl)-8-aza-bicyclo[3.2.1]octane |
| $[^{18}F]$JANZ | ([R]-1-((3-(18F)fluoranylmethyl)pyridin-3-yl)-2-azabicyclo[2.2.1]heptane |
| $[^{18}F]$DBT-10 | 7-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-2-[18F]fluorodibenzoc(1H)quinolin-2-ol |
| $[^{18}F]$DPA-714 | [[N,N-diethyl-2-(4-((18F)fluoroethoxy)phenyl)5,7-dimethylpyrazolo[1,5a]pyrimidin-3-yl]acetamide] |
| $[^{18}F]$FDOPA | (2S)-2-amino-3-(2-((18F)fluoroethyl)oxy)-4,5-dihydroxyphenyl)propanoic acid |
| $[^{18}F]$FDG | (2S,3R,4S,5S,6R)-3-(2-((18F)fluoroethyl)oxy)-6-(hydroxymethyl)oxane-2,4,5-triol |
| $[^{18}F]$FE-PE2I | N-(3-iodoprop-2-enyl)-2-β-carbo[18F]fluoroethoxy-3β-[(4′-methyl-phenyl)nortropane |
| $[^{18}F]$FEPPA | N-[2-((18F)fluoroethoxy)phenyl]N-(4-phenoxyphenyl)acetamide |
| $[^{18}F]$FIBT | 2-(p-methylaminophenyl)-7-(2-((18F)fluoroethoxy)imidazo-[2,1-b]benzothiazole |
| $[^{18}F]$Florbetaben | 4-[E]-2-[4-(2-((18F)fluoroethoxy)ethoxy)ethoxy]pyridin-3-yl-N-methylpyridine |
| $[^{18}F]$Florbetapir | 4-[E]-2-[6-(2-((18F)fluoroethoxy)ethoxy)]pyridin-3-yl-N-methylpyridine |
| $[^{18}F]$Flutemetamol | 2-[3-$[^{18}F]$fluoranyldiethylamino]phenyl]-1,3-benzothiazol-6-ol |
| $[^{18}F]$FDP1 | 3-[4-(2-((18F)fluoro-2,2-deuteroethyl)prop-2-yl]-benzo[4,5]imidazo[1,2-a]pyridine |
| $[^{18}F]$MK-6240 | 6-[18F]fluoranyldipyrrrolo[2,3-c]pyrrole-1-y asquinolin-5-amine |
| $[^{18}F]$MNII-1126 | 4,3,5-di[18F]fluorophenyl]-3-methylpyridin-4-ylcarboxylate |
| $[^{18}F]$NAV4694 | 2-[2-(18F)fluoro-6-(methylamino)-3-pyridinyl]-1-benzofuran-5-ol |
| $[^{18}F]$NIDA522131 | 6-chloro-3-((2S)-azetidinyl)ethoxy)-5-[2-(18F)fluoroethyl]pyridine |
Quantification of synaptic density is usually performed post-mortem. Development of levetiracetam-based PET radioligands targeting synaptic vesicle glycoprotein 2A (SVA2) now enables the in-vivo quantification of this parameter (Koole et al. 2018; Finnema et al. 2016). The most recently developed tracer \([^{11}C]\)UCB-J (Fig. 2) has demonstrated favorable pharmacokinetics and quantification properties in preclinical as well as in first-in-human studies (Finnema et al. 2016). An \([^{18}F]\)-labeled derivative (\([^{18}F]\)MNI-1126) (Fig. 2) has also been evaluated recently in non-human primates showing promising in-vivo characteristics (Constantinescu et al. 2018).

