Seminars in Nuclear Medicine: "Molecular imaging of dementia"

Imaging of tau pathology in neurodegenerative diseases: an update

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Abstract

Pathological accumulated misfolded tau underlies various neurodegenerative diseases and associated clinical syndromes. To diagnose those diseases reliable before death or even at early stages, many different tau-specific radiotracers have been developed in the last decade to be used with positron-emission-tomography. In contrast to β-amyloid imaging, different isoforms of tau exist further complicating radiotracer development.

First-generation radiotracers like [^{11}C]PBB3, [^{18}F]AV1451 and [^{18}F]THK5351 have been extensively investigated *in vitro* and *in vivo*. In Alzheimer's disease (AD), high specific binding could be detected, and evidence of clinical applicability recently led to clinical approval of [^{18}F]flortaucipir ([^{18}F]AV1451) by the FDA. Nevertheless, absent or minor binding to non-AD tau isoforms and high off-target binding to non-tau brain structures limit the diagnostic applicability especially in non-AD tauopathies demanding further tracer development.

In vitro assays and autoradiography results of next-generation radiotracers [^{18}F]MK-6240, [^{18}F]RO-948, [^{18}F]PM-PBB3, [^{18}F]GTP-1 and [^{18}F]PI-2620 clearly indicate less off-target binding and high specific binding to tau neurofibrils. First in human studies have been conducted with promising results for all tracers in AD patients, and also some positive experience in non-AD tauopathies. Overall, larger scaled autoradiography and human studies are needed to further evaluate the most promising candidates and support future clinical approval.

Radiotracers for tau

Tauopathies form a heterogeneous group of neurodegenerative diseases, ranging from Alzheimer's disease (AD), atypical parkinsonian syndromes like progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) to subtypes of frontotemporal dementia and various rare diseases[1]. Furthermore, in addition to primary tauopathies, other illnesses such as chronic traumatic encephalopathy are also characterized by aggregation of tau in the human brain[2]. Imaging of pathological accumulated misfolded tau is of special interest as clinical syndromes in tauopathies often overlap with other neuropathological entities[3]. **Figure 1** provides an overview of potential applications for tau-PET imaging, especially in terms of differential diagnosis.

Tau-specific radiotracers for use with positron emission tomography (PET) have been developed for nearly ten years. Compared to β-amyloid (Aβ), detection of tau is complicated by the presence of different isoforms and an overall lower quantity of tau aggregates in the brain[4]. Since the beginning, quinoline derivatives were seen as promising candidates with [^{18}F]THK523[5] as the first compound followed by [^{18}F]THK5105[6-8], [^{18}F]THK5117 ([^{18}F]THK5317)[8-12] and [^{18}F]THK5351[12 13]. Of the benzimidazole pyrimidines [^{18}F]T807 ([^{18}F]AV1451) and [^{18}F]T808, [^{18}F]AV1451 was found to be superior and led to extensive investigation of this compound[14]. Together with [^{11}C]PBB3[15-17], a benzothiazole derivate, [^{18}F]THK5317, [^{18}F]THK5351 and [^{18}F]AV1451 are the first-generation radiotracers that have been most widely examined *in vitro* and *in vivo*[18]. Autoradiography evaluation of all radiotracers showed specific binding to both intracellular and extracellular neurofibrillary/ ghost tangles[9 13 19 20]. Nevertheless, significant off-target binding was reported for all these compounds: [^{18}F]THK5351 and [^{18}F]AV1451 were found to bind to the monoaminoxidases A and B[21 22], [^{11}C]PBB3 and [^{18}F]AV1451 showed binding to

vascular structures (choroid plexus/ dural venous sinuses) and unspecific binding to neuromelanin has been observed for all tau tracers. Furthermore, off-target binding to non-tau protein deposits complicated the differentiation to other diseases. β-sheet structures do not only appear in misfolded tau, but also in amyloid fibers[23 24], α-synuclein[25] or TDP-43[26]. Also, the myelin basic protein forms β-sheet structures, leading to potential off-target sources in the white matter[27].

The main effort in the subsequent development of next-generation tau radiotracers was to reduce off-target binding by increasing tracer specificity. While some structures of next-generation radiotracers are based on existing scaffolds ([^{18}F]RO-948, [^{18}F]PI-2620, [^{18}F]GTP1), other were designed by different lead compounds ([^{18}F]MK-6240, [^{18}F]JNJ067). For chemical structures of selected and most frequently investigated first- and next-generation tau radiotracers see **Figure 2**.

First autoradiography and in-human studies indicated high specific binding to neurofibrillary tangles in AD and no off-target binding to Aβ for the majority of the mentioned next-generation tau radiotracers[28-31]. Additionally, [^{18}F]MK-6240 showed no binding to α-synuclein or TDP-43, but also no significant binding to tau aggregates in non-AD tauopathies[28].

