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Original Article

Tau-PET imaging as a molecular modality for Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is the most prevalent neurodegenerative condition. The definitive diagnosis of AD remains a post-mortem neuropathological study of the brain. Unfortunately, there are no established diagnostic criteria to achieve an accurate diagnosis of AD in a similarly objective fashion among living patients. Molecular imaging provides one way of enhancing clinical criteria where objective measures of AD correlate to the presence and progression of disease. In this article, the amyloid and tau hypotheses are considered with respect to pathological, imaging, and therapeutic studies. The value of beta-amyloid (Aβ) PET and tau PET are ascertained. Subsequently, the binding characteristics and quality of Aβ and tau tracers are explored. Finally, the value of Aβ and tau imaging in AD can be determined relevant from in-vivo studies of AD patients. Considering the evolving literature in AD and PET imaging, it has become clear that PET can play a role in the diagnosis and prognosis of AD. The use of Aβ imaging has been extensively studied with mixed results suggesting a limited clinical utility. Conversely, tau-PET has shown early success in similar applications as Aβ imaging. Specifically, we find that there is value in FDG-PET and prospective utility in tau-PET. Ultimately, the community must acknowledge that the role of Aβ imaging for diagnosing and managing AD is very limited and that FDG-PET will remain the study of choice at this time. Moreover, research efforts must continue to determine the prospective value of tau imaging to the assessment of this disease.

Keywords: Alzheimer's disease, Tau, Amyloid, PET, FDG

Defining Alzheimer's disease

Alzheimer's disease (AD) is clinically defined by age-related, progressive cognitive decline, including a spectrum of clinical diagnoses from mild cognitive impairment to clinical dementia [1]. Clinical dementia, marked by a measurable decline of cognitive function from baseline levels, is considered the most advanced state of cognitive decline [1]. The underlying cause of most diagnosed dementias is attributed to AD; other idiopathic causes of dementia include Parkinson's disease, frontotemporal lobar degeneration, and Lewy body dementia, or a mix of these etiologies [2]. AD dementia may present in conjunction with additional neurodegenerative diseases, most notably vascular dementia, caused by underlying cerebrovascular disease [3]. Atherosclerotic plaque deposition and subsequent arterial vasculature stenosis cause cerebral ischemia, neurological dysfunction, and clinical dementia [4, 5]. Reduced perfusion can often precede atrophy; this, in addition to generalized dysfunction, can occur concurrent to neurogenerative prion disease [6]. Fortunately, molecular imaging through positron emission tomography (PET) has proven sensitive to differentiating cerebrovascular disease from prion-based disease [3-5]. Nevertheless, the differential diagnoses among these etiologies of dementia remain quite difficult to parse. The most important risk factor of dementia and, specifically AD, is age; the incidence of these conditions greatly increases after the age of 60 [2]. Aging populations and increasing healthcare costs have driven global efforts to better detect pre-onset and progressive AD in order to provide earlier treatment, more appropriate management, and assess the efficacy of novel therapeutics [1].

Gross pathological examination of the post-mortem AD brain yields minimal information to specifically suggest AD. That is, common non-

specific anatomical findings in AD patients, such as atrophy, are not definitive for AD [2, 7]. Most cases show a moderate cerebral cortical atrophy often involving the frontotemporal association cortex; this atrophy often excludes sensory, primary motor, and visual areas [2, 7]. Nevertheless, observed atrophy and decreased cortical thickness are generally documented in those with AD along with age-matched control subjects with normal cognitive function [2, 7]. Exceptions where atrophy may be a defining feature of AD involve early-onset Alzheimer's disease (EOAD) [2, 7]. Those with the presenile onset of AD often present with reduced brain weight from atrophy which is notably not observed in age-matched controls [8]. In those with mild and prodromal AD, magnetic resonance imaging (MRI)-based computational segmentation techniques have attempted to detect subtle patterns of cortical atrophy as predictors of symptom severity; however, these techniques are chiefly experimental and not employed in clinical practice [9]. Furthermore, by now it is well established that structural changes are the latest manifestation of the disease compared to molecular abnormalities detected by PET.

Neuropathological examinations have noted certain defining microscopic characteristics of the Alzheimer's brain [7]. In accordance with macroscopic atrophy, loss of neurons and synaptic features are commonly observed [7]. Distinct neuropathological features include unique prion deposition consisting of extracellular beta-amyloid (Aβ) plaques, intracellular neurofibrillary tangles (NFT), neuropil threads, and dystrophic neurites [2, 7, 10]. Congophilic Aβ angiopathy is also found in most cases of AD [10].

Normal physiological processes involve the cleavage of the amyloid precursor protein (APP) [10]. Most APP is secreted into the extraneuronal space and is cleaved by α-secretase which produces a soluble product [11]. Alternatively, APP may be cleaved by a β-secretase plasma membrane protein which results in a soluble extracellular fragment and a membrane-bound C-terminal fragment (C99) [11]. C99 is then cleaved by the intracellular region of a γ-secretase plasma membrane protein; the resultant products include intracellular proteins and Aβ which is then secreted [11] (see **Figure 1** for details). Subsequently, these Aβ proteins are removed via the circulatory system or degraded through immunological mechanisms [11]. Pathological changes, such as mutated APP cleavage sites or mutated secretase enzymes, can impede this pathway [7]. As a result, less soluble APP derivatives may be exported into the extracellular matrix [7]. Specifically, extracellular deposition of Aβ proteins has been characterized with two possible isoforms of Aβ proteins; Aβ42 is generally less soluble and more inclined to fibrilization and thus is more often found in plaques than Aβ40 [2, 11]. Aβ aggregates can progress as oligomers, protofibrils, fibrils, and plaques that are subsequently unable to be cleared by physiological mechanisms [2, 11].

NFTs are defined as intraneuronal filament aggregates of microtubule-associated tau proteins; most fibrils are helical and paired though some are unpaired with a straight structure [12]. Other hybrid structures and more unique assemblies have recently been discovered [12]. Nevertheless, NFT tau proteins are hyperphosphorylated and misfolded; other minor components may include ubiquitin with cholinesterases, and Aβ [13]. Neuropil threads, which contain aggregated and hyperphosphorylated tau in axonal and dendritic segments, usually present in those neurons with observable intracellular NFT [10] (**Figure 1**).

The need for an objective characterization of disease severity has led to the creation of disease staging. Most commonly, researchers and clinicians use Braak staging to classify the state of disease progression in AD during postmortem autopsy [14, 15]. Proposed by Heiko Braak in 1991, AD can be divided into six distinct stages [14, 15]. Brains that display NFTs primarily in the transentorhinal cortex are identified as either stage I or II. Brains with additional involvement in the limbic regions are classified as stage III or IV, and brains with extensive involvement in the neocortex are classified as stage V or VI, depending on the extent of cortical expansion [14, 15]. It is important to note that the Braak staging system is dependent on tangle-based pathology, which has an entirely different progression and presentation in the brain than plaque-based pathologies.