### Table 2

| Abbreviation | Chemical Structure                                                                 |
|--------------|-----------------------------------------------------------------------------------|
| \([^{18}F]\)nifene | 3-\([(2S)-2,5\text{-dihydro-1H-pyrrol-2-yl\text{\text{-}}methoxy\text{-}}2\text{-}[^{18}F]\text{-fluoranylpyridine}}\) |
| \([^{18}F]\)nifrolene | 3-\[((2S)-2,5\text{-dihydro-1H-pyrrol-2-yl\text{\text{-}}methoxy\text{-}}3\text{-}[^{18}F]\text{-fluoropropylpyridine}}\) |
| \([^{18}F]\)nizetidine | 3-(2-S)-azetidinylmethoxy-5-(3-[^{18}F]\text{-fluoropropyl) pyridine}) |
| \([^{18}F]\)NS10743 | 2-(1,4-diabicyclo[3.2.2]nonan-4-yl)-5-(4-[^{18}F]\text{-fluoropyrenyl}-1,3,4-oxadiazole) |
| \([^{18}F]\)PBR06 | N-(2-[^{18}F]\text{-fluoranyl-N(2-phenoxyphenyl)acetamide}) |
| \([^{18}F]\)PBR111 | 2-(6-Chloro-2-(4-(3-[^{18}F]\text{-fluoropyrpyl)phenylimidazo[1,2-a]pyridin-3-yl\text{-}N\text{-}N\text{-}diethylacetamide}) |
| \([^{18}F]\)PI-2620 | 2-(2-[^{18}F]\text{-fluoro-pyridin-4-yl\text{-}}8a,9\text{-dihydr-4bH-1,6,9-triaca-fluorene}) |
| \([^{18}F]\)RO6958948 | 2-(6-[^{18}F]\text{-fluoro-pyridin-3-yl\text{-}}9H-1,6,9-triaza-fluorene) |
| \([^{18}F]\)THK5351 | (2S)-1-[^{18}F]\text{-fluoranyl-3-[2-(6-(methylamino)pyridin-3-yl\text{-}quinolinol-6-yl\text{-}oxypropan-2-ol\text{-})}] |
| \([^{18}F]\)XTRA | 2-[5-[2-[^{18}F]\text{-fluoropyridin-4-yl\text{-}pyridin-3-yl\text{-}}7\text{-methyl-7-azabicyclo[2.2.1]heptene})] |
| \([^{18}F]\)Z2W-104 | 5-[6-[^{18}F]\text{-fluorohexyn-1-yl\text{-}}3\text{-}[2\text{-azetidinylmethoxy)pyridine}}) |
| \([^{12}I]\)I-A-85380 | 5-[^{123}I]\text{-iodo-3-(2-S)-azetidinylmethoxy)pyridine}) |
| \([^{12}I]\)β-CIT | 2β-carbomethoxy-3β-(4-[^{123}I]\text{-iodophenyl)tropane}) |
| \([^{12}I]\)FP-CIT | methyl\{1,2,5,35,55\}-8-(3-fluoropyridi\{-3-(4-[^{123}I]\text{-iodophenyl)pyridinol-8-azabicyclo(3.2.1)octane-2-carboxylate\text{-})}\) |
| \([^{12}I]\)JPT | N\{-3-[^{123}I]\text{-iodopropen-2-yl\text{-}2β-carbomethoxy-3β-(chlorophenyl)tropane\text{-})}\) |
| \([^{12}I]\)IBVM | 5-[^{123}I]\text{-iodo-3-(4-phenyl-piperidin-1-yl\text{-}}1,2,3,4-tetrahydro-naphthalen-2-ol\} |
| \([^{12}I]\)IBZM | (S\{-2\text{-hydroxy-3-[^{123}I]\text{-iodo-6-methoxy-N\{1-ethyl-2-pyrolyridinyl\text{-}methyl\text{-}benzamide\text{-})}\}) |