Compared to first-generation tau radiotracers, significantly lower off-target binding to MAO-A/B was observed[28-31] with [^{18}F]MK-6240, [^{18}F]JNJ067and [^{18}F]PI-2620 appearing to have the lowest relative affinity for MAO-B[32]. In exemplary patient cases with clinical suspected tau-negative multi-system-atrophy of the cerebellar phenotype, elevated subcortical binding was observed for the first-generation tau-radiotracer [^{18}F]THK5351, but not for the next-generation tau-radiotracer [^{18}F]PI-2620 (see **Figure 3**). Further autoradiography studies are needed to validate binding affinities of all next-generation radiotracers in both AD and non-AD tauopathies.

Tau Imaging in Alzheimer's disease

In addition to the extracellular amyloid protein, intracellular fibrillar tau forms the second neuropathological hallmark of AD[33]. As the most common form of dementia, AD pathology leads to multiple sub-variants with different clinical dominant features[34]. Whereas typical variants of AD are often diagnosed clinically with relatively high diagnostic certainty, a lot of overlap with other neurodegenerative or vascular diseases is observed especially in atypical forms of AD[35 36]. Biomarker-based diagnostics were propagated for AD[37]. In the A/T/N classification scheme, characterization of amyloid- and tau-status and evidence of existing neurodegeneration is demanded for diagnosis of AD[38]. Amyloid (Aβ) can be assessed in the cerebrospinal fluid ($A\beta_{42}$) or by Aβ-PET-imaging (see section above). In analogy to Aβ, tau-status is captured by elevated phosphor-tau in cerebrospinal fluid or pathologic tau-PET imaging with tau-specific radiotracers. Neurodegeneration can be measured in the cerebrospinal fluid (levels of total-tau), by atrophy in structural magnetic resonance imaging or hypometabolism in ^{18}F-fluorodesoxyglucose (FDG) PET[38]. It has been shown for multiple amyloid-radiotracers and first- and next-generation tau-radiotracers, that early-phase perfusion images can also be used as a surrogate marker of neuronal injury to assess both biomarkers in one procedure[39-44]. Whereas three different amyloid-specific radiotracers have already been approved by regulatory authorities and are frequently used in the clinical routine, only one tau-PET tracer has been recently approved and other tau-PET radiotracers are investigational and still being evaluated in clinical trials.

First-generation tau radiotracers

Of the first-generation tau radiotracers, [^{18}F]AV1451 ([^{18}F]flortaucipir, TAUVID™) gained the highest attention, ultimately leading to FDA approval this year[45]. Since the first human brain imaging publication of [^{18}F]flortaucipir in 2013[14], binding affinities have been investigated intensively *in vitro* and *in vivo*. [^{18}F]AV1451 binding was found to be consistent with postmortem neurofibrillary tangle Braak staging[46]. PET-to-autopsy comparisons confirmed that advanced Braak tau pathology was reliably detectable, but early Braak stages of neurofibrillary tangle pathology did not show elevated tracer uptake compared to young, tau-negative controls[47]. *In vivo* studies also showed a significant correlation with clinical disease stages in AD with increasing tracer binding from Aβ+ cognitively normal elderly to mild cognitive impairment (MCI) and AD dementia[48]. Distribution patterns of tracer binding were similar to the topology of tau deposition described by Braak[49]. Tau-PET imaging with ^{18}F-flortaucipir differentiates very reliably between patients with MCI or AD and healthy controls (HC)[50-53] with lower off-target binding in the white matter, midbrain, thalamus and basal ganglia when compared to [^{18}F]THK5351[54].

In autosomal-dominant amyloid-positive AD mutation carriers and patients in presymptomatic stages, tracer retention was found in the medial temporal regions up to six years before clinical onset of cognitive impairment[55 56]. The hippocampus is known to be affected in early AD stages, but quantification of the hippocampal tau load in vivo is complicated by off-target binding to the choroid plexus[57 58]. Nevertheless, in those very early stages of presymptomatic patients and in early stages of AD, tracer uptake was in line with CSF measurements[56] and appears to be superior for accurate diagnosis in the dementia stage[59-61].

[^{18}F]flortaucipir was able to discriminate AD from various other neurodegenerative diseases[62], especially in subtypes with overlapping clinical features. In patients with posterior cortical atrophy, tau-PET imaging showed significantly higher binding

compared to patients with similar clinical features arising from dementia with Lewy bodies[63]. Within AD subtypes, different binding patterns matching the clinically phenotype and the known function of brain regions were observed[64-67]. Patients with posterior cortical atrophy presented with higher uptake in occipital and parietal brain regions, patients with amnestic-predominant presentation showed the highest binding in medial temporal and lateral temporoparietal regions whereas patients with a logopenic variant of primary progressive aphasia demonstrated asymmetric uptake between hemispheres[68].

