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Biomarkers for tau pathology

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A B S T R A C T

The aggregation of fibrils of hyperphosphorylated and C-terminally truncated microtubule-associated tau protein characterizes 80% of all dementia disorders, the most common neurodegenerative disorders. These so-called tauopathies are hitherto not curable and their diagnosis, especially at early disease stages, has traditionally proven difficult. A keystone in the diagnosis of tauopathies was the development of methods to assess levels of tau protein *in vivo* in cerebrospinal fluid, which has significantly improved our knowledge about these conditions. Tau proteins have also been measured in blood, but the importance of tau-related changes in blood is still unclear. The recent addition of positron emission tomography ligands to visualize, map and quantify tau pathology has further contributed with information about the temporal and spatial characteristics of tau accumulation in the living brain. Together, the measurement of tau with fluid biomarkers and positron emission tomography constitutes the basis for a highly active field of research.

This review describes the current state of biomarkers for tau biomarkers derived from neuroimaging and from the analysis of bodily fluids and their roles in the detection, diagnosis and prognosis of tau-associated neurodegenerative disorders, as well as their associations with neuropathological findings, and aims to provide a perspective on how these biomarkers might be employed prospectively in research and clinical settings.

1. Introduction

Proteinopathies are diseases where pathogenic post-translational modifications (PTMs), such as excess phosphorylation, misfolding, and aggregation of proteins are unregulated and misfolded proteins accumulate, harming cells and their environment (Fontaine et al., 2015; Ren et al., 2014; Walker and LeVine 3rd, 2012). Disorders associated with the accumulation of the microtubule-associated protein tau are thus termed tauopathies. Tau, among other physiological roles, stabilizes microtubules and maintains synaptic integrity and function. Under pathological conditions, however, its amyloidic ("starch-like") nature (Sipe et al., 2016) results in self-aggregation into aberrant fibrillar β-sheet structures, which accumulate intracellularly and cause synaptic dysfunction and degeneration (Iqbal et al., 2016). Six isoforms of tau are expressed in the human brain, resulting from alternate splicing of the *MAPT* gene on chromosome 17 and differing in the number of amino terminal inserts (0/1/2N) and the number of microtubule-binding domain repeats, either three (3R) or four (4R) (Goedert et al., 1989). The neuropathology of different tauopathies exhibits varying isoform composition of the different intracellular tau inclusions as well as distinct neuroanatomical distribution and relative amounts of tau inclusions. Common tauopathies include certain variants of frontotemporal lobe dementia (FTD) - frontotemporal lobar degeneration-tau (FTLD-tau) (Mackenzie and Neumann, 2016) - such as autosomal-dominant FTLD-17, where mutations in *MAPT* cause mixed 3R/4R tau inclusions whose grey and white matter distribution can overlap with sporadic tauopathies; Pick's disease (PiD), characterized by so-called Pick bodies, round inclusions formed almost exclusively by 3R tau aggregating along spatial phases in neocortical layers II-IV and certain cell populations of the hippocampus (Irwin et al., 2016); progressive

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nuclear palsy (PSP), characterized by predominant 4R tau inclusions mainly in specific nuclei of the basal ganglia, diencephalon, brainstem and cerebellum, with limited involvement of the neocortex (Dickson et al., 2010); corticobasal degeneration (CBD) with 4R-dominant tau pathology grossly overlapping with PSP with a tendency to greater involvement of the cerebral cortex and especially white matter (Dickson et al., 2011; Ouchi et al., 2014); and Alzheimer's disease (AD), which accounts for the vast majority of tauopathy cases and is characterized by mixed 3R/4R mixed tau pathology accumulating in distinct spatial and temporal stages (Braak stages, see below) (Braak and Braak, 1991; Braak et al., 2011).

In 1906, Alois Alzheimer presented what he had found in the brain of the alleged first patient to be diagnosed with AD. What he described as “Eigentümliche Veränderungen der Hirnrinde” (“Peculiar changes of the brain's cortex”) at a conference in Tübingen, Germany, was likely the first description of AD-typical neurofibrillary tangle pathology, which together with plaques, composed of fibrillar β-amyloid (Aβ) protein, constitute the macropathological hallmarks of AD. It would take another 80 years until hyperphosphorylated tau was identified as a core component of AD-related paired helical filaments (PHF), the main components of neurofibrillary tangles (NFT) (Grundke-Iqbal et al., 1986a; Grundke-Iqbal et al., 1986b; Ihara et al., 1986; Kosik et al., 1986; Wood et al., 1986). Another decade later, *in vivo* assessment of tau became possible through the development of assays for the detection of total (T-tau) and phosphorylated tau (P-tau) in cerebrospinal fluid (CSF) (Blennow et al., 1995). Five years ago, positron emission tomography (PET) ligands binding to tau with high affinity were introduced, enabling the visualization, mapping, and quantification of tau in the living brain (Chien et al., 2013).

Ongoing treatment trials targeting tau pathology now call for reliable and quantifiable tau biomarkers for the early identification of eligible study participants and the *in vivo* quantification of potential treatment effects (Cummings et al., 2018; Khanna et al., 2016). Furthermore, the National Institute on Aging and Alzheimer Association (NIA-AA) research criteria in the diagnosis of AD (Jack Jr. et al., 2018a) have implemented the use of tau biomarkers derived from PET and CSF, however, it remains unclear how the different biomarkers may be optimally operationalized.

Here, we summarize the current state of fluid- and imaging-derived markers for tau pathology.

2. Fluid biomarkers of tau

2.1. Tau in CSF

Over three decades ago, the finding that P-tau was the major component of tangles (Grundke-Iqbal et al., 1986b) made tau proteins in CSF prime candidates for quantitative immunoassays. Today, both CSF T-tau and P-tau assays (along with low Aβ42) are central to the Internal Working Group (IWG) (Dubois et al., 2014) and the NIA-AA (Jack Jr. et al., 2018a) research criteria in the diagnosis of AD. In AD, neurons release more tau proteins to the extracellular space, which is reflected in CSF from patients as increased concentrations of both T-tau, measured using antibodies against mid-domain tau epitopes that are not phosphorylated, and P-tau that is measured using antibody combinations that specifically recognize mid-domain P-tau epitopes (Olsson et al., 2016). These biomarker changes correlate with each other, however, this association is most pronounced in AD and less pronounced for isolated increases in T-tau (Skillback et al., 2015). CSF T-tau and P-tau correlate with AD-type neurodegeneration and tangle pathology in autopsy and biopsy studies (Buerger et al., 2006; Seppala et al., 2012; Tapiola et al., 2009), but the correlations are modest, and not reported in all studies (Engelborghs et al., 2007). This appears to be different from correlation studies between tau PET imaging and CSF tau biomarkers (see below), and immediately suggest differences in how these different biomarker modalities reflect the underlying processes in AD.

CSF T-tau has been postulated to reflect the severity of acute injury and/or on-going neurodegeneration (Blennow and Hampel, 2003). CSF T-tau is likely increased very early in the disease process since increased levels can be seen already in Aβ-positive cognitively unimpaired individuals (CU) (while other markers of injury, including neurogranin and neurofilament light protein were not increased until the prodromal stage in the same cohort (Mattsson et al., 2016a)). However, the increase in CSF T-tau is not specific to AD, since CSF T-tau levels are the highest in conditions with the most severe neurodegeneration, including Creutzfeldt-Jakob disease, which has been shown to be > 10-times higher in T-tau concentrations than dementia (Skillback et al., 2014). Following acute brain injury, a rapid spike in CSF T-tau is observed and maintained for a number of weeks before slowly declining to normal levels (Hesse et al., 2001; Zetterberg et al., 2006). In AD, higher T-tau values predict a more rapid cognitive decline (Buchhave et al., 2012; Wallin et al., 2010), and relate to more rapid hippocampal atrophy and reductions in FDG-PET binding (Mattsson et al., 2016a; Chiaravalloti et al., 2018), which supports the idea that T-tau levels are related to the intensity of neurodegeneration.

Several validated commercially available immunoassays targeting threonine 181 (P-tau181) consistently demonstrate an increase in AD. However, other mid-domain P-tau residues (threonine 231, serine 199 and 231) and C-terminal residues (Serine 396 and 404) are also increased in AD (Hu et al., 2002; Ishiguro et al., 1999; Kohnken et al., 2000). A limited number of studies seem to demonstrate co-linearity but specificity in P-tau181, 199 and 231 to distinguishing AD from other neurodegenerative disorder and aged healthy controls (Hampel et al., 2004).

A major outstanding research question is why other tauopathies, including some forms of FTD and associated disorders like PSP, do not show increased P-tau concentration in the CSF, at least not as robustly as in AD (Zetterberg, 2017). It is possible that disease-specific phosphorylation of tau occurs in these disorders, or that tau is processed or truncated in a way that is not recognized by the available assays. Another potential explanation for why increased CSF T-tau and P-tau are specific to AD is that this particular pathological change is simply more extensive and severe in AD than in other tauopathies. However, this seems contradicted by the fact that some non-AD tauopathy patients, most notably PSP patients, even have decreased CSF P-tau levels compared to control populations (Hall et al., 2012; Meeter et al., 2018; Wagshal et al., 2015).

Yet another possibility is that CSF T-tau and P-tau increase reflects a neuronal response to Aβ pathology, which precedes neurodegeneration and tangle pathology, as suggested by mouse model studies (Maia et al., 2013) and tau kinetics studies in humans (Sato et al., 2018). This is in agreement with the poor correlation between CSF T-tau and P-tau with [^{18}F]Flortaucipir (FTP) imaging in early stages of AD, as discussed further below.

It is known that the major proportion of tau is cleaved to N-terminally truncated or N-terminal to mid domain fragments before being secreted to the CSF, while C-terminal fragments are much less abundant (Barthelemy et al., 2016; Meredith Jr. et al., 2013). Recent studies have identified tau species cleaved by asparagine endopeptidase (AEP), that generate tau fragments ending at amino acid 368 (based on tau 2 N/4R tau numbering), which are up-regulated in aging and AD, and which have an increased tendency for aggregation into tangles (Zhang et al., 2014). Future research to evaluate if tau368 or other C-terminally extended tau fragments measured in CSF may serve as biomarkers for tau pathology is warranted.