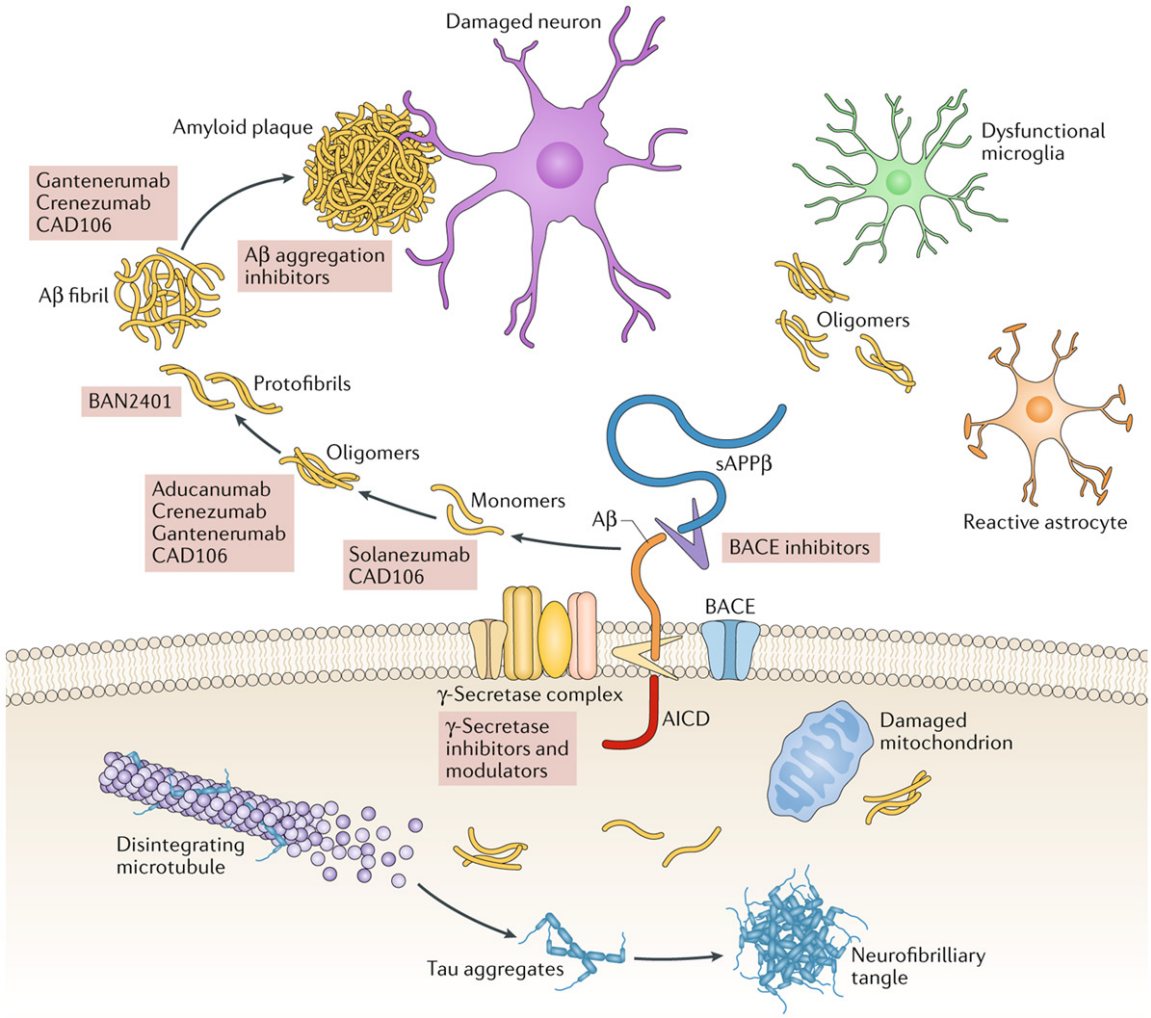

Figure 1. The figure above illustrates the development of amyloid-β (Aβ) plaques and tau aggregates in the development of Alzheimer's disease. Mechanisms many developmental anti-amyloid-β (Aβ) drugs are indicated. This image was reproduced with permission from Panza et al. [11].

Each class of prion expresses a broadly characteristic distribution. Generally, Aβ plaques are primarily distributed in the cortical mantle whereas NFTs are often most prevalent in the limbic and association cortices [10]. Aβ plaques accumulate mainly in the isocortex, however, deposition progression is highly variable. Most plaques begin to appear in the associative isocortex, then step-wise progression to the allocortex, basal ganglia, brainstem nuclei, and the cerebellum is observed; nevertheless, deposition is most pronounced in the associative isocortex [10]. The progression of deposition is prion-specific. NFT degeneration often appears in the entorhinal cortex, perirhinal cortex, hippocampus, association cortex, and primary neocortex in succession; significant sensory, motor and visual areas are generally not involved. Notably, NFT deposition patterns parallel neuronal loss [16].

As an added difficulty, any regions of the brain that are inclined to AD-related pathologies are also involved in other neurodegenerative conditions such as α-synucleinopathy and TDP-43 proteinopathy; thus, mixed pathologies are relatively common [17]. Nevertheless, cognitive impairment is most directly associated with continued degeneration of the limbic system, the basal forebrain, and neocortical areas; specifically, synaptic damage, retrograde degeneration of the axons, dendritic degradation, and eventual loss of neuronal bodies are closely associated with cognitive impairment [10].

Evolving etiologies of Alzheimer's disease

The prevailing explanatory hypothesis for AD has long centered on Aβ but this understanding has slowly evolved. The higher ratio of Aβ42 underlies Aβ fibril development where further accumulation leads to the formation of Aβ plaques [2, 7, 11]. Aβ plaque toxicity is hypothesized through several mechanisms that result in cognitive impairment, neuronal atrophy, tangle formation, and tau hyperphosphorylation [11]. The reliance upon the Aβ hypothesis was partly founded upon genetic studies. Familial AD (FAD) is a dominantly inherited condition that leads to an aggressive form of EOAD; similar AD aggressiveness and early onset are observed in Down's Syndrome (DS) [7]. While DS involves a trisomy of chromosome 13, FAD is linked to mutated APP, presenilin-1 (PS1), or presenilin-2 (PS2) on chromosome 21; PS1 or PS2 act as the catalytic subunit of γ-secretase [7, 11]. Recently, certain APP mutations were found to confer protection against AD and dementia [18]. The body of genetic literature is consistent in associating AD with APP production and subsequent processing, although the exact mechanism of toxicity is still undetermined [19].

Nevertheless, in-vivo investigations of these biological processes and therapeutic interventions have provided valuable insight into the mechanism of prion toxicity. For instance, animal models that overexpressed Aβ42 were observed to have increased Aβ deposition and plaque formation but no cognitive impairment was observed and neither was any gross or microscopic neuronal degeneration [20]. Generally, neuropathological studies in humans have found that Aβ aggregates correlated remarkably poorly with AD severity [21]. To this point, recent studies suggest that most Aβ extracted from the AD brain is innocuous and only some types underlie neurotoxicity [22].