Tracer uptake of [^{18}F]flortaucipir is limited to brain regions related to clinical symptoms that overlap with regions of hypometabolism whereas the Aβ-PET tracer signal is found to be located throughout the entire cortex[69 70]. Therefore, it is not surprising and in line with neuropathological studies that ^{18}F-flortaucipir binding correlated with clinical symptoms and the degree of cognitive impairment[71-76], whereas there is only very limited association between Aβ-PET quantification and cognition[77]. In longitudinal studies, tracer accumulation increased over time and in correlation with worsening of clinical symptoms[78 79]. In cases at early disease stages elevated [^{18}F]flortaucipir binding was even found in regions without significant atrophy at the time of tau-PET imaging[80] matching the biomarker-based model of disease progression in AD[81].

Based on these promising results, a prospective study (A16 study) was conducted with 156 patients with a terminal illness and a life expectancy of less than 6 months undergoing [^{18}F]flortaucipir PET imaging[45]. 73 participants deceased during the observation period and autopsy was subsequently performed in 67 cases. PET images were assessed visually and compared to neuropathological tau load and this approach resulted in a very high sensitivity and moderate specificity for detection of AD typical neuropathological changes (Braak stage III). To support the diagnosis of

AD, the U.S. Food & Drug Administration approved the intravenous use of [^{18}F]flortaucipir in May 2020 for adult patients with cognitive impairment and suspected AD.

Next-generation tau radiotracers

For all mentioned next-generation tau radiotracers, first in human studies have already been performed in healthy controls and AD patients. [^{18}F]RO-948 binding in AD subjects versus HC was significantly elevated in multiple regions known to be affected in AD (medial temporal areas, precuneus/ posterior cingulate cortex, lateral parietal and occipital lobes, prefrontal cortex)[82]. The same was true for [^{18}F]MK-6240 where slower clearance was observed in regions commonly associated with tau deposition (neocortical and medial temporal brain regions)[83 84]. Off-target binding was evident in the ethmoid sinus, clivus, meninges and the substantia nigra[84]. [^{18}F]PI2620 showed high uptake in target regions (temporal and parietal lobes, precuneus, posterior cingulate cortex) accompanied by fast wash-out in non-target regions[85]. Evaluation of dosimetry revealed fast kinetics with a tolerable effective dose and good quantification accuracy of tau deposits[86]. Tracer uptake remained stable over a time frame of 30-90 min after injection resulting in different possible time frames for acquisition[86 87]. In a mixed cohort of 26 patients with suspected tauopathies including seven AD patients, early-phase [^{18}F]PI2620 perfusion images were found to be a surrogate of neuronal injury, adding an additional biomarker information beyond tau accumulation[39 88]. Favorable dosimetry and brain kinetics were also reported for [^{18}F]GTP1 with specific binding in affected cortical brain regions and low test-retest variability[30]. In a cross-sectional population, binding increased with AD severity and was correlated with cognitive performance[30 89]. First-in-human data has also been published for [^{18}F]JNJ067 indicating increased uptake in AD patients when compared

to HC[90]. Exemplary cases of [^{18}F]PI-2620 next-generation tau-PET imaging in AD tauopathies are illustrated in **Figure 5**.

Tau imaging in non-Alzheimer's disease tauopathies

In addition to AD, different isoforms of accumulated pathological misfolded tau proteins are found in various other neurodegenerative diseases summarized as non-AD tauopathies. Those can be categorized according to different groups of underlying tau isoforms into dominant three repeat (3R), dominant four repeat (4R) and mixed 3R/4R tauopathies. The differing structure of those isoforms represents, besides off-target binding, a further hurdle in tracer development. All radiotracers that have been developed and tested in vivo so far indicate sufficient binding to AD as the most common 3R/4R tauopathy, but binding affinities to pure 3R or 4R tauopathies showed a large heterogeneity.

First-generation tau radiotracers

Many studies have been conducted with [^{18}F]flortaucipir not only in non-AD tauopathies but also in tau-negative neurodegenerative entities. Postmortem pathological confirmation is often missing and proven off-target binding calls into question that tau aggregates are actually responsible for the majority of tracer binding[57] [91]. Overall, non-Alzheimer tauopathies were not found to be reliably detected by [^{18}F]flortaucipir in postmortem comparisons[47].

In clinical PSP patients, bilateral elevated [^{18}F]flortaucipir uptake was found in globus pallidus, putamen, subthalamic nucleus, midbrain, and dentate nucleus and discriminated those PSP patients from HC and Parkinson's disease (PD) well[92]. This finding was confirmed by postmortem correlation of one patient with good agreement between *in vivo* tracer uptake and neuropathological findings[92]. In another study, no significant differences were detected between PSP and HC patients[93]. Autoradiography studies suggested binding to recombinant and purified native tau

fibrils from PSP patients[21], but could not be replicated on postmortem brain slices of PSP patients[94]. Therefore some studies concluded that tracer binding was dependent on off-target binding, mainly to MAO-B[21] and neuromelanin[95]. Comparable findings were obtained for [^{18}F]THK-5351 with detectable subcortical binding[96] but also significantly reduced *in vivo* uptake after monoamine oxidase B inhibitor treatment[97 98].