2.2. Tau in plasma

Both imaging (see below) and CSF biomarkers work well to identify AD pathophysiology. Nonetheless, PET imaging is costly and access is restricted to specialized centers. Gradually, CSF sampling for analysis of

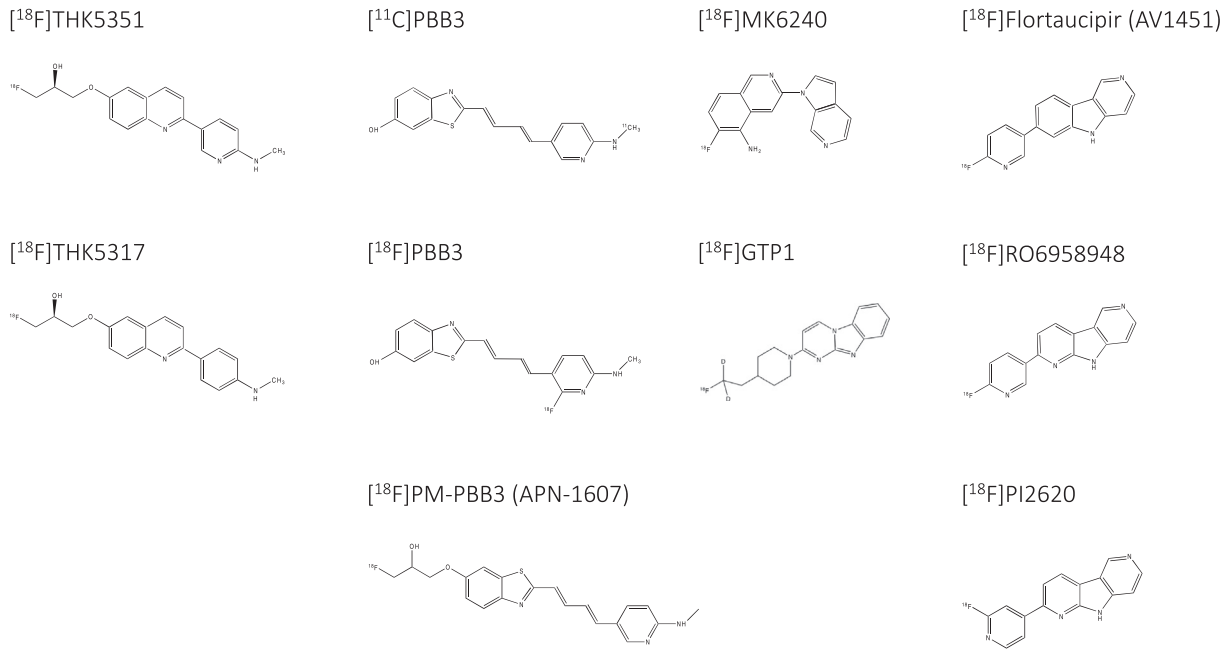

Fig. 1. Chemical structures of current PET ligands binding to PHF tau protein.

AD biomarkers is becoming increasingly used in clinical practice for management of neurodegenerative diseases, yet there remains a level of perceived invasiveness or complexity attached to a lumbar puncture in many countries. The accessibility and ease of blood sampling provides significant practical advantages for measuring AD biomarkers, for both clinical assessment or screening and repeated sampling in therapeutic trials.

Blood communicates with the brain across the blood-brain barrier, *via* lymph vessels and through the glymphatic system (Plog and Nedergaard, 2018; Zetterberg and Blennow, 2018). Despite this, it has proven difficult to establish the core CSF biomarkers for AD pathology in blood. Firstly, due to its continuous and uninhibited exchange with the brain, biomarkers in CSF will be considerably higher in concentration than biomarkers in blood. Furthermore, once entering the bloodstream, brain-derived proteins will compete in a complex matrix of highly abundant plasma proteins (*e.g.* albumin, IgG, transferrin, haptoglobin, and fibrinogen) that span > 10 orders of magnitude. Secondly, a brain-derived biomarker may undergo protease degradation, metabolized by the liver and cleared by the kidneys or simply have substantial expression by peripheral tissues. Lastly, analytical factors such as interference from heterophilic antibodies or variations in blood collection, processing and storage can have a major influence on an individual result. All these factors will introduce a high degree of variability that is unrelated to the disease pathogenesis and will be difficult to normalize.

In the advent of emerging ultrasensitive techniques that resolve confounding matrix effects, the femtomolar detection of proteins in blood has been demonstrated (Rissin et al., 2010). Indeed, increased plasma levels of T-tau in AD compared to CU and/or MCI (mild cognitive impairment) have been exhibited by immunomagnetic reduction (IMR) (Tzen et al., 2014) and Single molecule array (Simoa) (Zetterberg et al., 2013). More recently, in the ADNI and BioFINDER cohorts, this finding was confirmed but with large overlaps between the clinical groups, which almost certainly concludes that plasma T-tau is not diagnostically useful in a cross-sectional manner (Mattsson et al., 2016b). Conversely, baseline plasma T-tau might be useful in predicting future cognitive decline (Mattsson et al., 2016b; Mielke et al., 2017), atrophy and hypermetabolism (Mattsson et al., 2016b). Likewise, in cardiac arrest, with much greater acute neuronal injury than AD, baseline plasma T-tau may be used for prognosis of patients with poor neurological outcome (Mattsson et al., 2017c). Plasma T-tau, however, correlates poorly with CSF T-tau (Mattsson et al., 2016b; Zetterberg et al., 2013), which might have several explanations, *e.g.* rapid peripheral degradation of tau or that blood tau levels are confounded by expression of tau in peripheral tissues. As with CSF, assays directed towards truncated fragments of tau in plasma may yield greater disease specificity.

At this time there is no validated assay for P-tau in blood. Nonetheless, recent pilot data have reported encouraging findings. The Simoa and Meso Scale Discovery (MSD) platforms have both been utilized to demonstrate an increase of P-tau181 concentration in AD patients compared to healthy controls (Mielke et al., 2018; Tatebe et al., 2017). Importantly, however, both these studies reported weak but significant correlations with either CSF P-tau181 (Tatebe et al., 2017) or FTP (Mielke et al., 2018). Intriguingly, the stated concentrations of P-tau181 between the two methods differ substantially (Simoa assay reported a mean concentration of 0.171 pg/mL in AD patients *versus* 12 pg/mL on the MSD platform). In another recent paper, plasma P-tau231 was measured using a fiber optics technique in which antibody-based detection was combined with rolling circle amplification (Rubenstein et al., 2017). Increased concentrations of plasma P-tau231 in patients with traumatic brain injury (TBI) were observed but as of yet no data has been reported in AD. This promising data, albeit preliminary, on P-tau makes it one of the most anticipated areas of AD biomarker research alongside plasma $A\beta_{42}/A\beta_{40}$ (Ashton et al., 2018a, 2018b) and neurofilament light chain (Mattsson et al., 2017a).

Other areas of ongoing investigation for peripheral tau include, but are not limited to, exosomes and saliva. Increases in T-tau and P-tau within neuronal-derived exosomes in plasma have been a developing area of research (Fiandaca et al., 2015; Winston et al., 2016). As it stands, further validation of these results and methodologies are needed. It has previously been shown that T-tau is readily measurable in saliva (Ashton et al., 2018a). While concentrations are noticeably higher than plasma, no statistically significant difference across diagnostic groups was observed. Preliminary proteomic data suggests that certain P-tau fragments derived in saliva may be of importance in clinical AD, however this is yet to be determined using a robust platform in large sample sizes.

3. Tau positron emission tomography (PET)

Given the molecular diversity of tauopathies, it cannot be assumed that one PET ligand or even one class of chemically similar PET ligands will be useful in the research of all disorders. Several companies and academic groups have developed and are continuously developing ligands presumably binding to tau (please refer to Fig. 1 for the chemical structures of current alleged tau PET ligands). Based on the recently published cryo-EM structure for the tau fibril (Fitzpatrick et al., 2017), four binding sites have been suggested for current PET ligands, and different candidates show differential preference for each of these sites (Murugan et al., 2018).

3.1. First-generation tau PET ligands

The first PET ligand used to visualize the molecular underpinnings of AD was [^{18}F]FDDNP (Shoghi-Jadid et al., 2002), which binds to both Aβ fibrils and tau NFT. Due to its relative nonspecificity for one or the other it has largely been replaced by tau or Aβ-specific ligands.

One of the earliest agents developed specifically for tau imaging was the carbon-11 labelled PBB3, a pyrinated phenyl- and pyridinyl-butadienyl-benzothiazole with a 50-fold higher affinity to tau over Aβ deposits (Maruyama et al., 2013). [^{11}C]PBB3 was initially found to exhibit affinity to tau in AD, PSP and CBD tissue samples (Ono et al., 2017b), however its utility was hampered by high white matter uptake, low target to white matter ratio on autoradiography in AD tissue, its fast metabolism *in vivo* (< 8% remaining 3 min after injection) (Hashimoto et al., 2014), photo-isomerization upon exposure to fluorescent light, and a dominant brain-penetrant metabolite that complicated quantification of ligand uptake (Hashimoto et al., 2015). Finally, carbon-11 labelling with its short half-life (~20 min) limits potential use of any PET ligand as compared to fluorine-18 labelling (half-life ~ 110 min). To address these issues, the fluorine-18 analogues AM-PBB3 and PM-PPB3 were developed (Ono et al., 2017a; Shimada et al., 2017a) but limited data have been published to date.

A series of compounds have been developed at Tohuku University, Japan, the most widely used being the arylquinoline derivatives [^{18}F]THK5117 (Okamura et al., 2013) and [^{18}F]THK5351. Of these two, [^{18}F]THK5351 demonstrated favorable imaging characteristics, generally demonstrating higher grey matter and lower white matter uptake but lower lipophilicity (Betthauser et al., 2017a). The S-enantiomer form of [^{18}F]THK5117, [^{18}F]THK5317, has also been assessed *in vivo* (Chiotis et al., 2016; Jonasson et al., 2016). However, high off-target binding of [^{18}F]THK5351 was observed especially in the thalamus, and blocking studies with the monoamine oxidase B (MAO-B) inhibitor selegiline showed dramatic reduction in thalamic [^{18}F]THK5351 uptake (Ng et al., 2017a). Cortical uptake was also reduced significantly, indicating that this off-target binding also affected what had been previously assumed to be tau specific uptake in *in vivo* studies (see also below).

The radioligand [^{18}F]Flortaucipir (FTP, previously AV1451 or T807), a benzimidazole pyrimidine derivative, is the by far most widely studied tau PET tracer to date. It has been shown to bind with high affinity (25–27 fold larger than to Aβ) to 3R and 4R tau isoforms in PHF of AD patients (Chien et al., 2013; Lowe et al., 2016; Marquie et al., 2015). Smith and colleagues furthermore showed that *in vivo* FTP-binding and *post-mortem* PHF load were highly correlated in one subject with a *MAPT* R406W mutation causing AD-like tau pathology (Smith et al., 2016). However, large inter- and intraindividual differences were observed in a recent study in *post mortem* tissue from several neurodegenerative disorders (Wren et al., 2018), calling for further investigation of the binding characteristics. Nonetheless, on a group level, FTP demonstrated clinical usefulness when its discriminative accuracy between AD dementia and non-AD neurodegenerative disorders was examined in a large multisite study, yielding 89.9% (95% CI, 84.6%–93.9%) sensitivity and 90.6% (95% CI, 86.3%–93.9%) specificity or 96.8% (95% CI, 92.0%–99.1%) sensitivity and 87.9% (95% CI, 81.9%–92.4%) specificity based on different thresholds applied to medial-basal and lateral temporal cortex ligand uptake (Ossenkoppele et al., 2018).