### Table 3

| Disease | Relative glucose metabolism reduction | Disease | Relative glucose metabolism reduction |
|---------|-------------------------------------|---------|-------------------------------------|
| AD      | PCC, parieto-temporal. Advanced: frontal | PD/DLB | Parieto-temporo-occipital<sup>a</sup> |
| PCA     | Parieto-occipital                    | PSP     | Mesial and dorsolateral, caudate, thalamus, upper brain stem<sup>b</sup> |
| lvPPA   | Parieto-temporal (left pronounced)  | CBS     | Fronto-parietal, striatal (asymmetric)<sup>c</sup> |
| bvFTD   | Frontal, ACC, right anterior insula. Advanced: temporal and subcortical | MSA     | Striatum (posterior putamen), cerebellum<sup>d</sup> |
| svPPA   | Anterior temporal, subcallosal, amygdala, frontal midline | HD      | Striatum, insula, posterior cingulate, prefrontal, occipital cortex<sup>e</sup> |
| nfPPA   | Left hemisphere, frontotemporal, insula. Advanced: parieto-temporal |         |                                     |

<sup>a</sup>ACC Anterior cingulate cortex, AD Alzheimer’s disease, bvFTD Behavioural variant frontotemporal dementia, CBS Corticobasal syndrome, DLB Dementia with Lewy-bodies, FDG Fluorodesoxyglucose, HD Huntington’s disease, lvPPA Logopenic variant primary progressive aphasia, MSA Multisystem atrophy, nfPPA non-fluent/agrammatic variant primary progressive aphasia, PCA Posterior cortical atrophy, PCC Posterior cingulate cortex, PD Parkinson’s disease, PET Positron emission tomography, PSP Progressive supranuclear palsy, svPPA Semantic variant primary progressive aphasia

<sup>b</sup>(Meyer et al. 2017)  
<sup>c</sup>(Tang et al. 2013)
**Fig. 1** Chemical structure of $[^{18}\text{F}]$Fluorodesoxyglucose ($[^{18}\text{F}]$FDG)

**Fig. 2** Chemical structure of (R)-1-((3-$[^{11}\text{C}]$-methyl-$[^{11}\text{C}]$)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one ($[^{11}\text{C}]$UCB-J) and its F18-labeled radioligand derivative (R-$[^{18}\text{F}]$MNI-116)
Imaging of neuroinflammation

Many neurodegenerative diseases are also accompanied, if not - as some researchers believe (Krstic and Knuesel 2013) - caused by inflammatory processes which are mainly mediated by activated microglia. The 18 kDa translocator protein (TSPO) is upregulated in glial cells during inflammation (Albrecht et al. 2016) and, as such, a target for PET neuroimaging. \(^{[11C]}\text{PK-11195}\) (Fig. 3a) is the most-studied TSPO radiotracer. However, it has a low brain penetrance and a high non-specific binding resulting in a poor signal-to-noise ratio (Albrecht et al. 2016; Ory et al. 2014). The second-generation TSPO radiotracers (e.g. \(^{[11C]}\text{PBR-28}\), \(^{[18F]}\text{DPA-714}\), \(^{[18F]}\text{FEPPA}\), \(^{[11C]}\text{DAA1106}\), \(^{[18F]}\text{PBR06}\), \(^{[18F]}\text{PBR111}\)) (Fig. 3a) have several advantages as compared to \(^{[11C]}\text{PK-11195}\), like a higher signal-to-background-ratio. As a potential drawback, however, the interpretation of their uptake is confounded by the existence of three different binding affinities (low-affinity, high-affinity, and mixed-affinity binder) (Albrecht et al. 2016; Herrera-Rivero et al. 2015). Other targets for an indirect measure of neuroinflammation have been identified, e.g. cyclooxygenase 1, histamine 4 receptors, alpha7-nicotinic acetylcholine receptors, and others (Ory et al. 2014; Albrecht et al. 2016). Several PET tracers for these targets have been developed and optimized e.g., \(^{[11C]}\text{KTP-ME}\) (Fig. 3b) for imaging cyclooxygenase 1 and \(^{[11C]}\text{JNJ7777120}\) (Fig. 3c) for imaging histamine 4 receptors (Ory et al. 2014; Albrecht et al. 2016). However, neuroinflammation is a highly complex process which is not fully understood and more recently published data on PET imaging of cyclooxygenase 1 or histamine 4 receptors are missing. Radiotracers targeting alpha7-nAChRs are described in below in the Cholinergic System Imaging section.