In corticobasal degeneration (CBD), as another tau-positive parkinsonian syndrome, increased [^{18}F]flortaucipir uptake was found in parietal, frontal, precentral and postcentral cortices when compared to HC and MCI patients[88 99]. In vivo binding in CBD patients was confirmed in some postmortem cases[99-103] for both ^{18}F-flortaucipir and [^{18}F]THK-5351. Overall, regional tracer binding was found to be very heterogeneous and dependent on the Aβ status[104].

In Parkinson's disease (PD) with underlying α-synuclein pathology, no significant elevation in cortical [^{18}F]flortaucipir binding was observed in non-demented patients[105 106], but PD patients tended to show lower binding in the substantia nigra as an expression of nerve cell loss in this affected area[106]. In PD patients with cognitive impairment and Dementia with Lewy bodies (DLB), tau copathology is common and might explain elevated posterior temporoparietal and occipital [^{18}F]AV-1451 uptake[107].

Patterns observed in parkinsonian syndromes differed from those in AD and between tauopathies and α-synucleinopathies[108-112] which could lead to clinical applicability in those entities after all. A possible explanation is located in the astrogliosis-related monoaminoxidase elevation which is a common feature of all parkinsonian syndromes and therefore neuroimaging of inflammation itself remains an interesting target in neurodegenerative diseases[22 113].

Frontotemporal lobar degeneration (FTLD) comprises several clinical syndromes caused by different neuropathological verifiable misfolded proteins, mainly tau, TDP-43 and FUS[114]. The umbrella term frontotemporal dementia (FTD) is the second most common cause of presenile early onset dementia[115 116] and includes, together with the previously discussed tau-positive motor disorders PSP and CBD, clinical subtypes such as behavioral-variant FTD (bvFTD)[117] or primary progressive aphasia (PPA) variants[118].

Many studies investigating binding capacities of [^{18}F]flortaucipir included patients with FTD and increased [^{18}F]flortaucipir binding was found in different subtypes, but sensitivity and specificity between predicted tauopathies or TDP-43 pathology was limited, and large-scale pathological confirmation of specific binding is missing[119 120].

In patients with mutations of the MAPT gene that encodes tau and causes frontotemporal dementia with parkinsonism[121], elevated [^{18}F]flortaucipir binding was found in temporal and frontal regions and the basal ganglia and correlated with the amount of tau in post-mortem analyses[122 123].

In PPA, different clinical subtypes indicate differing proportions of underlying neuropathology: logopenic variant PPA (lvPPA) is mostly associated with AD pathology, non-fluent/agrammatic variant PPA (nfvFTD) with FTLD-tau and semantic variant PPA (svPPA) with TDP pathology[124]. In line, binding characteristics showed a different magnitude and pattern across the PPA variants and were excellent in distinguishing between them[125]. For example, [^{18}F]flortaucipir uptake patterns in lvPPA patients were similar to those in AD patients[126]. Interestingly, binding was also observed in svPPA patients with spatial pattern localized to areas of atrophy

indicating further mentioned off-target binding to non-tau features of neurodegeneration[127].

Only faint or no specific binding could be observed in a postmortem case series of five patients with chronic traumatic encephalopathy and histopathological confirmed tau aggregates[128].

Next-generation tau radiotracers

Whereas both *in vitro* and first *in vivo* results of all second-generation tau radiotracersshowed high affinity and specificity for tau in AD, only a few compounds showed potential for binding in non-AD tauopathies. Postmortem autoradiography showed specific [^{18}F]-PI-2620 in vitro binding in PSP patient cases, colocalized with AT8 positive tau depositions.[124] Suitability of [^{18}F]PI-2620 as biomarker in PSP patients was demonstrated in a cross-sectional multicenter-study involving 60 PSP patients, ten HC and 20 disease controls (10 PD or multi-system-atrophy and 10 AD)[124]. Compared to control groups, *in vivo* data indicated significant tracer binding in all subcortical PSP target regions but no significant correlation with age, disease severity and disease duration[124]. On a subject level, subjects with PSP could be clearly identified compared to diseased or non-diseased controls. Exemplary cases of [^{18}F]PI-2620 next-generation tau-PET imaging in non-AD tauopathies are illustrated in **Figure 5**.

A very recent study of [^{18}F]PM-PBB3 also showed tracer binding to 4R tau *in vitro* and autopsy controlled *in vivo* retention was observed in the motor cortex of few corticobasal syndrome patients[129]. Binding to subcortical structures of PSP patients was elevated in contrast to healthy controls and the authors reported a positive association of the tracer signal with disease severity. In addition, binding was verified in few deceased patients by pathology evaluation[129]. Whereas [^{18}F]RO948 yielded a

strong tracer signal in patients with AD no relevantly elevated binding was observed in non-AD tauopathies except for MAPT mutation carriers when compared to healthy controls[130]. Autoradiography evaluation of [^{18}F]MK-6240 did not reveal significant binding to non-AD tauopathies. As [^{18}F]MK-6240 was primarily optimized for high-affinity binding to AD[131] it can be assumed that this compound has only very limited utility for detection of non-AD tauopathies[28].