The *in vivo* kinetics of [^{18}F]FTP have been investigated in a number of studies, aiming at validating semi-quantitative estimates such as the standardized uptake value ratio (SUVR), which are more appropriate for clinical research than fully dynamic and quantitative approaches (Baker et al., 2017a; Barret et al., 2016; Golla et al., 2017; Hahn et al., 2017; Wooten et al., 2017). In those studies including blood sampling and metabolite analysis, 20–30% of [^{18}F]FTP was found to remain 60 min after injection, with the main metabolites being polar and thus not entering the brain. Free fraction in plasma was low (0.19%) (Barret et al., 2016). The different studies came to different conclusions regarding the most appropriate kinetic model to describe ligand uptake. Whereas the two-tissue compartment model was found to best describe the data, also in the cerebellar cortex for all subjects including controls (Barret et al., 2016), others found that in controls the uptake was best described by the 1-tissue compartment model (Golla et al., 2017), indicating that model preference depended on the underlying volume of distribution. A third study found that none of the compartment models adequately described the data (Hahn et al., 2017). Most importantly, however, all studies found that reference-based quantification of dynamic data correlated well with arterial blood-based quantification supporting the use of an 80–100 (75–105) min SUVR as an acceptable, yet not ideal, method for clinical studies (see also (Heurling et al., 2018) for assessment of how regionally and temporally different times to transient equilibria influence SUVR reliability). Regional increase of ligand uptake past 180 min in certain high-binding patients might also influence semi-quantification by SUVR in earlier time frames and needs to be evaluated further. Finally, analysis of *in vivo* test-retest reliability of FTP yielded low variability in SUVR (standard deviation of mean percent change 1.46–3.27% depending on brain region) (Devous Sr. et al., 2018).

3.2. Second-generation tau PET ligands

Numerous publications have applied FTP in clinical studies, as described in the next section. However, concerns about off-target binding issues (see below) have triggered the continuous development of a second generation of tau PET ligands. As data on most of these novel compounds have only been published or presented very recently, no head-to-head comparison has been conducted including any of these. Fig. 2 therefore displays current tau PET ligand uptake patterns in different representative cases of cognitively healthy elderly individuals and patients with early-onset and late-onset AD, respectively. The figure is intended to provide an impression of dynamic range and potential off-target binding patterns without claiming completeness.

After screening three final candidates (RO6958948, RO6931643, and RO6924963) (Gobbi et al., 2017), Roche decided on [^{18}F]RO6958948 as their lead compound (Wong et al., 2018). Chemically similar to [^{18}F]FTP (Fig. 1) and presumably binding to the T808 binding site, it is anticipated to exhibit higher affinity to mixed 3R/4R over isolated 3R or 4R tau pathology. [^{18}F]RO6958948 was reported to have a lipophilicity of log D = 3.22 and rather low plasma free fraction of 7%. Low non-specific binding was shown using autoradiography in tissue from healthy controls, and high grey/white matter ratio in tissue samples from AD subjects with tau pathology corresponding to Braak Stage V. No significant binding was observed *in vitro* in PSP, CBD or PiD tissue samples (Honer et al., 2018). In a first-in-man study, 90 min dynamic scans were performed with arterial blood sampling, demonstrating clear discrimination between healthy controls and AD patients both using SUVR and volume of distribution estimates (Wong et al., 2018). For SUVR creation, a 60–90 min frame was proposed, correlating well with arterial input-based quantification. After 15 min, 30% remained as parent fraction, and the uptake could be described by a

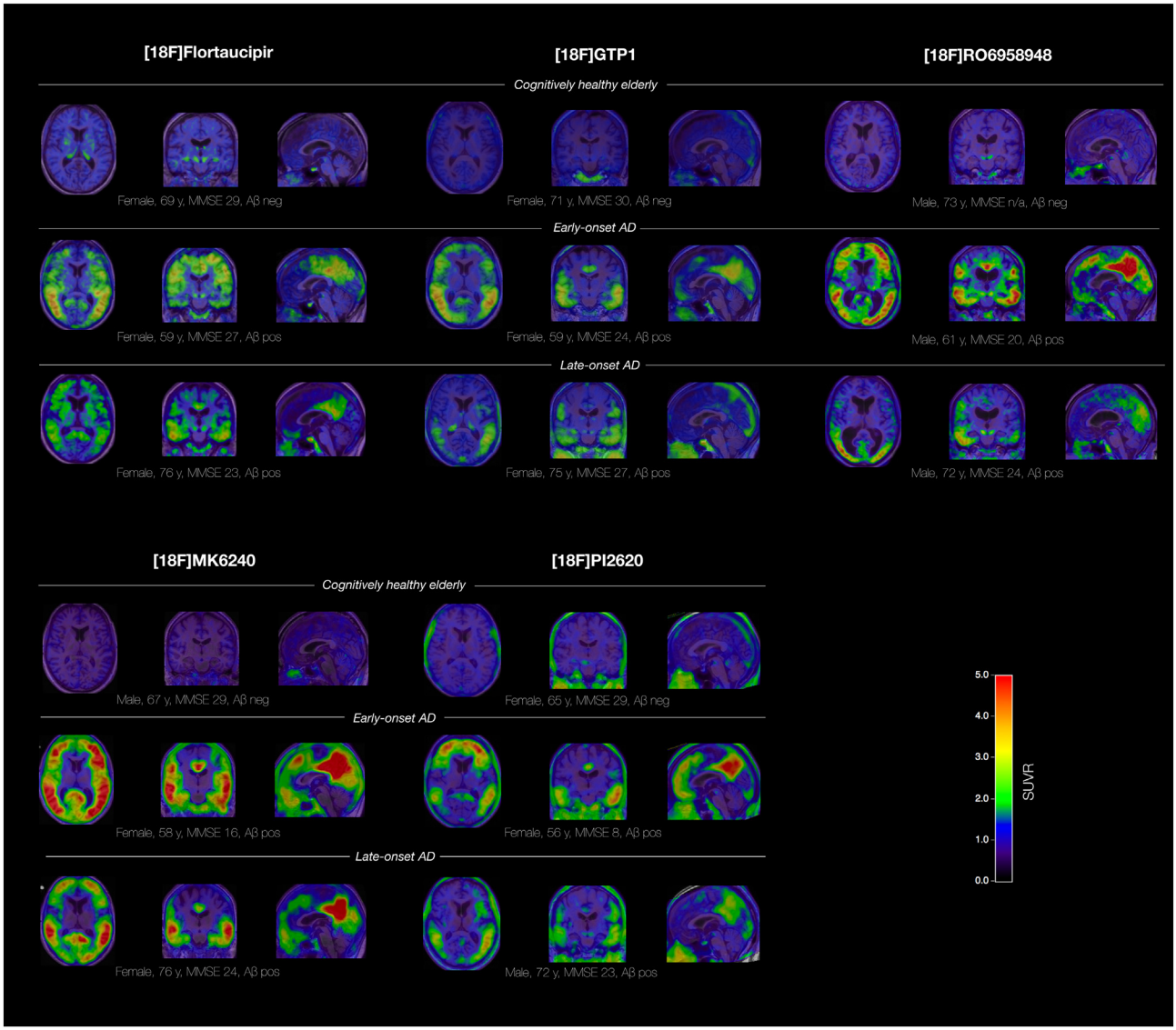

Fig. 2. Representative PET scans using different current ligands presumably specific for tau in cognitively healthy elderly individuals (upper rows), patients with early-onset (EOAD, middle rows) and late-onset Alzheimer's disease (LOAD, lower rows). All images were processed in a unified manner including co-registration of PET to its corresponding T1-weighted magnetic resonance imaging (MRI) scan, spatial normalization to Montreal Neurological Institute (MNI) template space and creation of standardized uptake value ratios (SUVR) using an inferior cerebellum reference region (see (Baker et al., 2017b) for methods). Note that this is not a head-to-head comparison but merely a display of sample scans from different representative cases, obtained at various sites using scanners with different spatial resolution, and non-harmonized image reconstruction. FTP images (80–100 min SUVR) were derived from the Berkeley Aging Cohort Study (BACS; University of California, Berkeley/San Francisco, Drs. William Jagust and Gil Rabinovici), [^{18}F]GTP1 (60–90 min SUVR) images were kindly provided by Genentech (Drs. Robby Weimer and Sandra Sanabria Bohorquez), RO6958948 images (60–90 min SUVR) by Roche (Drs. Gregory Klein and Edilio Borroni) and Drs. Dean Wong and Hiroto Kuwabara from Johns Hopkins University, Baltimore, Maryland, MK6240 images (90–110 min SUVR) by Drs. Pedro Rosa-Neto and Tharick Ali Pascoal at McGill University, Montreal, Canada, and PI2620 scans (60–90 min SUVR) by Drs. André Müller and Santaigo Bullich at Life Molecular Imaging GmbH (former Piramal Imaging). Aβ pos/neg: Amyloid status positive/negative based on Aβ PET scans; MMSE = Mini Mental State Examination.

two-tissue compartment model. No radiolabeled metabolites suspected to cross the blood-brain barrier were detected. Test-retest variability was 6–10% depending on brain region and quantification method (SUVR or DVR). [^{18}F]RO6958948 is currently employed in a longitudinal study, preliminary results showed increased ligand uptake over a < 1 year follow-up period (Wong et al., 2017).

Following extensive preclinical validation (Walji et al., 2016), Merck put forward [^{18}F]MK-6240 as lead compound (Hostetler et al., 2016), demonstrating a K_i = 0.36 nM in NFT-rich AD brain homogenate *versus* the high-affinity NFT ligand [^{3}H]-NFT-355, to be compared with a K_i = 10 μM in amyloid plaque rich AD homogenate *versus* the amyloid plaque ligand [^{3}H]-MK-3328 (Hostetler et al., 2016). Compared with [^{3}H]FTP, [^{3}H]-MK-6240 was found to have a two- to five-fold higher binding potential. Non-human primate blocking studies showed no apparent off-target binding. Three recently published studies have evaluated [^{18}F]MK-6240 *in vivo* (Betthauser et al., 2018; Lohith et al., 2018; Pascoal et al., 2018). Ligand binding patterns were described in regions associated with NFT deposition. All studies included dynamic scanning for between 90 and 180 min, demonstrating rapid brain delivery and washout, and tracer kinetics were investigated in healthy controls and AD patients using reference- or blood-input based modelling approaches. Distribution volumes correlated well with SUVR over either 70–90 (Betthauser et al., 2018; Lohith et al., 2018) or 90–110 min (Pascoal et al., 2018). Whereas non-AD tauopathies have not yet been investigated with [^{18}F]MK-6240, it presumably shares the same binding site as [^{18}F]FTP and is thus unlikely to exhibit high

affinity to isolated 3R or 4R tau pathology.