The most direct link to neurotoxicity is related to tau proteins and NFTs. The trigger of tau protein accumulation into NFTs is unknown in most neurodegenerative conditions, but studies suggest that soluble amyloid oligomers lead to the initial development of abnormal tau in the microtubules of the synapse [23]. Nonetheless, the presence of genetic tau abnormalities has been linked to accumulations of tau and neuronal degeneration via the inability of tau to function as a microtubule-stabilizing protein in the axon [24]. As noted, tau has been confirmed to propagate in a significantly more predictable manner than Aβ plaques where the progression of AD is tightly linked to tau burden (i.e. Braak Stage) in the brain [12]. This is likely due to the ability of small amounts of abnormally phosphorylated tau to be transmitted between cells and induce hyperphosphorylation of normal tau which is followed by fibrilization [25].

The therapeutic use of γ-secretase inhibitors, as means of accumulating APP C-terminal fragments and suppressing Aβ production, led to a significant worsening of AD in clinical trials [26]. Further, large scale trials of Aβ immunotherapy that reduce plaque burden have consistently proven ineffective over nearly two decades [11]. We specifically can look to the negative results of the Solanezumab and Aducanumab clinical trials. While both anti-amyloid antibodies were effective in relieving amyloid burden, there were no significant gains in reducing neurocognitive impairment [19, 27]. The failure of these trials further emphasizes the lack of validity of the Amyloid Hypothesis as a logical basis for AD. In an editorial that was published recently, 3 colleagues who were on the advisory board of the FDA described their views about the futility of the Amyloid Hypothesis and the related therapeutic interventions that are based on views of proponents of this concept [28]. Therefore, it is increasingly clear that amyloid plaques are the consequence of neurodegeneration, not the underlying cause. In the face of these clinical results, the revised Amyloid Hypothesis relies on two possible pathogenic mechanisms. First, impairments of APP metabolism and the prevalence of APP C99 fragments, instead of Aβ production and development, may be the triggering sources of AD [29]. Second, Aβ neurotoxicity could be mediated chiefly by soluble Aβ where insoluble aggregations of these oligomers are a means to making such oligomers inert [11, 30]. Many empirical studies have buoyed the former mechanism; yet the latter still holds significant weight in the community.

Molecular imaging in Alzheimer's disease

Structural imaging modalities, namely CT and MRI, were the first applied in the radiological

study of AD [31, 32]. Both modalities are often able to reflect significant atrophy of the cortex found in AD patients, and MRI is often preferred given its superior resolution for soft tissue morphologies in the cerebrum. Equally valuable has been the use of sub-modalities of MRI, such as MR spectroscopy and diffusion-weighted imaging MRI, which have been able to detect structural changes at a microscopic level prior to macroscopic changes which may be captured in T-1 or T-2 MRI [33]. While these methods developed, molecular imaging studies soon began to explore AD. Most notable was the application of [^{18}F]FDG-PET to patients with AD, which allowed for the characterization of neuronal hypometabolism observed in AD [31]. In an effort to mimic the successes of metabolic molecular imaging, there was an effort to develop the tracers to reflect the proliferation of prions that were beginning to be documented in the neuropathological study of AD. Since then, the pharmacological development of specific and selective radiotracers for tau and Aβ has been a dynamic field. The initial push towards molecular imaging for AD coincided with the previously mentioned reliance upon the Amyloid Hypothesis and Aβ plaques. Therefore, the earliest radiotracers aimed to image Aβ; unfortunately, most Aβ-specific radiotracers were greatly hindered by off-site binding and other significant inadequacies [15]. Compared to PET imaging, MRI and CT studies have relatively limited value. This primarily stems from PET imaging's ability to develop tracers for myriad biological compounds which can reflect the state of disease in a manner that is more specific than that of MRI or CT-measured atrophy. For instance, the macroscopic atrophy in AD patients observed by MRI and CT can be observed more precisely with SV2A PET which assesses synaptic density as well as neuroinflammatory processes (Adam P Mecca et al. 2020, In vivo measurement of widespread synaptic loss…).

Before continuing, it is important to note that [^{18}F]FDG-PET has been used to measure the state of disease in conditions other than AD. For instance, [^{18}F]FDG-PET has been successfully used in cancer imaging (in breast, colorectal, esophageal, head and neck, lung, pancreatic, thyroid, and more cancers) [34], in measuring inflammation and infection [35], in parkinsonian disorders [36], in AD and related dementias, in neurology, and in cardiology imaging studies [37].

The binding characteristics and other features of the most commonly used Aβ tracers have been well studied. [^{11}C]PiB was one of the earliest Aβ radiotracers developed. In vitro binding of [^{11}C]PiB was observed to be sufficiently specific though in vivo binding is a more disputed matter; otherwise, a significant limiting factor of [^{11}C]PiB involves its short half-life which introduces significant inconsistencies in imaging [38]. Importantly, higher in-vivo uptake across all age groups was noted in patients with ApoE-ε4 as opposed to those without [38]. The other commonly used Aβ radiotracer is [^{18}F] Florbetapir. [^{18}F]Florbetapir has presented relatively weaker binding strength than [^{11}C]PiB and similar specificity for Aβ [38]. Notably, in vivo studies and post-mortem studies have noted poor binding of [^{18}F]Florbetapir to Aβ in the postmortem brain [38]. Furthermore, there is significant concern that Aβ radiotracers confer significant off-target binding to non-Aβ targets [38]. Although the in vitro binding of [^{11}C]PiB and [^{18}F]Florbetapir to beta-amyloid plaques have been observed in vitro, there in vivo studies have uncovered significant off-target binding of these radiotracers to microhemorrhages neuromelanin, calcification, leptomeningeal melanocytes and monoamine oxidase [38].

Even when assuming ideal radiotracer adequacy, studies have suggested limited value of Aβ imaging in AD. The significant majority of Aβ-PET studies, across a variety of Aβ radiotracers, have consistently shown results which are indistinguishable between patient groups. Specifically, similar uptake patterns are often observed in non-symptomatic healthy control patients and AD patients; the only exception tends to be in younger controls, where higher uptake may be observed in those with EOAD though this is not fully appreciable [39]. The true reason for such results is likely to be a combination of radiotracer inadequacy and a similar degree of Aβ burden between the majority of healthy and AD individuals as aligned with the neuropathological consensus (**Figure 2**).