In summary, recent findings suggest that tau-PET imaging of 4R tauopathies is potentially feasible at least by some fluorinated next-generation tracers. Specific image acquisition protocols and analyses could be important for imaging non-AD tauopathies with next-generation tracers, given the lower target density and presumably reduced affinity to 4R tau when compared to 3/4R tau. Interestingly, binding to different tau isoforms seems to vary widely between tracers with similar structure[132]. This calls for detailed head-to-head comparisons of next-generation tau-PET tracers *in vivo*. Speculations regarding the superiority of one next generation tau-PET tracer over the other should be avoided until more detailed and comparable investigations with larger sample sizes are available.

Future perspectives of tau-PET imaging

Many tau-specific radiotracers have been developed so far highlighting the relevance of specific diagnostic tools to characterize neurodegenerative diseases reliable in vivo. Multiple investigations indicated diagnostic applicability in AD, but specific binding also to non-AD tauopathies (i.e. 4R tau) is a remaining challenge. Further larger-scaled studies and multi-regional correlations with autopsy are needed to validate detailed binding capacities and remaining off-target sources. Cryo-electron microscopy studies may facilitate to unravel mechanisms of amyloid formation, including different types of tau, of recombinant proteins to those in human brain[133].

Ultimately, such efforts could lead to the successful development of isoform specific tau-PET tracers.

Diagnostics algorithms recommend biomarker-supported diagnosis in neurodegenerative diseases. Compared to Aβ-PET imaging, which is mainly used in suspected AD patients, the indication spectrum in tau-PET imaging includes a broad range of suspected tauopathies and their related differential diagnoses. In AD, Aβ-PET imaging suffers from “physiological” Aβ deposition in older patients (> 80 years), thus limiting the diagnostic validity in aged patients[134]. Therefore, tau PET imaging could be favored in the clinical work-up of older patients with suspected AD. In addition to specific binding to tau, early-phase images of tau PET imaging can be used as a surrogate of neuronal injury, resulting in two assessable biomarkers with one procedure.

Upcoming anti-tau treatment studies deserve a reliable tau-PET read out as inclusion criteria during the screening phase of the trial. This procedure has already underpinned its importance in anti-amyloid trials where Aβ-PET served to prove Aβ positivity before patient inclusion. The main interest of baseline PET imaging in such trials consists in detection of patients that mimic the same amyloid- or tau-positive disease but are lacking the targeted protein inside their brain. Earlier anti-amyloid trials with bapineuzumab indicated that one third of patients was included without showing amyloid-positivity when Aβ-PET was analyzed after completion of the studies[135]. The value of tau-PET in clinical treatment studies of AD could even be higher since an assumption of tau-positivity will be challenging in mildly affected patients which are predominantly subject to those trials. In addition to potential use of tau-PET as an inclusion criterion biomarker, the methodology could also be used to monitor treatment efficacy of tau targeting therapies in vivo. Therapies that will focus on halting further progression of tau pathology will require imaging agents that are

sensitive enough to detect changes over time in the placebo group and a treatment/imaging period long enough to ensure that at least small changes take place in these patients. Noteworthy, preclinical studies already indicated the potential of PET imaging to monitor a reversal of metabolic decline during oligomer modulation by non-specific FDG[136]. Thus, specific tau-PET imaging could increase the sensitivity to track more subtle changes in such therapies in vivo. Furthermore, therapies that could also lead to removal of tau in the brain will might even profit from early imaging intervals to predict response to therapy. Taken together, application of tau-PET for establishing an earlier and more reliable diagnosis as well as its use in treatment trials will be the most promising fields for use of such ligands.