Data for the novel [^{18}F]GTP-1 (Genentech Tau Prope-1) and [^{18}F] PI2620 (Life Molecular Imaging, formerly Piramal Imaging) compounds have thus far only been presented at conferences. [^{18}F]GTP1 is currently evaluated in a longitudinal study, preliminary cross-sectional results demonstrated clearly increased uptake in expected regions in AD patients as well as an association between ligand uptake and cognitive impairment. Images showed increased retention in the basal ganglia relative to background in some subjects but kinetic analysis suggest the measured SUVR may not necessarily reflect specific tracer binding (Sanabria Bohorquez et al., 2016; Sanabria Bohorquez et al., 2017; Weimer et al., 2017).

[^{18}F]PI2620 is structurally similar to FTP (Fig. 1), again suggesting similar binding preferences to 3R/4R tau. *In vitro* binding characteristics were reported for PHF tau deposits (IC_{50} = 3.9 nM), K18 fibrils (4R, IC_{50} = 8.4 nM), homogenates of AD brain (IC_{50} = 1.9 nM), Pick's Disease (3R, IC_{50} = 2.6 nM), and PSP (4R, IC_{50} = 10.7 nM), indicating high affinity to 3R/4R tau deposits but potentially also 3R inclusions (Stephens et al., 2018). No binding to β-amyloid or MAO-A/B was reported. [^{18}F]PI2620 is currently evaluated in several clinical trials, including a test/retest study with arterial sampling. Initial *in vivo* data showed robust brain uptake and fast wash-out in non-target regions, no lipophilic metabolites, and 20% of the intact tracer in blood at 60 min p.i. (Seibyl et al., 2017). SUVR over a 60–90 min p.i. time frame were highly correlated with DVR and showed clear discrimination between AD patients and control individuals, as well as high correlation between test-retest results (Stephens et al., 2018).

4. Tau PET imaging in aging and Alzheimer's disease

4.1. Topography of tau ligand retention

Based on years of neuropathological evidence from autopsies, the presence and location of pathological tau accumulations in the human brain are well established (Braak and Braak, 1991). These studies have proposed a progression of stages of tau deposition based on cross sectional autopsy data (see Fig. 3A). These stages begin with tau deposits in the entorhinal cortex (Braak stages I/II), moving to inferolateral temporal cortex and parts of the medial parietal lobe (stages III/IV), and eventually throughout association cortex (V/VI). Interestingly, stages III/IV can be seen in both CU older people and those with AD while stages I/II are common in those who are cognitively normal and stages V/VI are almost universally associated with dementia (Bennett et al., 2006; Hyman et al., 2012).

The relatively recent advent of relevant PET radioligands has permitted the *in vivo* detection of tau which largely parallels these autopsy findings (see Fig. 3B). The radioligand [^{18}F]FTP has been most widely studied so far and binds with high affinity to PHF tau in AD patients (Chien et al., 2013; Lowe et al., 2016; Marquie et al., 2015). Tau tracer retention in aging and AD appears to follow a particular topography (*e.g.* Cho et al., 2016a) and although longitudinal data are sparse (Jack Jr. et al., 2018b; Southekal et al., 2018), the distribution can be captured as a regional pattern that appears to begin in entorhinal cortex, spreading through inferolateral temporal lobes and medial parietal lobes and eventually to wide areas of the neocortex. In contrast to Aβ, which is often found throughout neocortex in a regionally less specific manner using PET imaging, the quantitation of tau deposition requires careful selection of region-specific measures of tracer retention. A number of different approaches have been suggested included regional and global measures for binary categorization (Jack Jr. et al., 2017; Maass et al., 2017; Mishra et al., 2017; Wang et al., 2016) as well as topographical staging approaches that recapitulate *ex vivo* pattern of hierarchical tau spread (Maass et al., 2017; Schöll et al., 2016; Schwarz et al., 2016). Quantification from large regions may be sufficient to capture AD-related tau PET signal and progressive within-person accumulation of pathologic tau (Jack Jr. et al., 2018b; Maass et al., 2017). The high regionality of brain tau load as visualized with PET is further emphasized by studies employing data-driven approaches without prior definition of anatomical regions (Sepulcre et al., 2017a; Whitwell et al., 2018b).

4.2. Effects of Aβ and age on patterns of tau PET ligand uptake

Elevated tau tracer binding in the medial temporal lobe (MTL) is commonly seen in CU elderly, whereas widespread binding in neocortical regions usually requires the presence of aggregated Aβ (Cho et al., 2016a; Gordon et al., 2016; Johnson et al., 2016; Lockhart et al., 2017b; Maass et al., 2017; Pontecorvo et al., 2017; Schöll et al., 2016; Schwarz et al., 2016; Sepulcre et al., 2016).

Interestingly, although there is an overall correlation between the amount of Aβ in the brain and the amount of tau (Johnson et al., 2016), the spatial locations of these two aggregated proteins are discordant. Specifically, Sepulcre and colleagues (Sepulcre et al., 2016) demonstrated strong positive local-to-local tau *versus* Aβ PET correlations in lateral temporal, frontal and parietal lobes across 88 CU elderly, but tau in these regions further correlated with Aβ throughout the brain. Data

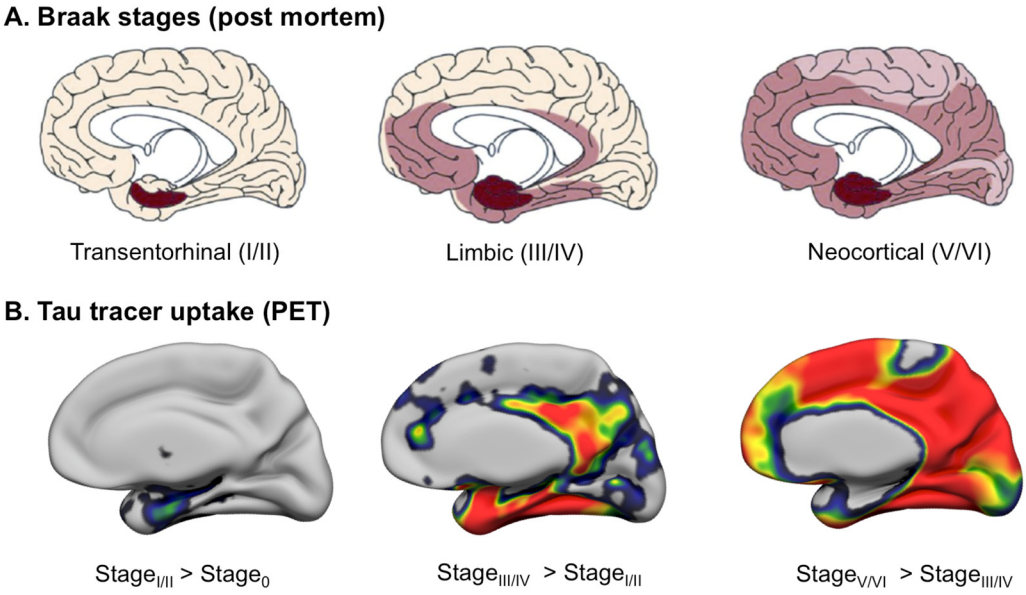

Fig. 3. Tau tracer uptake patterns resemble *ex vivo* Braak stages.
A. Schematic display of Braak stages in the development of Alzheimer's disease-associated tau pathology based on *post mortem* data. Reprinted from "Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years," (Braak et al., 2011). Copyright 2011 by Oxford University Press B. Voxel-wise two-sample *t*-tests on Flortaucipir SUVR images between subjects assigned to contiguous tau-PET based Braak stages. Results are Family-Wise Error (FWE) corrected at voxel level ($p_{voxel} < 0.05$, $k > 100$). Individuals included cognitively normal adults and AD patients. See (Maass et al., 2017) for more information.

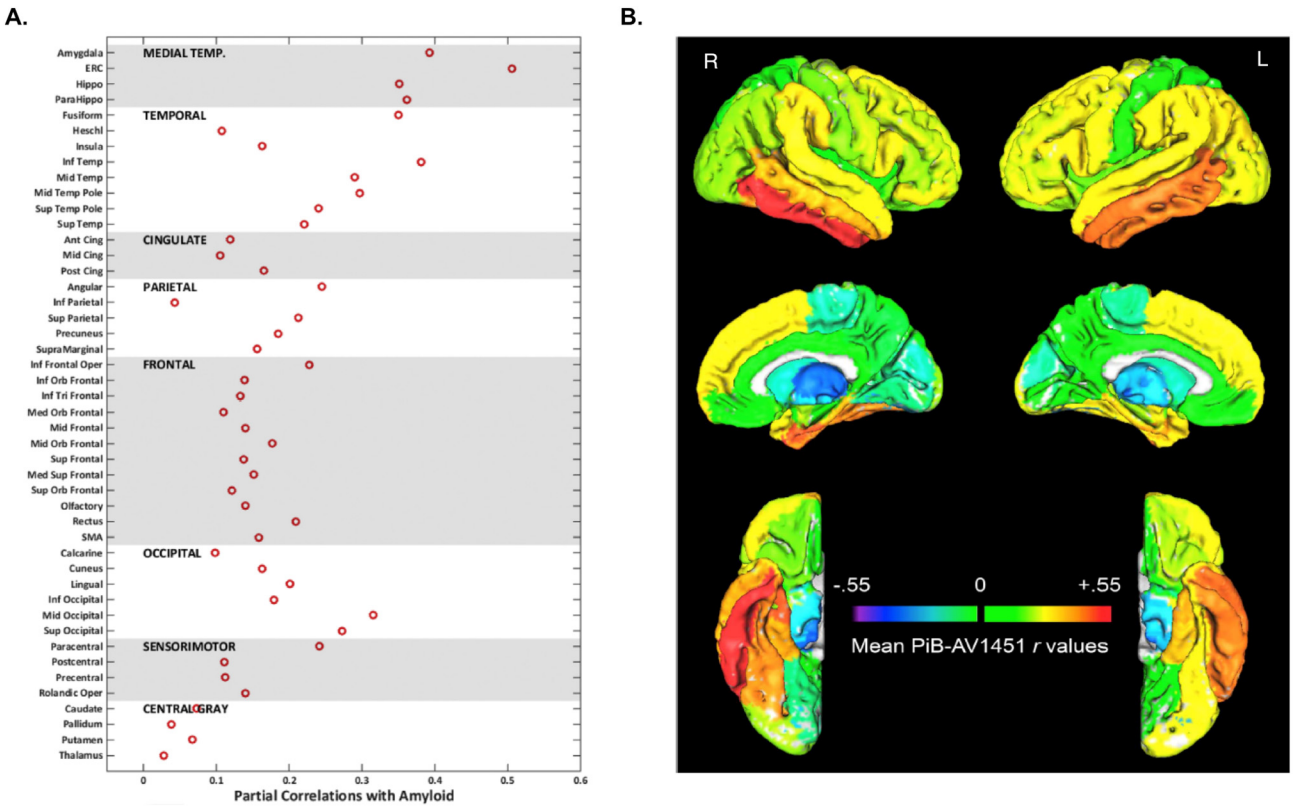

Fig. 4. Association between global Aβ and regional tau PET measures in cognitively normal elderly.
A. Partial correlation (r-values) of global PiB with regional FTP PET measures in 420 cognitively normal individuals (age 50 +) after adjusting for age. Highest correlations were in medial temporal regions, specifically entorhinal cortex (ERC). Reprinted from "Tau-PET uptake: Regional variation in average SUVR and impact of amyloid deposition," (Vemuri et al., 2017). Copyright 2017 by Elsevier Inc. (on behalf of the Alzheimer's Assocation) B. Mean partial correlation *r* values for associations between global PiB DVR and FTP SUVR in different ROIs in 46 normal elderly from BACS, demonstrating strongest correlation in temporal lobe. Adapted from "Amyloid and tau PET demonstrate region-specific associations in normal older people," (Lockhart et al., 2017b). Copyright 2017 by Elsevier.