Biased published data and public pressure over the past decade has led to FDA approval of a few 'specific Aβ tracers' for the application of PET in AD [40]. Generally, administration of

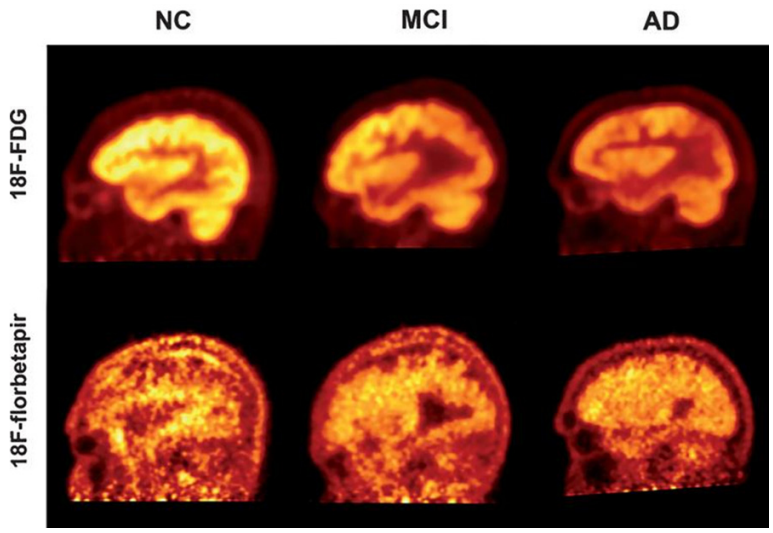

Figure 2. PET imaging using [^{18}F]FDG and [^{18}F]florbetapir in Alzheimer's disease (AD), mild cognitive impairment (MCI) patients, and normal controls (NC). There was significant loss of [^{18}F]FDG avidity observed in the cortices of the NC, MCI and AD patients in progressive fashion; such indicates progressive hypometabolism concurrent to disease progression. In the [^{18}F]florbetapir studies, there was moderate increase of radiotracer density when comparing the NC patient to the MCI and AD patients; however there was minimal difference between the MCI and AD patients. This image was reproduced with permission from Khosravi et al. [41].

these novel radiotracers have been performed during first in human studies via blood samples, urine samples, electrocardiograms, assessments for adverse events where most tracers have been assessed for tolerability. As a result, many studies have attempted to determine the value of Aβ-PET in altering the diagnosis of patients. Unfortunately, these studies rely on the clinical symptoms of the patients and do not definitively assign a relative value to Aβ positivity in the experimental diagnostic criteria [39]. Though this study has indicated that the course of clinical care was altered in some of these newly diagnosed patients, there is no evidence to confirm that the change in treatment improved subsequent patient health by any appreciable metric; this lack of specificity inclines Aβ positively to produce false positives nulling the value of PET imaging.

Beyond this, research by Khosravi et al. has simultaneously used [^{18}F]FDG-PET and Aβ-PET to detect dementia in 63 subjects to find that neuronal metabolism is a stronger diagnostic measure of AD, as shown in **Figure 2**; moreover, there was with minimal relationship between the two radiotracers, so to further limit the clinical relevance of Aβ imaging in clinical settings [41]. This inadequacy of Aβ-PET is predictable given the current scientific understanding of prions in AD. Specifically developed plaques are likely inert in the progression of AD and the production of Aβ prions may only be relevant in initiating the tau cascade, which is the main mechanism correlated to neuronal dysfunction [29]. Aβ-imaging and anti-Aβ therapies must be reassessed as the scientific evidence has all but exhausted the medical value of Aβ in AD.

The argument for the superior utility of tau imaging as opposed to Aβ imaging does not rely solely on the more persuasive biological relevance of tau in AD or the resulting need to characterize the in vivo tau burden in AD. We additionally point to a growing literature of tau-PET imaging studies that have substantiated the assumed value of tau imaging. Where Aβ has failed, tau has shown increasing promise; tau radiotracers have also received significant attention and multiple radiotracers have been tested in the context of AD. The first PET imaging probe used for detection of tau and Aβ aggregates in AD was [^{18}F]FDDNP, introduced in 1999 [42]. [^{18}F]FDDNP binds to 3R/4R tau and Aβ *in vivo*, and has been used extensively in mild cognitive impairment and AD [43]. [^{18}F]FDDNP PET findings were also correlated with [^{18}F]FDG in AD, with cortical areas of hypometabolism having significant correlation with tau and Aβ neuroaggregate depositions [44].

Because of its affinity to other tau isoforms, [^{18}F]FDDNP has also been applied with high levels sensitivity and specificity in other predominant tauopathies like progressive supranuclear palsy [45] and chronic traumatic encephalopathy in football players and veterans [46]. Where these studies have found consistent radiotracer binding patterns mirroring distinctive tau deposition patterns per the respective neurodegenerative condition as understood by neuropathological studies [45, 47]. In these dis-

eases, the presence of significant Aβ aggregates is only observed in late stages. The utility of [^{18}F]FDDNP is based on its specificity for amyloid-like segments of tau and Aβ as determined by X-ray crystallography [48]. No off-label binding (e.g., to receptors of enzymes) has been observed with [^{18}F]FDDNP *in vitro* or *in vivo*. Unfortunately, the radiotracer's affinity for Aβ plaques, which are not able to be distinguished with the [^{18}F]FDDNP, performs poorly in the diagnostic context of AD as Aβ plaques have more variable presentation in the AD brain as compared to tau NFTs.

In recent years, the most widely used radiotracer has been [^{18}F]Flortaucipir, noted for its significant affinity for mature NFT and not immature plaque. However, [^{18}F]Flortaucipir has been reported to present "inconsistent binding to regions that had extensive tau neuritic pathology, most notably in superficial cortical layers" [49, 50]. Of note, due to the notable affinity of [^{18}F]Flortaucipir for monaamine oxidase (MAO)-A, and MAO-B, significant non-specificity or off-target labeling has been documented *in vivo* [51]. Further studies also showed that [^{18}F]Flortaucipir binding was strongest among 3R/4R tau isoforms (i.e. primarily neurofibrillary tangles and paired helical filaments containing neurites in patients with AD), suggesting that its clinical utility may be confined to certain isoforms of tau, many of which are present in AD [52-54]. [^{18}F]Flortaucipir *in vivo* binding in tangle-predominant dementia has been reported as variable, with tau disease progression due to variations in tau location and isoforms [52-54]. As such, [^{18}F]Flortaucipir has shown somewhat limited utility for *in vivo* selective and reliable detection of tau aggregates non-Alzheimer tauopathies [53].

Another commonly used tracer, [^{18}F]THK-5351, has expressed superior kinetics and selectivity for tau protein deposits [38]; off-site binding to MAO-B and neuromelanin has also been noted [38]. While these tracers are far from perfect, they have produced compelling findings. As such second-generation tracers with enhanced specificity and selectivity have the potential to build on this promising foundation and establish the robust diagnostic value of tau-PET. Thus far, multiple small-scale studies of these second-generation radiotracers have produced similar or superior results in AD patients [55-60]. Of particular note are [^{18}F] RO-948, [^{18}F]PI-2620, [^{18}F]GTP1, [^{18}F]MK-6240, and [^{18}F] PM-PBB3, however, these tracers require extensive in vivo study, and significant replication of results is required. Other radio tracer studies have also confirmed the ability to delineate AD from healthy controls. Studies examining [^{18}F]THK-5351 and [^{18}F]THK-5117, [^{18}F]MK-6240 [56], and [^{18}F]RO-948 [61] have all demonstrated an ability to distinguish AD from healthy controls and assist clinicians in disease staging in some cases, too [62].