Figures

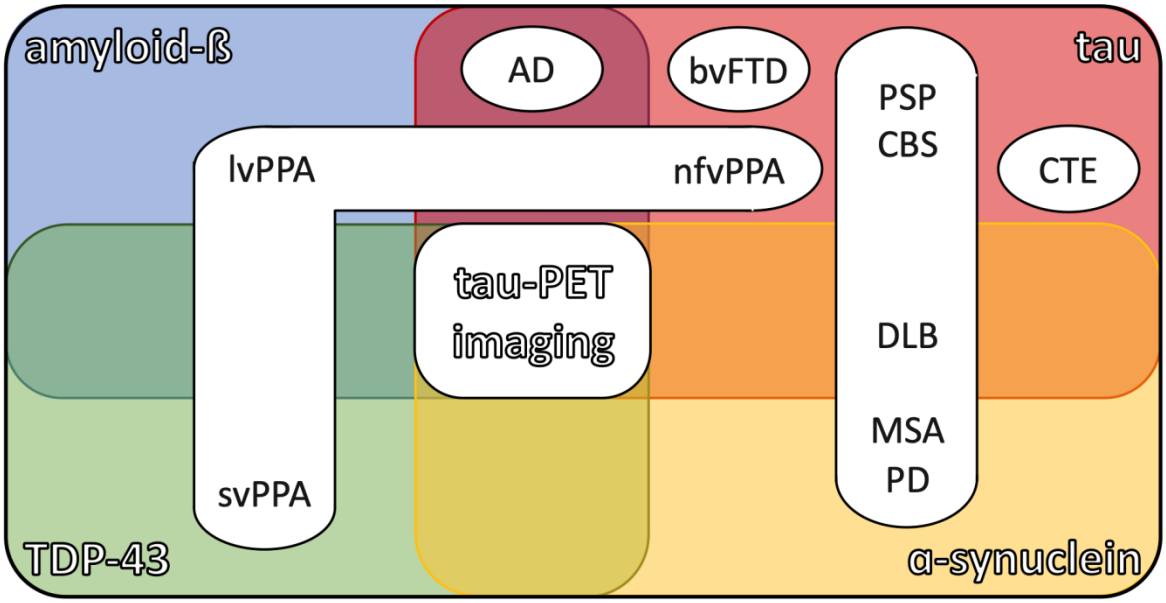

Fig. 1 Potential applications for tau-PET imaging. Neuropathological overlap between clinical syndromes and most common underlying pathology (amyloid-β, tau, α-synuclein, TDP-43). AD, Alzheimers disease; CTE, chronic traumatic encephalopathy; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; MSA, multi-system atrophy; PD, parkinsons disease; bvFTD, behavioral-variant frontotemporal dementia; svPPA, semantic-variant primary progressive palsy (PPA); lvPPA, logopenic-variant PPA; nfvPPA, non-fluent/ agrammatic PPA.

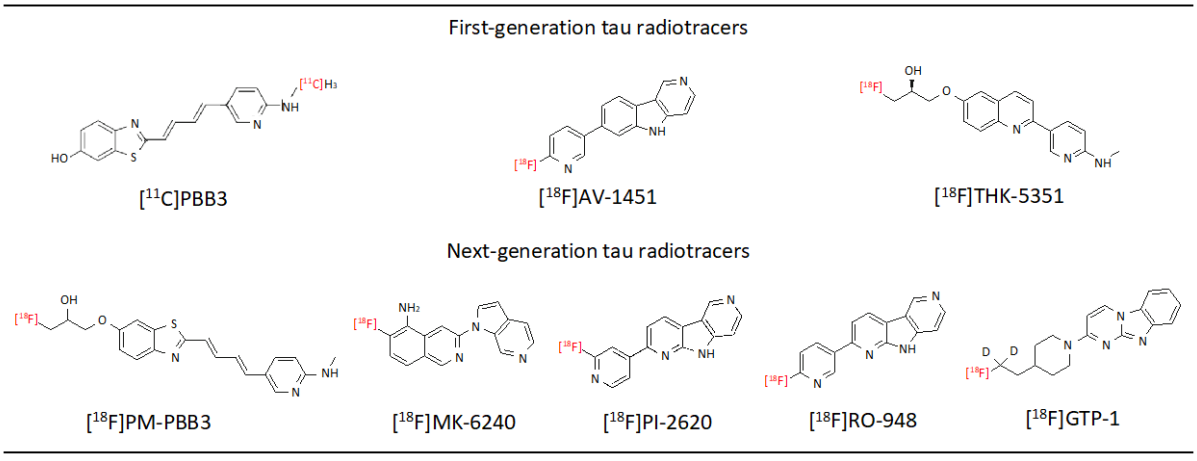

Fig. 2 Chemical structures of selected first- and next-generation tau radiotracers.