from Lockhart and colleagues (Lockhart et al., 2017b) confirmed these findings in 46 CU showing that tau PET signal in the temporal lobe and some frontal areas correlated with Aβ measures among widespread neocortical regions (see Fig. 4). Together these data indicate a regional vulnerability of temporal brain regions to tau regardless of where Aβ is deposited. Notably, associations between global Aβ and regional tau PET signal seems to be strongest in the entorhinal cortex (Vemuri et al., 2017) as demonstrated in in large sample of 420 CU elderly, suggesting that this "early tau region" should be included in meta regions for detection of AD-related tau PET signal.

Extra-MTL tau deposition is more common in those with AD, although elevated tau tracer signal in neocortical areas such as inferior temporal or occipital cortex has been reported in those who are cognitively normal and even Aβ-negative (Lowe et al., 2018a; Lowe et al., 2018b). While on average AD patients have more widespread and severe tau deposition than controls, some AD patients who are Aβ-positive may in fact show relatively low levels of tau deposition (one possibility is that such patients are clinically misdiagnosed and have incidental Aβ-co-pathology) (Pontecorvo et al., 2017; Wang et al., 2016).

More Aβ deposition is not only associated with more tau deposition in cross sectional studies, but longitudinal studies have also shown that increasing levels of brain Aβ predict more tau deposition after several years in limbic and neocortical Braak regions even in those who are nominally Aβ-negative (Leal et al., 2018; Tosun et al., 2017). Longitudinal data also suggest that Aβ facilitates the spread of tau from the MTL to the medial parietal cortex through the cingulum bundle in the normal older brain (Jacobs et al., 2018). Although there are still relatively limited longitudinal data, it appears that longitudinal tau accumulation is measurable in the temporal lobes in cognitively normal individuals and those with AD, although changes have not been detected in those who are Aβ-negative (Jack Jr. et al., 2018b; Southekal et al., 2018).

Compared to associations with Aβ, correlations between tau PET measures and age across CU elderly seem to be weaker and be confined to MTL regions (Maass et al., 2018; Schöll et al., 2017b). Among 83 CU (Maass et al., 2018), both Aβ and age independently predicted MTL FTP uptake, with age only accounting for 8% of the variance compared to 25% variance explained by global Aβ. When age effects in CU adults with normal levels of Aβ were studied across the life span (Lowe et al., 2018b), modest age-related increases in tau PET signal were found in most regions of the brain. Strongest differences in tau tracer binding between young and elderly subjects are usually seen in choroid plexus and basal ganglia, but these are thought to reflect off-target binding (Lowe et al., 2016; Lowe et al., 2018b).

Age of symptom onset among AD patients clearly affects tau PET uptake patterns. Sporadic early-onset AD patients (EOAD) exhibit distinctly greater parietotemporal and frontal ligand uptake when compared with LOAD which exhibits rather confined temporal lobe uptake (Schöll et al., 2017a) (see also Fig. 2). Data from studies in early-onset familial/autosomal-dominant AD are limited, suggesting earliest FTP uptake in the MTL of Aβ-positive presymptomatic mutation carriers but high cortical uptake, spatially comparable to sporadic EOAD cases in later symptomatic stages (Quiroz et al., 2018; Schöll et al., 2017a).

In summary, tau PET imaging data indicate that tau deposition occurs on a continuum from normal aging through AD, likely beginning in the entorhinal cortex within the MTL in normal aging and increasing in both quantity and distribution with the deposition of Aβ and the

progression towards AD with clearly different patterns in EOAD and LOAD.

4.3. Relationships between tau PET, cognition, and measures of neurodegeneration

For years, the role of Aβ in the development of AD has been perplexing because of the relatively weak association between measurements of this protein in the brain and concomitant measures of cognitive decline, whether in autopsy studies (Nelson et al., 2012), cross sectional imaging-cognition studies (Hedden et al., 2013; Jansen et al., 2018), or longitudinal imaging studies (Donohue et al., 2017; Dubois et al., 2018). It now seems likely that this weak relationship may be explained by the intermediary factor of tau, which is correlated with both Aβ and cognition. Greater tau tracer retention is related to both poorer cognitive function cross-sectionally, and decline in cognition longitudinally although this decline has generally been measured retrospectively because of the relative novelty of tau imaging (Aschenbrenner et al., 2018; Maass et al., 2018; Schöll et al., 2016).

4.4. Findings in cognitively normal elderly

While most tau PET studies examined tau–cognition relationships in samples that included symptomatic patients with MCI or AD dementia (Aschenbrenner et al., 2018; Brier et al., 2016; Cho et al., 2016b; Johnson et al., 2016; Maass et al., 2017; Ossenkoppele et al., 2016; Schwarz et al., 2016), a few studies focused on CU elderly (Buckley et al., 2017; Maass et al., 2018; Mishra et al., 2017; Schöll et al., 2016; Shimada et al., 2017b). Within CU elderly, associations are most strongly seen between episodic memory measures and tau tracer uptake in the temporal lobe (particularly entorhinal cortex, see Fig. 5), whereas associations with global cognition are either absent or found with tau PET signal in wider neocortical regions. Global Aβ does not seem to alter or account for the effect of MTL tau on episodic memory in these CU individuals (Schöll et al., 2016, Maass et al., 2018; Fig. 5A). Interestingly, similar associations have been seen between entorhinal tau load and subjective cognitive decline (Buckley et al., 2017), and these were also not altered by Aβ status. The likelihood that MTL tau accumulation is not a benign event in early stages is supported by associations between tau deposition and both brain atrophy and glucose hypometabolism in CU older people that are topographically similar to the patterns seen in patients with AD (Adams et al., 2018; Das et al., 2018; Gordon et al., 2018; Hanseeuw et al., 2017; LaPoint et al., 2017).

4.5. Findings in patients

Relationships between tau deposition, cognition, and measures of neurodegeneration are stronger yet in patients with AD. Initial studies confirmed an association between tau deposition and cognition that is stronger than the association between Aβ and cognition (Brier et al., 2016; Johnson et al., 2016). Associations with cognition are particularly striking in cases of EOAD that frequently present with dysfunction in language, visuospatial, or executive systems. In these syndromes, tau deposition bears a strong relationship to clinical phenotype, a relationship that is not seen between Aβ and clinical findings (Ossenkoppele et al., 2016; Xia et al., 2017). In AD patients, tau deposition is also associated with the neurodegenerative biomarkers of atrophy and glucose hypometabolism (Bischof et al., 2016; Iaccarino et al., 2018; Wang et al., 2016). This is also particularly marked in the syndromic variants of EOAD wherein patterns of atrophy and hypometabolism correlate better with tau than with Aβ (Ossenkoppele et al., 2016). In fact, while cognition is explained by both atrophy and tau, after accounting for atrophy tau remains correlated with cognitive function in multivariate models (Bejanin et al., 2017). EOAD has also been associated with more severe glucose hypometabolism that has not been explained by the amount or distribution of Aβ (Rabinovici et al.,

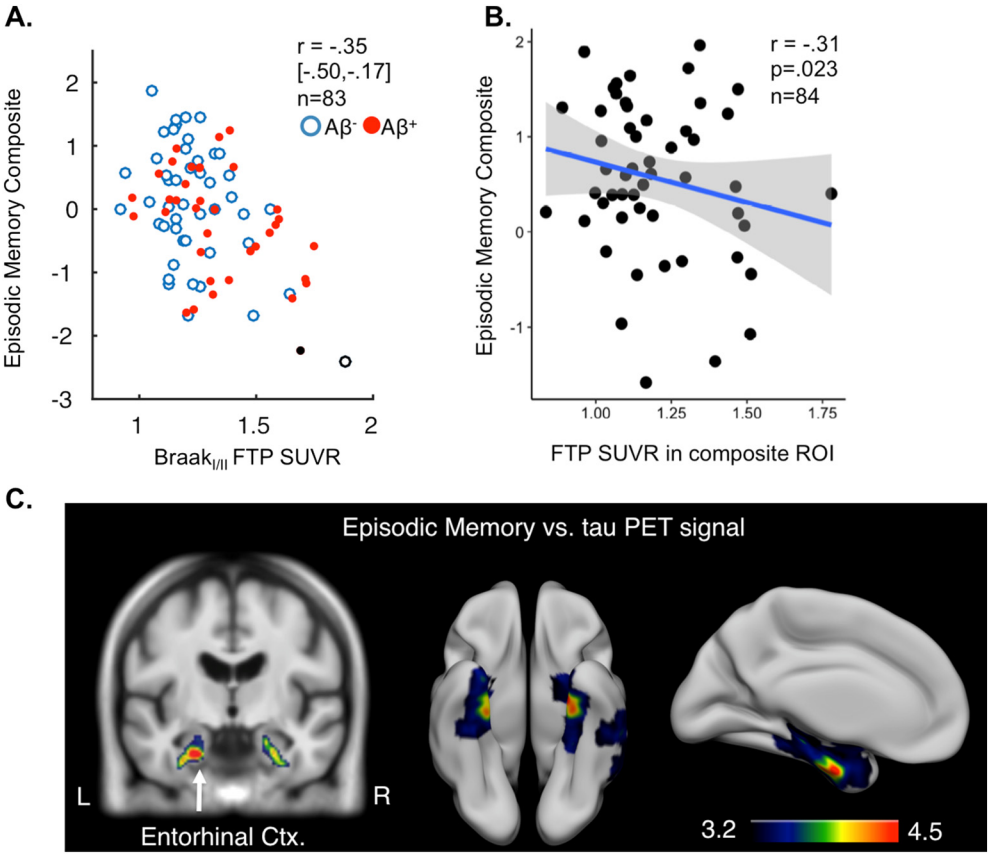

Fig. 5. Tau PET signal relates to episodic memory performance in cognitively normal elderly.
A. Higher Braak I/II FTP SUVR (mean across entorhinal cortex and hippocampus after partial volume correction) relates to worse episodic memory (*Z*-score of verbal and visual recall) in 83 older adults from BACS. R denotes skipped Pearson correlation coefficient with bootstrapped 95% CI from robust correlations; outliers colored in black. See Maass et al., 2018 for details. B. Higher mean FTP SUVR across amygdala, entorhinal, lateral occipital and inferior temporal cortex relates to worse episodic memory in elderly sample from WashU. Adapted from "AV-1451 PET imaging of tau pathology in preclinical Alzheimer disease: Defining a summary measure," by Mishra et al., 2017, *Neuroimage*, *161*:*171–178*. Copyright 2017 by Elsevier C. Voxel-wise regressions of episodic memory on FTP SUVR in subjects from A. (whole brain, $p_{cluster} < 0.05$, $p_{voxel} < 0.001$, no explicit mask). Significant regions include bilateral entorhinal/parahippocampal cortex, left inferior temporal gyrus and middle temporal gyrus.