Nevertheless, countless tau-PET studies have consistently proven to be useful in characterizing tau pathology in AD and other predominant tauopathies in a unique fashion. Most studies use a group of cognitively normal (CN) individuals along with an age-matched group of AD patients. Tau-PET studies have shown that whole-brain retention of the radiotracer positively correlates to the symptomatic progression of AD as well as the plaque and NFT load, although regional retention is typically most predictive of clinical progression [63-66]. In a recent study examining different measures of tau-PET and Aβ-PET imaging, researchers found that Braak staging, regional tau imaging, and whole-brain retention measures accurately distinguished MCI and AD patients from those who were cognitively normal [66]. Similarly, a recent review of the clinical findings of tau radiotracers concluded that the anatomical patterns of tau accumulation seen post-mortem correlate with the regional uptake of most tau radiotracers with relatively minimal off-target binding and with overall brain atrophy [67]. There is specific retention in areas known to be affected by tau pathology among patients with AD; specifically, tracer accumulation is often most notable in the medial temporal cortex, limbic system, and extends into neocortical regions depending upon the severity of AD in the patient [60, 68-70], as shown in **Figures 3** and **4**. Thus, the greater degree of retention and the specific distribution of tracer retention suggest tau as a valuable biological marker of AD and tau-PET as a procedure may have utility within the diagnostic or clinical staging process. Importantly, given the aforementioned overlap of symptoms and mix of neurodegenerative pathologies, it is imperative that any imaging procedure must specifically differentiate between neurodegenerative conditions.

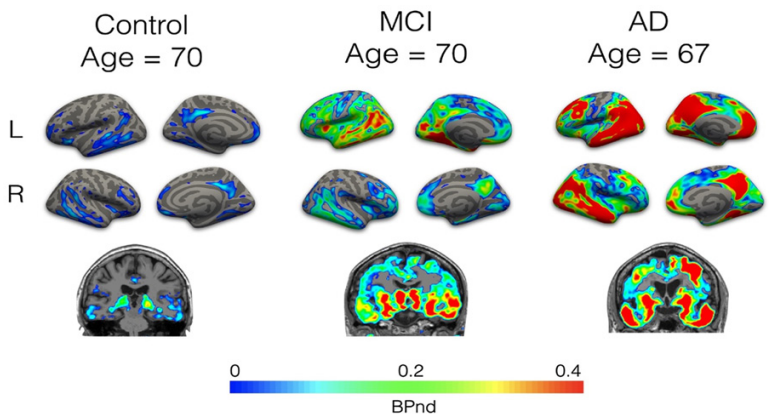

Figure 3. Visualizing the progressive extent of [^{18}F]AV1451 retention on the cortex across the spectrum of normal aging, mild cognitive impairment and Alzheimer's disease. Consistent with the neuropathological progression of tau deposition, several studies have identified focal tau accumulation in cognitively normal adults, most prominently in the medial temporal lobe structures (Left). In contrast, mild cognitive impairment is characterized with increased uptake in the temporal and posterior cingulate regions (Middle), before progressively spreading widely across the temporo-parietal cortices in AD (Right). Volumetric data of representative subjects are represented in radiological convention. This image was reproduced with permission from Hall et al. with permission [67].

While we have well-founded doubts in the ability of Aβ-PET to do so based on the variability of AB plaque pathology and the potential inadequacy of Aβ radiotracers, evidence indicates that tau may succeed where Aβ has failed.

Several studies have extensively assessed AD and other forms of dementia in an effort to examine differential binding patterns. Among those with AD and non-AD tauopathies, tau radiotracers have consistently shown the ability to distinguish between the pattern of tau pathologies, suggesting tau radiotracers' potential utility as a discriminatory diagnostic tool [60]. For instance, in a study examining the utility of [^{18}F]Flortaucipir in distinguishing among healthy patients, patients with CBD, patients with PSP, and those with AD, differences in spatial binding patterns and cortical atrophy allowed researchers to clearly distinguish patients with CBD from those with AD, PSP, or healthy controls; some imprecision of the tracer's diagnostic capabilities were noted [57]. Thus, there is certainly potential for tau-PET to be specific in diagnosing AD, however, better tracers or additional modalities (e.g. [^{18}F]FDG-PET) may be required.

Many studies have employed [^{18}F]FDG-PET, which assesses neuronal metabolic activity, as a standard for comparing the results of their tau-PET. To this point, most of these studies have demonstrated a negative correlation between [^{18}F]FDG uptake and tracer retention, suggesting that imaging agents accurately bind to regions with substantial tau deposition and extensive metabolic dysfunction [57, 68, 71] (**Figure 4**). In one study, Chiotis found such negative correlations in focal areas of the prefrontal, lateral temporal, and lateral and medial parietal cortices bilaterally [68]. Interestingly, positive correlations between [^{18}F]FDG and [^{18}F]THK5317 were found bilaterally in the superior temporal, primary motor, and occipital cortices; the study also found positive correlations between THK5317 retention and [^{11}C]PiB uptake bilaterally in the inferior and medial temporal, and anterior and superior frontal, lateral and medial parietal, and occipital cortices [68]. Further, Chiaravalloti and colleagues found a substantial negative correlation between cerebrospinal fluid tau burden and [^{18}F]FDG uptake in the frontal, parietal, and right temporal lobe, concluding that tau deposition is associated with hypometabolism in these areas [71]. These data suggest that tau-PET is not only sensitive in detecting tau deposition but also directly correlates to neuronal dysfunction and clinical disease progression.

The heightened value of tau imaging is well aligned with the current literature regarding the competing influence of Aβ plaques and tau NFTs. While the true relevance of Aβ in AD is unknown, the combined body of neuropathological studies and anti-Aβ therapeutic trials strongly suggests that Aβ is an early but distant factor in the initiation and progression of AD, whereas tau proteins have been strongly implicated in the direct neuropathological mechanism of neurotoxicity in AD. For instance, tau burden has been more tied to the clinical progression of AD, whereas imaging in AD aims to create an objective standard of diagnosis and