Imaging of neurotransmission

**Dopaminergic system imaging**

Dopamine is a neurotransmitter involved in movement, cognition, motivation and addiction. Because the dopaminergic system is crucially involved in the pathophysiology of Parkinson’s disease or variants of atypical parkinsonism. The PET tracer \(^{[18F]}\text{FDOPA}\) (Fig. 4a) is a structural analogue of L-DOPA which is a precursor of dopamine. By measuring the uptake of dopamine precursors, \(^{[18F]}\text{FDOPA}\) can be used to investigate the integrity of the dopaminergic system (Leenders et al. 1990). Another approach to detecting the integrity of dopaminergic neurons is imaging of presynaptic membrane DAT using SPECT tracer tropane derivatives (i.e. \(^{[123I]}\text{β-CIT}\), \(^{[123I]}\text{FP-CIT (DaTSCAN™)}\), \(^{[123I]}\text{IPT}\)) and PET tracers \(^{[11C]}\text{methylphenidate}\), \(^{[11C]}\text{Cocaine}\), or \(^{[18F]}\text{FE-PE2I}\) (Seibyl 2008) (Fig. 4a).

Most neurodegenerative Parkinsonian syndromes such as idiopathic PD, atypical PD and DLB are associated, in contrast to drug-induced parkinsonism or essential tremor, with a loss of presynaptic dopaminergic neurons. Thus, imaging of the integrity of presynaptic dopaminergic function enables to differentiate neurodegenerative Parkinsonian syndromes from essential tremor or drug-induced parkinsonism (Seibyl 2008). Further, imaging of the integrity of presynaptic dopaminergic function is useful to differentiate AD from DLB (Minoshima et al. 2004).

Imaging of postsynaptic D\(_{2/3}\) receptors with selective radioligands such as \(^{[11C]}\text{raclopride}\) (for PET) and \(^{[123I]}\text{IBZM}\) (for SPECT) (Fig. 4b) was used for a
longer time to differentiate PD from atypical (i.e., PSP, MSA, CBD, DLB) parkinsonism. Recent research, however, demonstrated that $[^{18}\text{F}]$FDG PET is superior to $[^{123}\text{I}]$IBZM SPECT in this regard. This is as $[^{18}\text{F}]$FDG PET allows not only to discriminate specific variants of atypical parkinsonism with high accuracy (Hellwig et al. 2012).

**Fig. 3** Chemical structures of PET radioligands for imaging neuroinflammation – targeting: a TSPO, b cyclooxygenase 1 and c histamine 4 receptor.
Cholinergic system imaging