2010). The interplay between tau patterns and variants of AD is also seen in studies that include both EOAD and LOAD patients. For example, most patients with relatively low FTP binding in the entorhinal cortex, compared to overall cortical binding, have EOAD with atypical clinical presentations, while most patients with high FTP binding in both entorhinal and neocortex have EOAD with typical amnestic presentation, and most with low FTP binding in both entorhinal and neocortex have late onset typical AD (Whitwell et al., 2018b). Differences in tau patterns have also been detected when stratifying by *APOE* ε4-status. AD patients that carry the *APOE* ε4 risk allele have lower overall cortical FTP binding (especially in the parietal and occipital cortex) but relatively higher binding in the entorhinal cortex compared to *APOE* ε4-negative AD patients, with corresponding differences in atrophy patterns (in a mix of EOAD and LOAD patients, without age differences between the *APOE*-groups) (Mattsson et al., 2018a).

Thus, the measurement of tau accumulation in aging and AD has revealed a pattern of deposition that parallels neuropathological data but offers the possibility of prospective longitudinal studies. The strong relationship between tau and both neurodegeneration and cognition, along with its relationship with Aβ suggest that it may well be the "missing link" in establishing a relationship between amyloid-β and the downstream structural, functional, and molecular events that are linked to cognitive decline and dementia. This emphasizes the need to understand how Aβ relates to the development of tau pathology in AD, a question that remains largely unanswered.

4.6. Tau PET and brain connectivity

Over the last decade, the spatial correspondence between Aβ PET burden and intrinsic connectivity networks has been extensively studied, and prominent overlap with the default mode network (DMN) has been observed (Buckner et al., 2005; Grothe et al., 2016; Sperling et al., 2009). With the availability of tau PET imaging, topographical similarities between tau pathology and functional brain networks have been recently explored (Hansson, Grothe et al., 2017; Hoenig et al., 2018). In the study by Hansson and colleagues, AD-related tau PET signal primarily overlapped with the dorsal attention network and to a lower extent with higher visual, limbic and DMN network components. Hoenig et al., 2018, who identified independent coherent networks of AD-related tau PET signal, also observed a spatial correspondence of tau seed-based functional networks with multiple resting-state networks. In their data, spatial similarities were highest with ventral and dorsal DMN but also evident with salience, language, primary and higher visual, as well as hippocampal networks. Together these findings indicate that tau pathology does not exclusively distribute along one particular network.

Other studies characterized the spatial associations of tau and Aβ PET load with functional connectivity changes in the brains of CU elderly (Schultz et al., 2017; Sepulcre et al., 2017b) and AD dementia patients (Cope et al., 2018; Jones et al., 2017; Wiepert et al., 2017). Among older adults, an inverse relationship of tau *versus* Aβ PET measures with functional connectivity hubs was observed such that tau tended to be located in areas of hypoconnectivity (*e.g.* temporal lobe) but Aβ in areas of hyperconnectivity (*e.g.* occipital and parietal lobe) (Sepulcre et al., 2017b). Schultz and colleagues (Schultz et al., 2017) furthermore showed an interactive effect of global Aβ and neocortical tau PET measures on functional connectivity. While hyperconnectivity in DMN and salience networks was seen in OA with high Aβ but low levels of inferior temporal tau, hypoconnectivity was present when both global Aβ and neocortical tau were high. These cross-sectional findings could be interpreted as support for a phase of hyperconnectivity in Aβ-positive aging, followed by a loss of connectivity with spread of tau to neocortical regions in the progression of AD.

The cascading network failure model proposed by Jones and colleagues (Jones et al., 2016) incorporated findings about the relationship between tau, Aβ and functional network changes (Jones et al., 2017; Wiepert et al., 2017). The model suggests that local tau-associated network disruptions (*e.g.* in temporal lobe) lead to compensatory load shift to the posterior DMN and subsequently other connectivity hubs (evident as increased connectivity) that are associated with amyloidosis and network failure. Longitudinal data across the AD spectrum will be necessary to elucidate the sequential order of tau and Aβ accumulation and associated functional network changes.

5. Off-target binding of tau PET ligands

Off-target binding of tau PET ligands is one of the current major limitations and challenges to be addressed in novel tracer development (see also (Bischof et al., 2017, Lemoine et al., 2018, Lois et al., 2018) for recent reviews).

5.1. Flortaucipir (FTP)

Among tracers, FTP off-target binding has been characterized best and has been most frequently reported in the basal ganglia, substantia nigra, choroid plexus, meninges and vessels (see also Fig. 2).

5.1.1. Basal ganglia and substantia nigra

The strong FTP uptake in caudate, putamen, and pallidum seen in elderly individuals regardless of their clinical diagnosis (*e.g.* (Baker et al., 2017b, Brier et al., 2016, Lowe et al., 2016, Vemuri et al., 2017, Winer et al., 2018)) has been attributed to iron binding. In groups of patients and controls, basal ganglia FTP signal correlated with age-related increases in iron accumulation measured by iron-sensitive R2* MRI (Choi et al., 2018).

Similarly, FTP binds strongly to substantia nigra, also in cases with no tau pathology, which has been related to neuromelanin (Marquie et al., 2015; Marquie et al., 2017b; Marquie et al., 2017c). This is in accordance with reduced substantia nigra FTP signal seen in PD patients without (Hansen et al., 2016) or with (Smith et al., 2018) dementia compared to age-matched controls, that might reflect decreases in neuromelanin containing dopaminergic neurons (but see Winer et al., 2018 for different findings). Other neuromelanin and melanin containing structures that show elevated FTP binding include pituitary, retinal pigment epithelial cells, leptomeninges, and malignant melanocytes in metastatic melanoma (Lowe et al., 2016; Marquie et al., 2015; Marquie et al., 2017b).

5.1.2. Choroid plexus

High FTP signal in choroid plexus is commonly seen in older individuals and interferes with quantification of hippocampal uptake due to the close proximity of both structures. In choroid plexus, FTP signal has been shown to co-localize with calcification/mineralization (Lowe et al., 2016). Histology data has further suggested that there might be "on-target" binding in the choroid plexus to tangle-like structures corresponding to Biondi "ring" tangles (Ikonomovic et al., 2004). Moreover, melanocyte FTP binding might partially account for high choroid plexus signal (Marquie et al., 2015; Marquie et al., 2017c) as proposed by race differences seen between Black/African American and white participants from the Harvard Aging Brain Study (HABS) (Lee et al., 2018).

PVC approaches that include choroid plexus (Baker et al., 2017b; Wolters et al., 2018) as region of interest can help to reduce spill-in effects of choroid plexus signal to hippocampal signal (Lee et al., 2018; Maass et al., 2017; Maass et al., 2018; Schöll et al., 2016).

5.1.3. MAO

In vitro data (Vermeiren et al., 2018) showed that FTP binds to MAO-A and B at a similarly high affinity as it binds to tau fibrils in brain homogenates. MAO-B is a protein highly expressed in all brain regions and increases with age (*e.g.* Fowler et al., 1997). Hansen and colleagues (Hansen et al., 2018), however, did not observe significant differences

in vivo between FTP scans of non-demented PD patients with and without MAO-B inhibitors, suggesting that FTP does not bind significantly to MAO-B *in vivo*.

Increased FTP signal is further seen in blood vessels, hemorrhages and infarcts, and suggests binding to blood components (Lockhart et al., 2017a; Lowe et al., 2016; Marquie et al., 2015).

5.2. Other tau PET ligands

Similar off-target binding profiles as seen for FTP have been described for [11C]PBB3 and [^{18}F]THK compounds with off-target binding in choroid plexus, basal ganglia, substantia nigra and meninges (Betthauser et al., 2017b; Chiotis et al., 2018; Lemoine et al., 2017).

For [^{18}F]THK5351, strong binding to MAO-B has been demonstrated *in vivo* and *ex vivo* (Harada et al., 2018; Ng et al., 2017b). In particular, application of the MAO-B inhibitor selegiline in eight patients reduced regional SUVRs by > 50% in the thalamus and basal ganglia, and > 40% in cerebellar cortex, preventing accurate quantification of tau levels by means of this tracer (Ng et al., 2017b).

Second-generation tau tracers (see above) seem to be hampered less by off-target binding (see also Fig. 2), however, most of these results have to be replicated in larger samples *in vivo*. For instance, preclinical evaluation of three novel Roche compounds ([^{18}F]RO6958948, [11C]RO6931643 and [11C]RO6924963) suggests lack of any significant off-target binding *in vitro* demonstrated by autoradiography and displacement studies (Honer et al., 2018). *In vivo* imaging with [^{18}F]MK6240 in a sample of patients and OA revealed off-target binding to ethmoid sinus, clivus, meninges, substantia nigra, but not the basal ganglia or choroid plexus (Betthauser et al., 2018; Pascoal et al., 2018). Although the lack of off-target binding to choroid plexus is a major advance allowing quantification of hippocampal signal, ethmoid sinus uptake that spills into the orbitofrontal cortex and meningeal uptake affecting various cortical regions does still limit quantification in these areas (see Fig. 2). Defluorination of MK-6240 yields a low bone signal (Lohith et al., 2018) at late scanning time points that does likely not affect the quantification of cortical signal. It has been speculated that tracer accumulation around the skull might derive from a non-brain penetrant circulating metabolite. Considering extracortical hotspots in PVC approaches might thus be useful for all current tau PET tracers (Baker et al., 2017b).