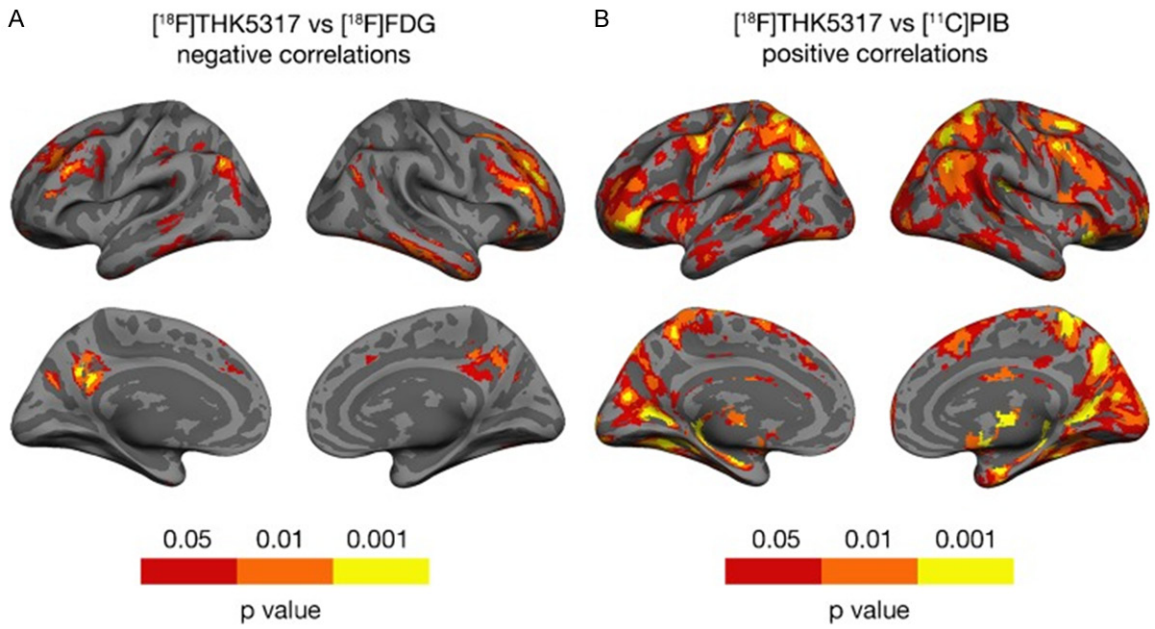

Figure 4. Correlations between tracers, two by two, across all Alzheimer's disease patients (n=20). Voxel-based negative correlations between [^{18}F]THK5317 DVR retention and [^{18}F]FDG SUVR uptake (A). Voxel-based positive correlations between [^{18}F]THK5317 DVR and [^{11}C]PIB SUVR retention (B). Three thresholds for statistical significance were applied (P<0.001, P<0.01, and P<0.05) as indicated. The peak voxels of clusters meeting the P<0.001 threshold. DVR = distribution volume ratio; SUVR = standard uptake value ratio. This image was reproduced with permission from Chiotis et al. with permission [68].

disease progression; the present scientific literature mandates a reorientation to make tau the focal point of molecular imaging initiatives in AD. That said, it is possible that future research could identify synergistic methods of using distinct tau and Aβ radiotracers that provide clinical benefit above and beyond the use of tau or Aβ imaging alone.

Conclusion

Considering the evolving literature in AD and PET imaging, it has become clear that PET can play a role in the advancement of diagnosis and prognosis in clinical practice. The use of Aβ imaging has been extensively studied to find mixed results suggesting a limited clinical utility. On the other hand, tau-PET has shown early success in similar applications as Aβ imaging. Specifically, we find that there is value in [^{18}F]FDG-PET and prospective utility in tau-PET. Currently, the present use of tau-PET in the diagnosis of AD requires metabolic concordance through [^{18}F]FDG-PET studies; however, with development of more specific and valid tau-PET radiotracers, we believe that tau imaging may succeed where Aβ imaging has failed. Regardless, the community must acknowledge that the role of Aβ imaging for diagnosing and managing AD is very limited and that [^{18}F]FDG-PET will remain the study of choice at this time. Moreover, research efforts must continue to elucidate the prospective value of tau imaging to the assessment of this disease.

Disclosure of conflict of interest

None.

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References

[1] Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B and Phelps CH. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 257-62.

[2] Wenk GL. Neuropathologic changes in Alzheimer's disease. J Clin Psychiatry 2003; 64: 7-10.
[3] Broich K, Alavi A and Kushner M. Positron emission tomography in cerebrovascular disorders. Semin Nucl Med 1992; 22: 224-32.
[4] Borja AJ, Hancin EC, Zhang V, Revheim ME and Alavi A. Potential of PET/CT in assessing dementias with emphasis on cerebrovascular disorders. Eur J Nucl Med Mol Imaging 2020; 47: 2493-2498.
[5] Alavi A, Clark C and Fazekas F. Cerebral ischemia and Alzheimer's disease: critical role of PET and implications for therapeutic intervention. J Nucl Med 1998; 39: 1363-5.
[6] Love S and Miners JS. Cerebrovascular disease in ageing and Alzheimer's disease. Acta Neuropathol 2016; 131: 645-58.
[7] Perl DP. Neuropathology of Alzheimer's disease. Mt Sinai J 2010; 77: 32-42.
[8] Pini L, Pievani M, Bocchetta M, Altomare D, Bosco P, Cavedo E, Galluzzi S, Marizzoni M and Frisoni GB. Brain atrophy in Alzheimer's disease and aging. Ageing Res Rev 2016; 30: 25-48.
[9] Bakkour A, Morris JC and Dickerson BC. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. Neurology 2009; 72: 1048-55.
[10] Serrano-Pozo A, Frosch MP, Masliah E and Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011; 1: a006189.
[11] Panza F, Lozupone M, Logroscino G and Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. Nat Rev Neurol 2019; 15: 73-88.
[12] Wegmann S, Jung YJ, Chinnathambi S, Mandelkow EM, Mandelkow E and Muller DJ. Human Tau isoforms assemble into ribbon-like fibrils that display polymorphic structure and stability. J Biol Chem 2010; 285: 27302-13.
[13] Al Mamun A, Uddin MS, Kabir MT, Khanum S, Sarwar MS, Mathew B, Rauf A, Ahmed M and Ashraf GM. Exploring the promise of targeting ubiquitin-proteasome system to combat Alzheimer's disease. Neurotox Res 2020; 38: 8-17.
[14] Braak H and Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991; 82: 239-59.
[15] Braak H and Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 1995; 16: 271-8.
[16] Kimura T, Fukuda T, Sahara N, Yamashita S, Murayama M, Mizoroki T, Yoshiike Y, Lee B, Sotiropoulos I, Maeda S and Takashima A. Aggregation of detergent-insoluble tau is involved in neuronal loss but not in synaptic loss. J Biol Chem 2010; 285: 38692-9.
[17] DeTure MA and Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener 2019; 14: 1-18.
[18] Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, Stefansson H, Sulem P, Gudbjartsson D, Maloney J, Hoyte K, Gustafson A, Liu Y, Lu Y, Bhangale T, Graham RR, Huttenlocher J, Bjornsdottir G, Andreassen OA, Jönsson EG, Palotie A, Behrens TW, Magnusson OT, Kong A, Thorsteinsdottir U, Watts RJ and Stefansson K. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 2012; 488: 96-9.
[19] Selkoe DJ and Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016; 8: 595-608.
[20] Kim WS, Li H, Ruberu K, Chan S, Elliott DA, Low JK, Cheng D, Karl T and Garner B. Deletion of Abca7 increases cerebral amyloid-β accumulation in the J20 mouse model of Alzheimer's disease. J Neurosci 2013; 33: 4387-94.
[21] Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ, Davies P, Del Tredici K, Duyckaerts C, Frosch MP, Haroutunian V, Hof PR, Hulette CM, Hyman BT, Iwatsubo T, Jellinger KA, Jicha GA, Kövari E, Kukull WA, Leverenz JB, Love S, Mackenzie IR, Mann DM, Masliah E, McKee AC, Montine TJ, Morris JC, Schneider JA, Sonnen JA, Thal DR, Trojanowski JQ, Troncoso JC, Wisniewski T, Woltjer RL and Beach TG. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 2012; 71: 362-81.
[22] Hong W, Wang Z, Liu W, O'Malley TT, Jin M, Willem M, Haass C, Frosch MP and Walsh DM. Diffusible, highly bioactive oligomers represent a critical minority of soluble Aβ in Alzheimer's disease brain. Acta Neuropathol 2018; 136: 19-40.
[23] He Z, Guo JL, McBride JD, Narasimhan S, Kim H, Changolkar L, Zhang B, Gathagan RJ, Yue C, Dengler C, Stieber A, Nitla M, Coulter DA, Abel T, Brunden KR, Trojanowski JQ and Lee VM. Amyloid-β plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation. Nat Med 2018; 24: 29.
[24] Ding H, Matthews TA and Johnson GV. Site-specific phosphorylation and caspase cleavage differentially impact tau-microtubule interactions and tau aggregation. J Biol Chem 2006; 281: 19107-14.
[25] Goedert M and Spillantini MG. Propagation of Tau aggregates. Mol Brain 2017; 10: 1-9.
[26] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H and Mohs R; Alzheimer's Disease Cooperative Study Steering Committee; Solanezumab Study Group.

Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014; 370: 311-21.
[27] Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, Hager K, Andreasen N, Scarpini E, Liu-Seifert H, Case M, Dean RA, Hake A, Sundell K, Poole Hoffmann V, Carlson C, Khanna R, Mintun M, DeMattos R, Selzler KJ and Siemers E. Trial of Solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med 2018; 378: 321-30.
[28] Alexander GC, Emerson S and Kesselheim AS. Evaluation of Aducanumab for Alzheimer disease: scientific evidence and regulatory review involving efficacy, safety, and futility. JAMA 2021; 325: 1717-1718.
[29] Kametani F and Hasegawa M. Reconsideration of amyloid hypothesis and tau hypothesis in Alzheimer's disease. Front Neurosci 2018; 12: 25.
[30] Cline EN, Bicca MA, Viola KL and Klein WL. The amyloid-β oligomer hypothesis: beginning of the third decade. J Alzheimers Dis 2018; 64: S567-S610.
[31] Alavi A, Newberg AB, Souder E and Berlin JA. Quantitative analysis of PET and MRI data in normal aging and Alzheimer's disease: atrophy weighted total brain metabolism and absolute whole brain metabolism as reliable discriminators. J Nucl Med 1993; 34: 1681-7.
[32] Fazekas F, Chawluk JB, Alavi A, Hurtig HI and Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987; 149: 351-6.
[33] Sultan AA, Ali M, El-Badrawy AG and Bayoumi DM. Role of DWI and MRS in diagnosis of Alzheimer's and pre-Alzheimer's disease. Egypt J Radiol Nucl Med 2017; 48: 231-6.
[34] Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, Einhorn LH, Suh WW, Samson D, Delbeke D, Gorman M and Shields AF. Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med 2008; 49: 480-508.
[35] Love C, Tomas MB, Tronco GG and Palestro CJ. FDG PET of infection and inflammation. Radiographics 2005; 25: 1357-68.
[36] Eckert T, Barnes A, Dhawan V, Frucht S, Gordon MF, Feigin AS and Eidelberg D. FDG PET in the differential diagnosis of parkinsonian disorders. Neuroimage 2005; 26: 912-21.
[37] Hoh CK. Clinical use of FDG PET. Nucl Med Biol 2007; 34: 737-42.
[38] Ayubcha C, Revheim ME, Newberg A, Moghbel M, Rojulpote C, Werner TJ and Alavi A. A critical review of radiotracers in the positron emission tomography imaging of traumatic brain injury: FDG, tau, and amyloid imaging in mild traumatic brain injury and chronic traumatic encephalopathy. Eur J Nucl Med Mol Imaging 2021; 48: 623-641.
[39] Matsuda H, Shigemoto Y and Sato N. Neuroimaging of Alzheimer's disease: focus on amyloid and tau PET. Jpn J Radiol 2019; 37: 735-49.
[40] Shea YF, Barker W, Greig-Gusto MT, Loewenstein DA, Duara R and DeKosky ST. Impact of amyloid PET imaging in the memory clinic: a systematic review and meta-analysis. J Alzheimers Dis 2018; 64: 323-35.
[41] Khosravi M, Peter J, Wintering NA, Serruya M, Shamchi SP, Werner TJ, Alavi A and Newberg AB. 18F-FDG is a superior indicator of cognitive performance compared to 18F-florbetapir in Alzheimer's disease and mild cognitive impairment evaluation: a global quantitative analysis. J Alzheimers Dis 2019; 70: 1197-207.
[42] Agdeppa ED, Kepe V, Petri A, Satyamurthy N, Liu J, Huang SC, Small GW, Cole GM and Barrio JR. In vitro detection of (S)-naproxen and ibuprofen binding to plaques in the Alzheimer's brain using the positron emission tomography molecular imaging probe 2-(1-[6-[(2-[(18)F]fluoroethyl)(methyl)amino]-2-naphthyl]ethylidene)malononitrile. Neuroscience 2003; 117: 723-30.
[43] Small GW, Kepe V, Ercoli LM, Siddarth P, Bookheimer SY, Miller KJ, Lavretsky H, Burggren AC, Cole GM, Vinters HV, Thompson PM, Huang SC, Satyamurthy N, Phelps ME and Barrio JR. PET of brain amyloid and Tau in mild cognitive impairment. N Engl J Med 2006; 355: 2652-63.
[44] Shoghi-Jadid K, Small GW, Agdeppa ED, Kepe V, Ercoli LM, Siddarth P, Read S, Satyamurthy N, Petric A, Huang SC and Barrio JR. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. Am J Geriatr Psychiatry 2002; 10: 24-35.
[45] Kepe V, Bordelon Y, Boxer A, Huang SC, Liu J, Thiede FC, Mazziotta JC, Mendez MF, Donoghue N, Small GW and Barrio JR. PET imaging of neuropathology in tauopathies: progressive supranuclear palsy. J Alzheimers Dis 2013; 36: 145-53.
[46] Barrio JR, Small GW, Wong KP, Huang SC, Liu J, Merrill DA, Giza CC, Fitzsimmons RP, Omalu B, Bailes J and Kepe V. In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging. Proc Natl Acad Sci U S A 2015; 112: E2039-2047.
[47] Landau M, Sawaya MR, Faull KF, Laganowsky A, Jiang L, Sievers SA, Liu J, Barrio JR and Eisenberg D. Towards a pharmacophore for amyloid. PLoS Biol 2011; 9: e1001080.
[48] Landau M, Sawaya MR, Faull KF, Laganowsky A, Jiang L, Sievers SA, Liu J, Barrio JR and Eisenberg D. Towards a pharmacophore for amyloid. PLoS Biol 2011; 9: e1001080.