Autoradiographic data revealed a significant reduction of different compartments of cholinergic neurotransmission, like nicotinic acetylcholine receptors (nAChRs) in patients with AD, PD and DLB (Perry et al. 1995; Martin-Ruiz et al. 2000; Flynn and Mash 1986; Sihver et al. 1999). These data are in support of the cholinergic hypothesis.
of geriatric memory dysfunction which assumes that cognitive declines are mainly caused by a reduction of acetylcholine in the synaptic cleft as a consequence of a reduction of nicotinic neurons (Bartus et al. 1982). In autoradiographic studies, reductions of the α4 subunit of the nAChR were detected in the range of 50–65% in moderate-severe stage AD (Sihver et al. 1999; Martin-Ruiz et al. 2000) and 30–50% in moderate stage DLB (Martin-Ruiz et al. 2000). In contrast, in-vivo PET/SPECT studies using α4β2 nAChR-targeting radioligands demonstrated reductions to a more variable degree. This can be at least partly explained by the fact that distinct methods for quantification (e.g. binding potentials, distribution volumes, distribution volume ratios) of α4β2 nAChR availability were used and by the fact that patients cohorts differed between studies in severity of disease ranging from mild to moderate stage of the disease (O’Brien et al. 2007; Sabri et al. 2008; Meyer et al. 2009; Kendziorra et al. 2011; Meyer et al. 2014; Sultzer et al. 2017; Sabri et al. 2018). Most important and widely used early-generation α4β2 nAChR PET ligands are 3-pyridylether derivatives such as 2-[18F]A-85380, 6-[18F]A-85380 and 5-[123I]A-85380 (Fig. 5a). As these radioligands exhibit slow kinetics resulting in long scanning times, new radioligands with more favourable characteristics have been developed and tested in preclinical and first clinical trials (Horti et al. 2013). These next-generation α4β2 nAChR radioligands are derivatives of homoeopibatidine ((−)-[18F]Flubatine, (+)-[18F]Flubatine), epibatidine ([18F]AZAN, [18F]XTRA) or 3-pyridylether derivatives ([18F]Nifene, [18F]Nifrolene and [18F]NIDA522131, [18F]Nifzetidine and [18F]ZW-104) (Horti et al. 2013; Meyer et al. 2014) (Fig. 5a). Results of the first applications in humans of these next-generation α4β2 nAChR-targeting PET radioligands such as (−)-[18F]Flubatine, [18F]AZAN and [18F]XTRA are promising (Sabri et al. 2015a, 2015b; Sabri et al. 2018; Wong et al. 2013; Coughlin et al. 2018a, 2018b). Especially, the faster kinetics with sufficient estimation of radiotracer binding within 90 min (Sabri et al. 2015a, 2015b; Wong et al. 2013; Coughlin et al. 2018a, 2018b) is an advantage compared to the early-generation α4β2 nAChR PET ligands. Further advantages are: (a) for (−)-[18F]Flubatine a small metabolization which allows quantification without metabolite correction (Sabri et al. 2015a, 2015b), (b) for [18F]AZAN a greater specific binding compared to 2-[18F]A-85380 (Wong et al. 2013) and (c) for [18F]XTRA higher distribution volumes in extrathalamic brain regions compared to the published data of [18F]AZAN and (−)-[18F]Flubatine, whereby a displacement study needs to clarify whether these higher distribution volumes are due to specific or nonspecific binding (Coughlin et al. 2018a, 2018b).

In addition to the α4β2 subtype, also α7 nAChRs should play an important role in the pathophysiologic processes, for instance, in AD (Bao et al. 2017). α7 nAChRs seem to mediate Aβ-induced tau protein hyperphosphorylation (Wang et al. 2003) and modulate immunological process in AD (Conejero-Goldberg et al. 2008) and probably, in other neurodegenerative diseases. First α7 nAChR-targeting PET radioligands i.e. [11C]CHIBA-1001 and [18F]ASEM (Fig. 5b) have been evaluated in humans (Ishikawa et al. 2011; Wong et al. 2014; Coughlin et al. 2018a, 2018b) and other promising radioligands e.g. [11C]A-582941 and [14C]GA-844606 (Toyohara et al. 2010), [18F]NS10743 (Deuther-Conrad et al. 2011) [11C]NS14492 (Ettrup et al. 2011), [18F]DBT-10 (Hillmer et al. 2016) have been preclinically examined (Fig. 5b).

Apart from nAChR deficiency, post-mortem data revealed reductions of vesicular acetylcholine transporter (VChAT) and acetylcholinesterase (AChE) in AD patients
Fig. 5  Chemical structures of radiotracers for imaging the cholinergic system – targeting: a $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs), b $\alpha_7$ nAChRs, c vesicular acetylcholine transporter and d acetylcholinesterase
compared to healthy controls (HCs) and, further, a correlation between neocortical AChE activity and dementia severity (Bierer et al. 1995). Therefore, ante-mortem examination of VChAT and AChE activity could be also of interest in AD. A radioligand targeting VChAT is \([^{123}I]\)IBVM (Fig. 5c) and radioligands targeting AChE are \([^{11}C]\)MP4A and \([^{11}C]\)PMP (Kuhl et al. 1996; Kuhl et al. 1999; Roy et al. 2016) (Fig. 5d). Furthermore, \([^{18}F]\)FEOBV, a novel, very promising PET radioligand targeting VChAT has been developed and successfully applied in patients with AD and PD (Aghourian et al. 2017; Bohnen et al. 2019). Thus, using abovementioned radioligands, reduced activities of VChAT and AChE were demonstrated in various neurodegenerative diseases like AD, PD and DLB (Kuhl et al. 1996; Kuhl et al. 1999; Roy et al. 2016; Aghourian et al. 2017; Bohnen et al. 2019).