6. Tau PET findings in other tauopathies

Autoradiography studies in *post mortem* tissue have so far found only weak to moderate binding of existing tau PET ligands to pure 3R- or 4R tau pathology, suggesting limited usefulness in tauopathies such as PSP, CBD, PiD, diseases within the tau-associated fronto-temporal dementia spectrum (FTDP-17), or neurodegenerative disorders associated predominantly with alpha-synuclein or TDP-43 pathology (Josephs et al., 2016; Lowe et al., 2016; Marquie et al., 2017a; Marquie et al., 2015; Sander et al., 2016). One study reported that *post mortem* tau neuropathology correlated with regional hypometabolism but not *ante mortem* FTP uptake in a case of PSP (Smith et al., 2017b). Nevertheless, several studies have investigated *in vivo* tau PET ligand uptake in non-AD tauopathies, albeit generally in small samples.

Increased subcortical [^{18}F]FTP and [^{18}F]THK5351 uptake was found in PSP patients, mainly in midbrain structures and the basal ganglia (Cho et al., 2017; Ishiki et al., 2017; Smith et al., 2017a; Whitwell et al., 2018a). Clinical relevance and interpretation of these findings might be compromised by age-related and off-target ligand binding in these areas. Interestingly, one study reported an association between higher FTP uptake impairment of functional connectivity in PSP (Cope et al., 2018).

In vivo data from CBS (corticobasal syndrome) patients proposed that FTP PET might be useful for distinguishing *e.g.* CBD pathology from AD or PSP (Josephs et al., 2016; Smith et al., 2017c). Weakly increased uptake was demonstrated in subcortical structures, the motor cortex in the hemisphere contralateral brain to the most affected body side, and white matter tracts corresponding to the cortoco-spinal tract (Smith et al., 2017c). However, grey matter atrophy was more pronounced and not associated with FTP uptake in these patients.

Finally, slightly elevated cortical tau PET uptake has been observed in Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) (Smith et al., 2018) while substantia nigra signal was decreased in Parkinson's disease (PD) (Cho et al., 2017; Coakeley et al., 2018; Smith et al., 2018). In PDD patients, cognitive impairment was correlated with increased tau burden. Another study reported no difference in cortical FTP uptake between CU elderly, patients with PD-MCI and PD without cognitive impairment (Winer et al., 2018).

Further *in vitro* and *in vivo* studies are needed, especially for second-generation tau ligands, to inform the use of tau PET in non-AD neurodegenerative disorders.

7. Concordance between imaging and fluid biomarkers for tau

To our knowledge, only six studies have simultaneously tested CSF tau biomarkers and tau PET imaging (using data from four different cohorts). Some studies have largely focused on CU individuals (Brier et al., 2016; Chhatwal et al., 2016; Gordon et al., 2016), while others have focused more on symptomatic stages of AD (La Joie et al., 2018; Mattsson et al., 2017b; Mattsson et al., 2018b), or other neurodegenerative diseases (La Joie et al., 2018). All these studies used FTP PET. Chhatwal et al. (Chhatwal et al., 2016) tested 31 CU persons from HABS, with CSF biomarkers analyzed by the AlzBio3 assays, and FTP quantified in predefined ROIs. Correlations between CSF biomarkers and FTP were strongest for CSF P-tau, and were significant in total cortex, several temporal ROIs and a parietal ROI (the strongest correlation was seen in inferior temporal cortex). Both CSF T-tau and P-tau were significantly correlated with FTP in entorhinal, parahippocampal, middle temporal, and inferior temporal cortex.

Brier et al. (Brier et al., 2016) tested 31 CU and 5 impaired persons (two CDR 0.5 and three CDR > 0.5) from a St Louis cohort, with CSF biomarkers analyzed by INNOTEST assays. The mean grey matter FTP correlated with greater CSF T-tau (but not significantly with P-tau). Brier et al. used an elastic net procedure to define regional PET "topographies". The strongest contributions to prediction of CSF T-tau came from cuneus, entorhinal cortex, transverse temporal sulcus, and (with a negative coefficient) hippocampus. The authors found similar topographies for P-tau. In another study from the St Louis cohort, Gordon et al. (Gordon et al., 2016), studied 41 CU (15 of these were Aβ + defined by [11C]PiB or [^{18}F]FTP PET imaging) and 11 impaired persons (seven CDR 0.5, four CDR > 0.5; 10 of these were Aβ+). In the entire cohort, there were significant relationships for all CSF biomarkers and FTP, but when the correlations were restricted to CU, CSF T-tau and P-tau were no longer associated with FTP (but reduced CSF Aβ42 was associated with greater FTP in both the whole cohort and in CU).

In the Swedish BioFINDER cohort, Mattsson et al. tested 30 CU (15 of these were Aβ + defined by CSF Aβ42), 14 prodromal AD (Aβ + MCI) and 39 AD dementia (all Aβ+) patients, with CSF biomarkers analyzed by INNOTEST assays. CSF T-tau and P-tau were moderately associated with retention of FTP, and associations were mainly seen in the dementia group (Mattsson et al., 2017b). Voxelwise analyses (adjusted for diagnostic group) showed widespread associations in frontal, temporal and parietal regions between the CSF biomarkers and FTP, with more prominent associations for T-tau than P-tau. CSF tau biomarkers were increased in preclinical AD, while FTP was more strongly increased in symptomatic stages of the disease. In line with this, FTP but not CSF T-tau or P-tau, was strongly associated with atrophy and results on cognitive tests, (even when adjusting for diagnostic group). When using dichotomous classifications, regional FTP and CSF tau measures were most often concordant, especially in

dementia patients. Another paper on the same cohort presented diagnostic accuracies for the different biomarkers (Mattsson et al., 2018b). The diagnostic accuracies for prodromal AD *versus* CU were similar for CSF tau biomarkers (both T-tau, AUC 0.86; and P-tau, AUC 0.94) and FTP (using a temporal lobe composite, AUC 0.92), while FTP had superior accuracy for AD dementia *versus* CU (AUC 1.00; T-tau, AUC 0.88; P-tau, AUC 0.89).

In a study on a UCSF cohort, La Joie et al. (La Joie et al., 2018) tested 28 AD patients (3 with prodromal AD and 25 with AD dementia) and 25 non-AD neurodegenerative patients. CSF biomarkers were analyzed by AlzBio3. Cortical FTP and P-tau both had excellent discrimination for Aβ-positive AD *versus* non-AD conditions (AUC 0.92–0.94), with high classification agreement (83%). When restricted to Aβ-positive patients with AD, FTP correlated modestly with both P-tau and T-tau. Regionally, FTP correlated with CSF P-tau in temporoparietal cortices and with T-tau in medial prefrontal regions. Within AD, MMSE scores were associated with FTP, but not CSF biomarkers.

In summary, these six studies found that CSF tau measures were moderately correlated with FTP, with strongest correlations in symptomatic stages of AD, and weaker or non-significant correlations in CU. CSF T-tau and P-tau were similarly correlated to FTP in CU and AD (Brier et al., 2016; Chhatwal et al., 2016; Gordon et al., 2016; Mattsson et al., 2017b; Mattsson et al., 2018b), but when non-AD neurodegenerative patients were included, P-tau rather than T-tau provided more FTP-like information (La Joie et al., 2018). This suggests that in non-AD conditions, these CSF biomarkers may be differentially regulated, perhaps because T-tau (but not P-tau) secretion is increased in a non-disease specific fashion due to neuronal injury. Another common finding was that cognitive measures (La Joie et al., 2018; Mattsson et al., 2017b) and atrophy (Mattsson et al., 2017b) were related to FTP but not to CSF tau measures (when adjusting for clinical diagnosis of AD, otherwise CSF tau measures are strongly correlated to both atrophy and cognition, as shown many times before). One possible interpretation is that CSF tau biomarkers reach a plateau during the prodromal stage of the disease, when the FTP uptake still continues to increase. One study (Mattsson et al., 2017b) suggested that changes in CSF tau measures may be detectable before changes in the FTP signal. Notably, the overall results were quite similar between the different studies, despite the use of different methods for FTP quantification, different CSF assays and different statistical procedures.

The different dynamics of imaging and fluid markers of tau pathology at different stages of AD may have implications for their use in clinical trials and practice. Taken together, the results suggest that CSF tau biomarkers have properties that make them suitable for the identification of “disease state”, *i.e.* the presence of a pathological process associated with AD. Their relative lack of dynamic changes later during the disease and their poor correlation with measures of cognition and atrophy at the symptomatic stages of AD make them less suitable as markers of “disease stage”. In contrast, tau PET imaging may lack sensitivity very early in the disease, but the continuous accumulation of signal, and the strong correlations with cognition and atrophy make tau PET imaging a powerful marker of “disease stage” in AD.

8. Conclusions and future perspectives

The availability of techniques to measure and map Aβ transformed clinical and translational research on aging and dementia many years ago. Now, within the past several years, methods of measuring tau pathology in the brain, following the earlier development of tau measures in CSF, have furthered this transformation. The clearest example of this is the proposal of a new framework for biomarker applications in which the conjoint presence of Aβ and tau pathology, regardless of the presence or nature of symptoms, establishes an individual as having AD (Jack Jr. et al., 2018a). While this approach is not proposed for clinical use, the research definition of AD as a biological entity, as opposed to a clinical syndrome, will further mechanistic studies and therapeutic developments. These advances in both methods and concepts have of course not yet lead to an effective treatment for AD. However, the availability of both Aβ and tau biomarkers derived from both bodily fluid analyses and brain imaging is changing the landscape of human AD research.

Measurement of tau in CSF and brain are relatively recent developments, and longitudinal data, especially for tau PET, are only just being acquired. Longitudinal studies of both Aβ and tau biomarkers, paired with measurements of neurodegeneration and cognition, will be necessary to establish temporal relationships between molecular events. These studies will take time to accrue the necessary samples, but should pay off in important scientific knowledge. Some of the most basic questions in the field involve the relationships between Aβ and tau, and how or whether one protein leads to aggregation of the other. Similarly, the time course of aggregation, spread, and pathological effects needs to be elucidated. Large, longitudinal cohort studies using multiple biomarkers will be crucial in answering these basic questions.

Use of biomarkers in the development of therapeutic trials is also important and growing. We have already witnessed new approaches based on measurement of Aβ; clinical trials using Aβ-lowering therapies now require measurement of Aβ for enrollment and usually measure treatment effects on biomarkers to track target engagement. Tau measurements are sure to serve similar roles in the development of anti-tau therapeutics. Furthermore, tau may be useful in providing a measure of disease progression even for therapeutic approaches that do not target tau directly. That is, therapies may be targeted to a “sweet spot” such that symptoms are at a stage where amelioration is possible, but treatment is not yet futile. Tau measurements may help to identify this timing.

There are indeed many major technical and methodological challenges yet to overcome. For PET, while Aβ imaging agents seem to be largely comparable and methods for their quantitative comparison have been proposed (*i.e.*, the CENTILOID approach (Klunk et al., 2015)), it is not clear that this is the case for tau ligands. Some tau ligands have not yet seen wide application, and methods for quantitation even for a single tracer are not uniformly established. Comparability across methods and tracers will require attention, as will the assessment of comparability between fluid- and imaging-derived biomarkers.