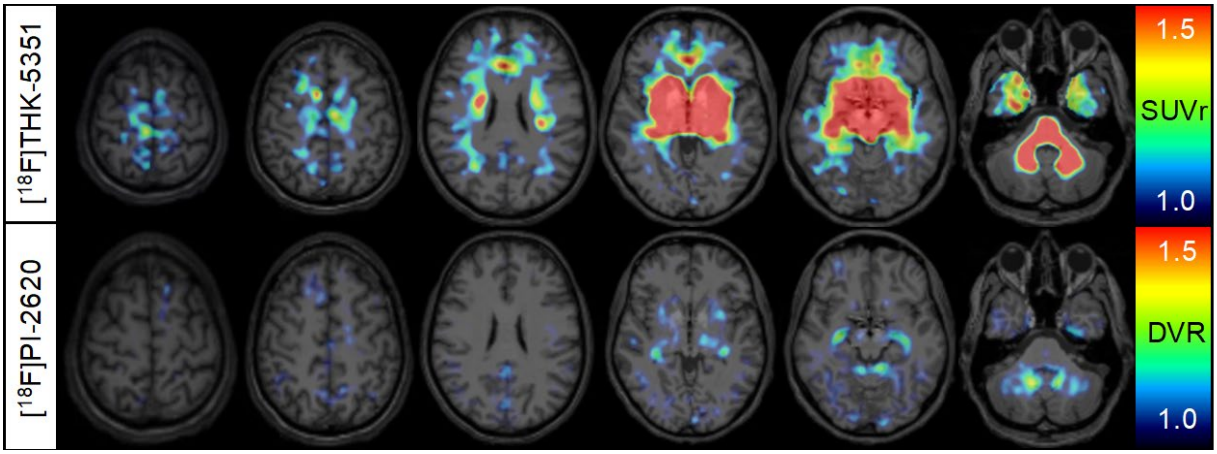

Fig. 3 Exemplary axial images of two patients with assumed tau-negative multi-system-atrophy of the cerebellar phenotype (upper row: male, 65 years, MoCA 25/30; lower row: male, 55 years, MoCA 26/30) being imaged with either the first-generation tau-radiotracer [^{18}F]THK-5351 or the next-generation tau-radiotracer [^{18}F]PI-2620. MoCA, Montreal Cognitive Assessment; SUVr, standard-uptake-value-ratio; DVR, distribution volume ratio. Case compilation of the Ludwig-Maximilians-Universität (LMU) Munich.

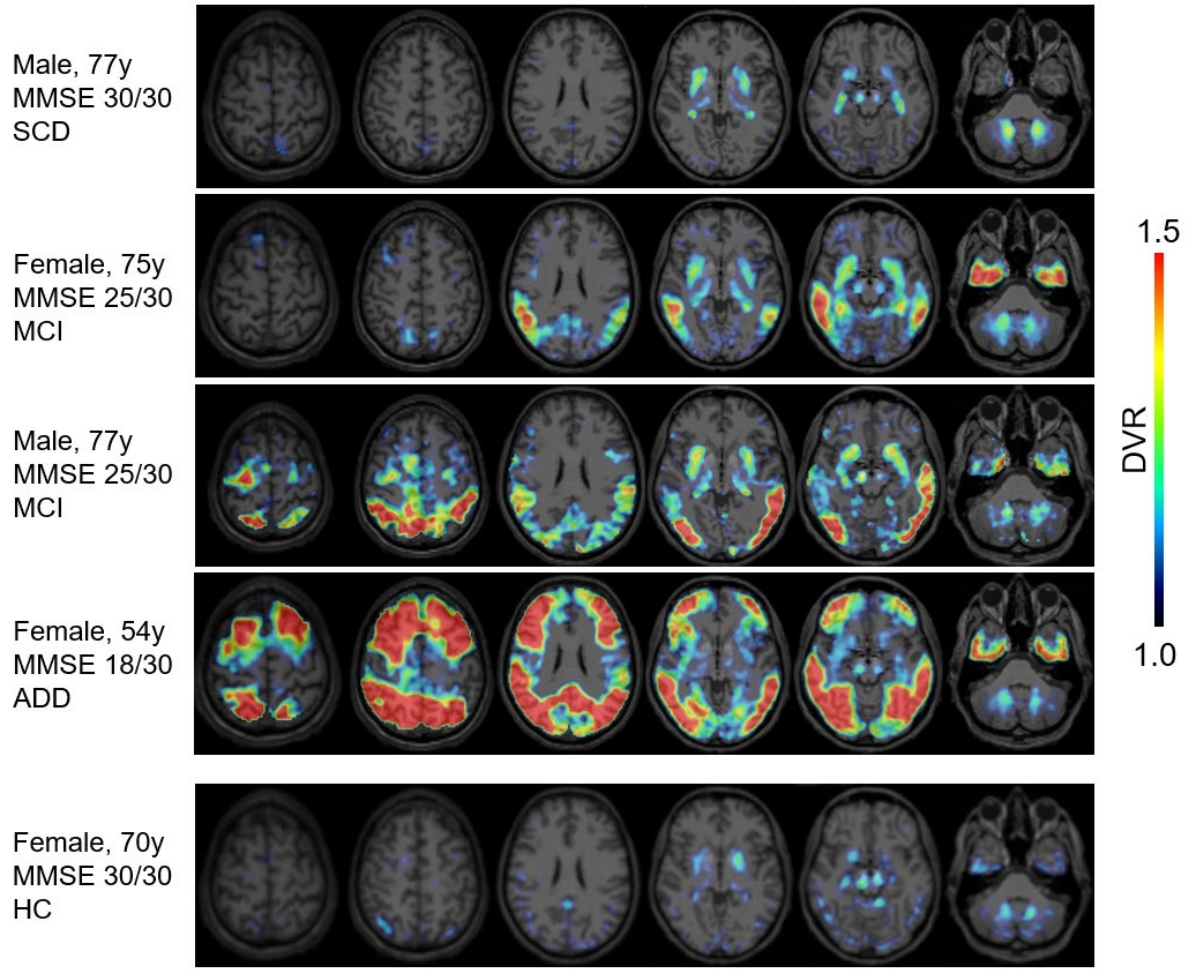

Fig. 4 Exemplary axial images of patients of the AD-continuum imaged with the next-generation tau-radiotracer [^{18}F]PI-2620. All patients had a positive β-amyloid PET scan. The HC was Aβ-negative. MMSE, Mini-Mental-State-Examination; SCD, subjective cognitive decline; MCI, mild cognitive

impairment; ADD, Alzheimer's disease dementia; HC, healthy control; DVR, distribution volume ratio. Case compilation of the Ludwig-Maximilians-Universität (LMU) Munich