**Monoamine system imaging**

The vesicular monoamine transporter 2 (VMAT2) is a membrane protein that transports monoamines (e.g. dopamine or serotonin) into the presynaptic vesicles. \([^{18}F]\)AV-133 (Fig. 6) is a PET radiotracer targeting VMAT2. In patients with PD, a reduced \([^{18}F]\)AV-133 uptake was found in the basal ganglia, more pronounced in the putamen and contralateral to the predominantly affected side at onset (Gao et al. 2016). An accuracy in differentiating PD patients from HCs similar to that of DAT SPECT has been reported. Furthermore, \([^{18}F]\)AV-133 PET data might better correlate to clinical characteristics than PET/SPECT imaging data of DAT (Hsiao et al. 2014).

**Imaging of misfolded proteins**

**β-Amyloid (Aβ) PET imaging**

Aβ plaques are the histopathological hallmark of AD. Moreover, their appearance in the brain is an early, if not the causal event in AD. The most widely used Aβ-targeting
PET tracer is \([^{11}C]\)Pittsburgh Compound B (PiB) (Fig. 7). However, the short half-life hampers the use of this tracer for clinical routine applications. Thus, three \(^{18}F\)-labeled radiotracers (i.e. florbetapir, florbetaben, flutemetamol) Fig. 7) have been developed and approved for clinical usage. The phase 3 data of all 3 radiotracers demonstrated high sensitivity (\(^{18}F\)florbetapir: 96%, \(^{18}F\)florbetaben: 98%, \(^{18}F\)flutemetamol: 88%) and specificity (\(^{18}F\)florbetapir: 100%, \(^{18}F\)florbetaben: 89%, \(^{18}F\)flutemetamol: > 80%) in detecting A\(\beta\) plaques in-vivo compared to the postmortem data (Clark et al. 2012; Sabri et al. 2015a, 2015b; Curtis et al. 2015). Other A\(\beta\) PET tracers, such as \([^{11}C]\)AZD2184, \([^{18}F]\)FIBT, and \([^{18}F]\)NAV4694 (Fig. 7), are under clinical examination (Ito et al. 2014; Grimmer et al. 2018). Results of the first in humans studies revealed a fast kinetics of \([^{11}C]\)AZD2184 and \([^{18}F]\) FIBT, and a time-window of 40–60 min p.i. was determined as reliable to calculate standard uptake value ratios (SUVRs) (Ito et al. 2014; Grimmer et al. 2018). The kinetics is therefore comparable to that of \([^{18}F]\)florbetapir and \([^{18}F]\)florbetaben where an acquisition start 30 min p.i. (\([^{18}F]\)florbetapir) and 45 min p.i. for the USA/90 min p.i. for Europe (\([^{18}F]\)florbetaben) is recommended (https://eanm.org/publications/guidelines/Amyloid-Guideline-J_Nucl_Med-2016-Minoshima-1316-22.pdf).

Compared to the three approved \(^{18}F\)-labeled radiotracers, \([^{11}C]\)AZD2184 and \([^{18}F]\)NAV4694 seem to show lower white matter binding (Ito et al. 2014; Rowe et al. 2013) which principally might translate to a higher sensitivity in detecting subtle amyloid pathology.