[49] Barrio J, Huang S, Cole G, Satyamurthy N, Petric A, Phelps M, et al. PET imaging of tangles and plaques in Alzheimer disease with a highly hydrophobic probe. J Label Compd Radiopharm 1999; 42: S194-S195.
[50] Rigney G, Ayubcha C, Werner TJ and Alavi A. An update on the state of Tau radiotracer development: a brief review. Mol Imaging Biol 2021: [Epub ahead of print].
[51] Barrio JR. The irony of PET tau probe specificity. J Nucl Med 2018; 59: 115-6.
[52] Lowe VJ, Curran G, Fang P, Liesinger AM, Josephs KA, Parisi JE, Kantarci K, Boeve BF, Pandey MK, Bruinsma T, Knopman DS, Jones DT, Petrucelli L, Cook CN, Graff-Radford NR, Dickson DW, Petersen RC, Jack CR Jr and Murray ME. An autoradiographic evaluation of AV-1451 Tau PET in dementia. Acta Neuropathol Commun 2016; 4: 58.
[53] Marquié M, Normandin MD, Meltzer AC, Siao Tick Chong M, Andrea NV, Antón-Fernández A, Klunk WE, Mathis CA, Ikonomovic MD, Debnath M, Bien EA, Vanderburg CR, Costantino I, Makaretz S, DeVos SL, Oakley DH, Gomperts SN, Growdon JH, Domoto-Reilly K, Lucente D, Dickerson BC, Frosch MP, Hyman BT, Johnson KA and Gómez-Isla T. Pathological correlations of [F-18]-AV-1451 imaging in non-alzheimer tauopathies. Ann Neurol 2017; 81: 117-28.
[54] Marquié M, Normandin MD, Vanderburg CR, Costantino IM, Bien EA, Rycyna LG, Klunk WE, Mathis CA, Ikonomovic MD, Debnath ML, Vasdev N, Dickerson BC, Gomperts SN, Growdon JH, Johnson KA, Frosch MP, Hyman BT and Gómez-Isla T. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann Neurol 2015; 78: 787-800.
[55] Aguero C, Dhaynaut M, Normandin MD, Amaral AC, Guehl NJ, Neelamegam R, Marquie M, Johnson KA, El Fakhri G, Frosch MP and Gomez-Isla T. Autoradiography validation of novel tau PET tracer [F-18]-MK-6240 on human postmortem brain tissue. Acta Neuropathol Commun 2019; 7: 37.
[56] Pascoal TA, Therriault J, Benedet AL, Savard M, Lussier FZ, Chamoun M, Tissot C, Qureshi MNI, Kang MS, Mathotaarachchi S, Stevenson J, Hopewell R, Massarweh G, Soucy JP, Gauthier S and Rosa-Neto P. 18F-MK-6240 PET for early and late detection of neurofibrillary tangles. Brain 2020; 143: 2818-30.
[57] Smith R, Schöll M, Honer M, Nilsson CF, Englund E and Hansson O. Tau neuropathology correlates with FDG-PET, but not AV-1451-PET, in progressive supranuclear palsy. Acta Neuropathol 2017; 133: 149-51.
[58] Mueller A, Bullich S, Barret O, Madonia J, Berndt M, Papin C, Perrotin A, Koglin N, Kroth H, Pfeifer A, Tamagnan G, Seibyl JP, Marek K, De Santi S, Dinkelborg LM and Stephens AW. Tau PET imaging with 18F-PI-2620 in patients with Alzheimer disease and healthy controls: a first-in-humans study. J Nucl Med 2020; 61: 911-9.
[59] Teng E, Ward M, Manser PT, Sanabria-Bohorquez S, Ray RD, Wildsmith KR, Baker S, Kerchner GA and Weimer RM. Cross-sectional associations between [18F] GTP1 tau PET and cognition in Alzheimer's disease. Neurobiol Aging 2019; 81: 138-45.
[60] Suhara T, Shimada H, Shinotoh H, Hirano S, Eguchi Y, Takahata K, Kimura Y, Yamada M, Ito H and Higuchi M. In vivo tau PET imaging using [11C] PBB3 in Alzheimer's disease and non-Alzheimer's disease tauopathies. J Nucl Med 2014; 55: 1824.
[61] Kuwabara H, Comley RA, Borroni E, Honer M, Kitmiller K, Roberts J, Gapasin L, Mathur A, Klein G and Wong DF. Evaluation of 18F-RO-948 PET for quantitative assessment of tau accumulation in the human brain. J Nucl Med 2018; 59: 1877-84.
[62] Lemoine L, Gillberg PG, Svedberg M, Stepanov V, Jia Z, Huang J, Nag S, Tian H, Ghetti B, Okamura N, Higuchi M, Halldin C and Nordberg A. Comparative binding properties of the tau PET tracers THK5117, THK5351, PBB3, and T807 in postmortem Alzheimer brains. Alzheimers Res Ther 2017; 9: 1-13.
[63] Shcherbinin S, Schwarz AJ, Joshi A, Navitsky M, Flitter M, Shankle WR, Devous MD Sr and Mintun MA. Kinetics of the Tau PET tracer 18F-AV-1451 (T807) in subjects with normal cognitive function, mild cognitive impairment, and Alzheimer disease. J Nucl Med 2016; 57: 1535-42.
[64] Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, Lopresti BJ, Ziolko S, Bi W, Paljug WR, Debnath ML, Hope CE, Isanski BA, Hamilton RL and DeKosky ST. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain J Neurol 2008; 131: 1630-45.
[65] Harada R, Ishiki A, Kai H, Sato N, Furukawa K, Furumoto S, Tago T, Tomita N, Watanuki S, Hiraoka K, Ishikawa Y, Funaki Y, Nakamura T, Yoshikawa T, Iwata R, Tashiro M, Sasano H, Kitamoto T, Yanai K, Arai H, Kudo Y and Okamura N. Correlations of 18F-THK5351 PET with postmortem burden of Tau and astrogliosis in Alzheimer disease. J Nucl Med 2018; 59: 671-4.
[66] Maass A, Landau S, Baker SL, Horng A, Lockhart SN, La Joie R, Rabinovici GD and Jagust WJ; Alzheimer's Disease Neuroimaging Initiative. Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. NeuroImage 2017; 157: 448-63.
[67] Hall B, Mak E, Cervenka S, Aigbirhio F, Rowe J and O'Brien J. In vivo tau PET imaging in de-

mentia: pathophysiology, radiotracer quantification, and a systematic review of clinical findings. Ageing Res Rev 2017; 36: 50-63.

[68] Chiotis K, Saint-Aubert L, Savitcheva I, Jelic V, Andersen P, Jonasson M, Eriksson J, Lubberink M, Almkvist O, Wall A, Antoni G and Nordberg A. Imaging in-vivo tau pathology in Alzheimer's disease with THK5317 PET in a multimodal paradigm. Eur J Nucl Med Mol Imaging 2016; 43: 1686-99.

[69] Lockhart SN, Schöll M, Baker SL, Ayakta N, Swinnerton KN, Bell RK, Mellinger TJ, Shah VD, O'Neil JP, Janabi M and Jagust WJ. Amyloid and tau PET demonstrate region-specific associations in normal older people. NeuroImage 2017; 150: 191-9.

[70] Okamura N, Harada R, Furumoto S, Arai H, Yanai K and Kudo Y. Tau PET imaging in Alzheimer's disease. Curr Neurol Neurosci Rep 2014; 14: 500.

[71] Chiaravalloti A, Barbagallo G, Ricci M, Martorana A, Ursini F, Sannino P, Karalis G and Schillaci O. Brain metabolic correlates of CSF Tau protein in a large cohort of Alzheimer's disease patients: a CSF and FDG PET study. Brain Res 2018; 1678: 116-22.