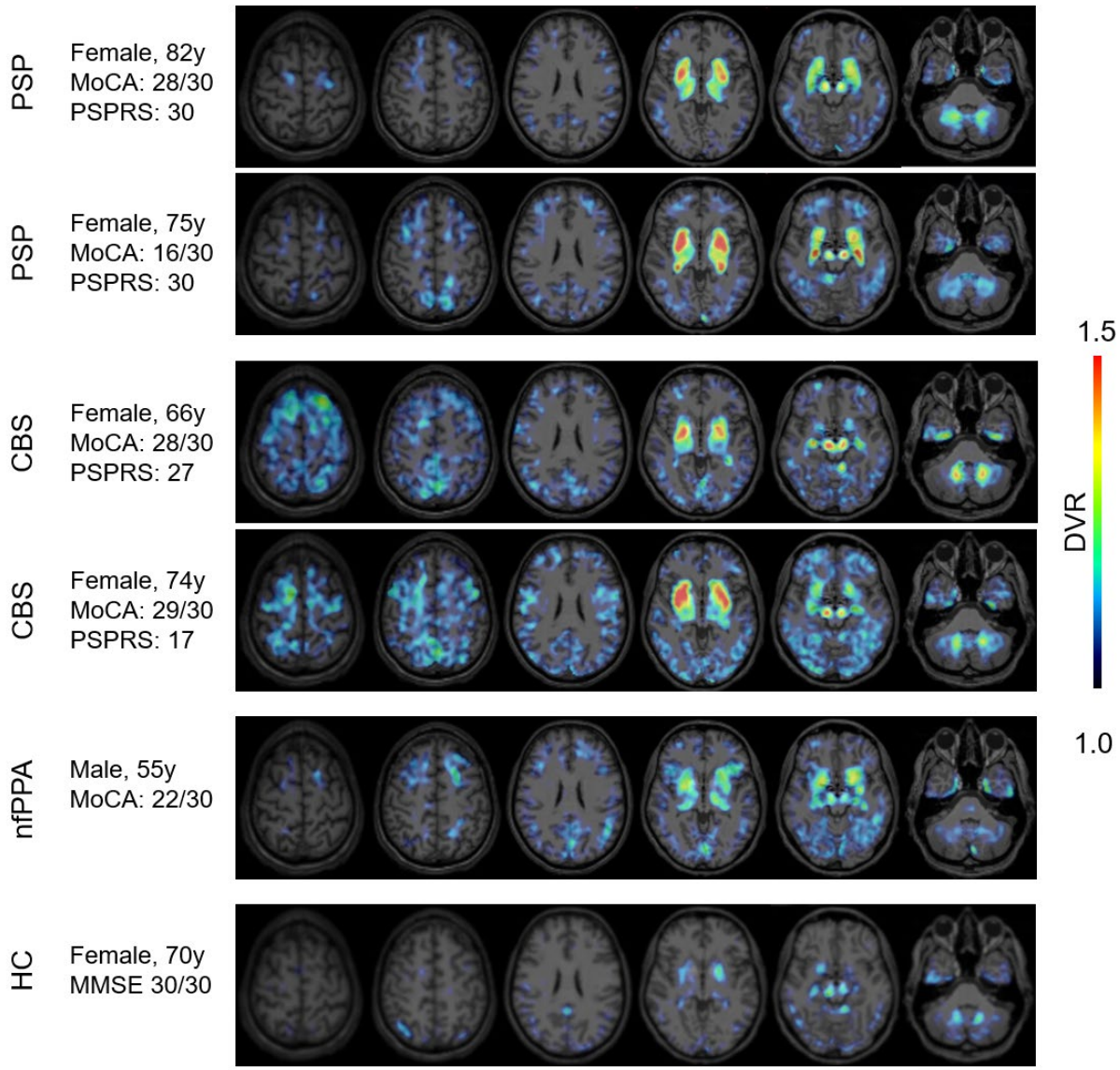

Fig. 5 Exemplary axial images of patients with suspected non-AD tauopathies imaged with the next-generation tau-radiotracer [^{18}F]PI-2620. All patients and the HC had a negative β-amyloid PET scan. PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; nfPPA, non-fluent variant of primary progressive aphasia; HC, healthy control; MoCA, Montreal Cognitive Assessment; DVR, distribution volume ratio. Case compilation of the Ludwig-Maximilians-Universität (LMU) Munich.

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