Over the last few years, the clinical and research diagnostic criteria especially for AD (McKhann et al. 2011; Albert et al. 2011; Dubois et al. 2014; McKeith et al. 2017; Jack et al. 2018) but also for other neurodegenerative diseases have been revised (McKeith et al. 2017; Berg et al. 2013), resulting in an implementation of biomarkers such as A\(\beta\) PET or \(^{18}F\)FDG PET. However, the validation process of these biomarkers is still incomplete (Frisoni et al. 2017). Especially, clinical outcome and cost-effectiveness studies are still missing (Frisoni et al. 2017). As such studies are the decisive
prerequisite for reimbursement within many healthcare systems, these PET imaging biomarkers are so far not regularly applied in clinical routine.

**Tau PET imaging**

Physiological tau is a phosphoprotein which stabilizes the microtubules. In the brain, six isoforms of tau exist with either three repeats (3R) or four repeats (4R) of the microtubules-binding domain (Buée et al. 2000). Aggregated tau proteins consist of post-translationally modified tau isoforms, whereby specific phenotypes/neurodegenerative diseases are associated with specific tau deposits that differ in microscopic appearance and ultrastructure (Buée et al. 2000; Villemagne et al. 2015). Importantly, the same clinical tauopathy phenotype can be caused by different misfolded tau proteins and vice-versa (Villemagne et al. 2015). In general, aggregated tau proteins are mainly located intracellularly and therefore a complex target for PET imaging. Current tau radiotracers share β-sheet binding properties. Since other misfolded proteins have similar structures, high selectivity for aggregated tau proteins is necessary (Lois et al. 2018). This is of particular interest, as tau aggregates can be co-localized to Aβ plaques with much higher concentrations of Aβ plaques compared to tau deposits (Villemagne et al. 2015). First-generation tau PET radiotracers – [18F]AV-1451, [11C]PBB3, [18F]THK5351 (Fig. 8) – showed favourable kinetics and high affinity to the 3R/4R tau isoform combination which is typical in AD (Villemagne et al. 2015; Lois et al. 2018; Villemagne 2018). However, the limitation of the first-generation tau PET radiotracers are a
relevant off-target binding as well as ante-mortem vs. post-mortem inconsistencies (Villemagne et al. 2015; Harada et al. 2018; Lois et al. 2018; Villemagne 2018). Second-generation selective tau PET radiotracers, such as $[^{18}F]$RO6958948, $[^{18}F]$GTP1, $[^{18}F]$PI-2620, $[^{18}F]$MK-6240 (Fig. 8), have been preclinically evaluated and demonstrated high affinity, selectivity and specificity (Lois et al. 2018). Preliminary clinical data, partially available as conference abstracts, are promising (Mueller et al. 2017; Barret et al. 2017; Bohorquez et al. 2016; Wong et al. 2018; Bohorquez et al. 2017; Betthauser et al. 2018). However, $[^{18}F]$GTP1 showed off-target binding in the basal ganglia (Bohorquez et al. 2017), while $[^{18}F]$RO6958948 did so in the substantia nigra (Wong et al. 2018). So far, for $[^{18}F]$MK-6240 and $[^{18}F]$PI-2620 off-target binding was not observed (Betthauser et al. 2018; Barret et al. 2017). Noteworthy, preliminary data also suggest that $[^{18}F]$PI-2620 might not only be able to visualize the 3R/4R tau isoform combination in AD, but also the 4R isoform in 4R-tauopathies such as PSP/CBD (https://www.alzforum.org/news/conference-coverage/next-generation-tau-pet-tracers-strut-their-stuff). Although the available data on the second-generation tau PET radiotracers are encouraging, the usefulness of these radiotracers for research and clinical approaches remains to be demonstrated in larger clinical trials.

**Imaging of other misfolded proteins**

Following the recent success with bringing amyloid and tau PET tracers into humans, the desire for radioligands targeting other misfolded proteins like $\alpha$-synuclein or TDP-43 is evident. However, developing PET radiotracers that target misfolded proteins beyond Aβ is challenging as these proteins (i) are mainly intracellularly localized, (ii) appear in a much lower concentration than Aβ plaques (Villemagne et al. 2015; Lois et al. 2018; Harada et al. 2018; Verdurand et al. 2018), and (iii) have $\beta$-sheet binding motives which are rather similar to those of amyloid aggregates. Despite intensive efforts to develop $\alpha$-synuclein- and TDP-43-targeting PET radiotracers, until now no suitable substance has been described (Mathis et al. 2017).

The FET protein family consists of fused in sarcoma (FUS), Ewing sarcoma (EWS) and TATA-binding protein associated factor 15 (TAF15) and was first discovered as components of fusion oncogenes causing specific malignancies (Mackenzie and Neumann 2016). As DNA/RNA binding proteins, they are predominantly located in the cell nucleus and are involved in DNA/RNA metabolism as well as in the maintenance of genomic stability (Mackenzie and Neumann 2016; Svetoni et al. 2016). In approximately 5–10% of all FTLD cases, the intracellular inclusions are FTLD-Tau- and TDP-43-negative in immunohistochemical examination. But they can be labeled using FUS/EWS/TAF15 antibodies and are therefore classified as FTLD-FUS or FTLD-FET group (Mackenzie and Neumann 2016). Similar to $\alpha$-synuclein and TDP-43, the existing literature does not reveal any reports regarding FTLD-FET targeting radiotracers. Considering the low prevalence of these diseases (FTLD-TDP is rare, FTLD-FET is even rarer), the search for suitable radiotracers targeting these proteins is so far less active.

**Summary and conclusion**

In the last two to three decades, a large number of novel radiotracers for direct and indirect imaging neurodegenerative processes and their underlying pathology have been
developed. Several of them have been approved and are used in clinical routine for early and differential diagnosis as well as for evaluation of disease progression. Others are appreciated as valuable research tracers. However, the more pathological components of the different neurodegenerative diseases are discovered, the more new and interesting issues occur. Such issues are (i) the classification of neurodegenerative disorders in clinical routine, (ii) the identification of targets for possible new radiotracers, (iii) the identification of novel radiotracer targets, (iv) the accurate monitoring strategy of such therapy trials. Some of them could be answered by PET studies with new radiotracers. But as important as the development of new radiotracers seems to be, at the moment it is equally important to sum up our gathered pieces of knowledge, combine them and try to get a more comprehensive understanding of the entire spectrum of neurodegenerative disorders (Fig. 9).

**Abbreviations**

3R: Three repeat tau isoform; 4R: Four repeat tau isoform; AChE: Acetylcholine esterase; AD: Alzheimer’s disease; Aβ: β-amyloid; bvFTD: Behavioural variant of frontotemporal dementia; CBD: Corticobasal degeneration; DAT: Dopamine transporter; DLB: Dementia with Lewy-bodies; EWS: Ewing sarcoma; FET: Fused in sarcoma, Ewing sarcoma, TATA-binding protein associated factor 15; FTLD: Frontotemporal lobar degeneration; FUS: Fused in sarcoma; HD: Huntington’s disease; lvPPA: Logopenic variant primary progressive aphasia; MSA: Multisystem atrophy; nAChR: Nicotinic acetylcholine receptors; nfvPPA: Non-fluent/agrammatic variant primary progressive aphasia; PCA: Posterior cortical atrophy; PD: Parkinson’s disease; PDD: Parkinson’s disease dementia; PET: Positron emission tomography; PPA: Primary progressive aphasia; PSP: Progressive supranuclear palsy; SPECT: Single photon emission computed tomography; SVA2: Synaptic vesicle glycoprotein 2A; svPPA: Semantic variant primary progressive aphasia; TAF15: TATA-binding protein associated factor 15; Tau: Hyperphosphorylated neurofibrillary tau protein; TDP-43: Transactive response DNA binding protein of about 43 kDa; TSPO: 15 kDa translocator protein; VChAT: Vesicular acetylcholine transporter; VMAT2: Vesicular monoamine transporter 2.

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