Finally, it is increasingly recognized that Aβ and tau biomarkers, while the most ubiquitously expressed pathologically aggregated proteins, are not the only ones involved in neurodegenerative diseases. Methods for measurement of alpha-synuclein and TDP-43 will likely be important in establishing an even more complete picture of the brain in aging and dementia.

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References

Adams, J.N., Lockhart, S.N., Li, L., Jagust, W.J., 2018. Relationships between tau and glucose metabolism reflect Alzheimer's disease pathology in cognitively normal older adults. Cereb. Cortex(Apr 18). https://doi.org/10.1093/cercor/bhy078.

Aschenbrenner, A.J., Gordon, B.A., Benzinger, T.L.S., Morris, J.C., Hassenstab, J.J., 2018. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. Neurology 91 (9), e859–e866 (Aug 28).

Ashton, N.J., Ide, M., Schöll, M., Blennow, K., Lovestone, S., Hye, A., Zetterberg, H., 2018a. No association of salivary total tau concentration with Alzheimer's disease. Neurobiol. Aging 70, 125–127.

Ashton, N.J., Schöll, M., Heurling, K., Gkanatsiou, E., Portelius, E., Hoglund, K., Brinkmalm, G., Hye, A., Blennow, K., Zetterberg, H., 2018b. Update on biomarkers for amyloid pathology in Alzheimer's disease. Biomark. Med 12, 799–812.

Baker, S.L., Lockhart, S.N., Price, J.C., He, M., Huesman, R.H., Schonhaut, D., Faria, J., Rabinovici, G., Jagust, W.J., 2017a. Reference tissue-based kinetic evaluation of ^{18}F-AV-1451 for tau imaging. J. Nucl. Med. 58, 332–338.

Baker, S.L., Maass, A., Jagust, W.J., 2017b. Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data. Data Brief 15, 648–657.

Barret, O., Alagille, D., Sanabria, S., Comley, R.A., Weimer, R.M., Borroni, E., Mintun, M., Seneca, N., Papin, C., Morley, T., Marek, K., Seibyl, J.P., Tamagnan, G.D., Jennings, D., 2016. Kinetic modeling of the tau PET tracer ^{18}F-AV-1451 in human healthy volunteers and Alzheimer's Disease subjects. J. Nucl. Med. 58, 1124–1131.

Barthelemy, N.R., Gabelle, A., Hirtz, C., Fenaille, F., Sergeant, N., Schraen-Maschke, S., Vialaret, J., Buee, L., Junot, C., Becher, F., Lehmann, S., 2016. Differential mass spectrometry profiles of tau protein in the cerebrospinal fluid of patients with Alzheimer's disease, progressive supranuclear palsy, and dementia with Lewy bodies. J. Alzheimers Dis. 51, 1033–1043.

Bejanin, A., Schonhaut, D.R., La Joie, R., Kramer, J.H., Baker, S.L., Sosa, N., Ayakta, N., Cantwell, A., Janabi, M., Lauriola, M., O'Neil, J.P., Gorno-Tempini, M.L., Miller, Z.A., Rosen, H.J., Miller, B.L., Jagust, W.J., Rabinovici, G.D., 2017. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain 140, 3286–3300.

Bennett, D.A., Schneider, J.A., Arvanitakis, Z., Kelly, J.F., Aggarwal, N.T., Shah, R.C., Wilson, R.S., 2006. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 66, 1837–1844.

Betthauser, T., Lao, P.J., Murali, D., Barnhart, T.E., Furumoto, S., Okamura, N., Stone, C.K., Johnson, S.C., Christian, B.T., 2017a. In vivo comparison of tau radioligands ^{18}F-THK-5351 and ^{18}F-THK-5317. J. Nucl. Med. 58, 996–1002.

Betthauser, T.J., Cody, K.A., Zammit, M.D., Murali, D., Converse, A.K., Barnhart, T.E., Stone, C.K., Rowley, H.A., Johnson, S.C., Christian, B.T., 2018. In vivo characterization and quantification of neurofibrillary tau PET radioligand [(18)F]MK-6240 in humans from Alzheimer's disease dementia to young controls. J. Nucl. Med. https://doi.org/10.2967/jnumed.118.209650. pii: jnumed.118.209650. [Epub ahead of print].

Betthauser, T.J., Lao, P.J., Murali, D., Barnhart, T.E., Furumoto, S., Okamura, N., Stone, C.K., Johnson, S.C., Christian, B.T., 2017b. In vivo comparison of tau radioligands (18)F-THK-5351 and (18)F-THK-5317. J. Nucl. Med. 58, 996–1002.

Bischof, G.N., Endepols, H., van Eimeren, T., Drzezga, A., 2017. Tau-imaging in neurodegeneration. Methods 130, 114–123.

Bischof, G.N., Jessen, F., Fliessbach, K., Dronse, J., Hammes, J., Neumaier, B., Onur, O., Fink, G.R., Kukolja, J., Drzezga, A., van Eimeren, T., Alzheimer's Disease Neuroimaging, I., 2016. Impact of tau and amyloid burden on glucose metabolism in Alzheimer's disease. Ann. Clin. Transl. Neurol. 3, 934–939.

Blennow, K., Hampel, H., 2003. CSF markers for incipient Alzheimer's disease. Lancet Neurol. 2, 605–613.

Blennow, K., Wallin, A., Agren, H., Spenger, C., Siegfried, J., Vanmechelen, E., 1995. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol. Chem. Neuropathol. 26, 231–245.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.

Braak, H., Thal, D.R., Ghebremedhin, E., Del Tredici, K., 2011. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J. Neuropathol. Exp. Neurol. 70, 960–969.

Brier, M.R., Gordon, B., Friedrichsen, K., McCarthy, J., Stern, A., Christensen, J., Owen, C., Aldea, P., Su, Y., Hassenstab, J., Cairns, N.J., Holtzman, D.M., Fagan, A.M., Morris, J.C., Benzinger, T.L., Ances, B.M., 2016. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. Sci. Transl. Med. 8, 338–366.

Buchhave, P., Minthon, L., Zetterberg, H., Wallin, A.K., Blennow, K., Hansson, O., 2012. Cerebrospinal fluid levels of beta-amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch. Gen. Psychiatry 69, 98–106.

Buckley, R.F., Hanseeuw, B., Schultz, A.P., Vannini, P., Aghjayan, S.L., Properzi, M.J., Jackson, J.D., Mormino, E.C., Rentz, D.M., Sperling, R.A., Johnson, K.A., Amariglio, R.E., 2017. Region-specific association of subjective cognitive decline with tauopathy independent of global beta-amyloid burden. JAMA Neurol. 74, 1455–1463.

Buckner, R.L., Snyder, A.Z., Shannon, B.J., Larossa, G., Sachs, R., Fotenos, A.F., Sheline, Y.I., Klunk, W.E., Mathis, C.A., Morris, J.C., Mintun, M.A., 2005. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J. Neurosci. 25, 7709–7717.

Buerger, K., Ewers, M., Pirttila, T., Zinkowski, R., Alafuzoff, I., Teipel, S.J., Debernardis, J., Kerkman, D., McCulloch, C., Soininen, H., Hampel, H., 2006. CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. Brain 129, 3035–3041.

Chhatwal, J.P., Schultz, A.P., Marshall, G.A., Boot, B., Gomez-Isla, T., Dumurgier, J., LaPoint, M., Scherzer, C., Roe, A.D., Hyman, B.T., Sperling, R.A., Johnson, K.A., 2016. Temporal T807 binding correlates with CSF tau and phospho-tau in normal elderly. Neurology 87, 920–926.

Chiaravalloti, A., Barbagallo, G., Ricci, M., Martorana, A., Ursini, F., Sannino, P., Karalis, G., Schillaci, O., 2018. Brain metabolic correlates of CSF Tau protein in a large cohort of Alzheimer's disease patients: A CSF and FDG PET study. Brain Res. 1678, 116–122.

Chien, D.T., Bahri, S., Szardenings, A.K., Walsh, J.C., Mu, F., Su, M.Y., Shankle, W.R., Elizarov, A., Kolb, H.C., 2013. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. J. Alzheimers Dis. 34, 457–468.

Chiotis, K., Saint-Aubert, L., Savitcheva, I., Jelic, V., Andersen, P., Jonasson, M., Eriksson, J., Lubberink, M., Almkvist, O., Wall, A., Antoni, G., Nordberg, A., 2016. Imaging in-vivo tau pathology in Alzheimer's disease with THK5317 PET in a multimodal paradigm. Eur. J. Nucl. Med. Mol. Imaging 43, 1686–1699.

Chiotis, K., Stenkrona, P., Almkvist, O., Stepanov, V., Ferreira, D., Arakawa, R., Takano, A., Westman, E., Varrone, A., Okamura, N., Shimada, H., Higuchi, M., Halldin, C., Nordberg, A., 2018. Dual tracer tau PET imaging reveals different molecular targets for (11)C-THK5351 and (11)C-PBB3 in the Alzheimer brain. Eur. J. Nucl. Med. Mol. Imaging 45, 1605–1617.

Cho, H., Choi, J.Y., Hwang, M.S., Kim, Y.J., Lee, H.M., Lee, H.S., Lee, J.H., Ryu, Y.H., Lee, M.S., Lyoo, C.H., 2016a. In vivo cortical spreading pattern of tau and amyloid in the Alzheimer disease spectrum. Ann. Neurol. 80, 247–258.

Cho, H., Choi, J.Y., Hwang, M.S., Lee, J.H., Kim, Y.J., Lee, H.M., Lyoo, C.H., Ryu, Y.H., Lee, M.S., 2016b. Tau PET in Alzheimer disease and mild cognitive impairment. Neurology 87, 375–383.

Cho, H., Choi, J.Y., Hwang, M.S., Lee, S.H., Ryu, Y.H., Lee, M.S., Lyoo, C.H., 2017. Subcortical (18) F-AV-1451 binding patterns in progressive supranuclear palsy. Mov. Disord. 32, 134–140.

Choi, J.Y., Cho, H., Ahn, S.J., Lee, J.H., Ryu, Y.H., Lee, M.S., Lyoo, C.H., 2018. Off-target (18)F-AV-1451 binding in the basal ganglia correlates with age-related Iron accumulation. J. Nucl. Med. 59, 117–120.

Coakeley, S., Cho, S.S., Koshimori, Y., Rusjan, P., Ghadery, C., Kim, J., Lang, A.E., Houle, S., Strafella, A.P., 2018. [^{18}F]AV-1451 binding to neuromelanin in the substantia nigra in PD and PSP. Brain Struct. Funct. 223 (2), 589–595. https://doi.org/10.1007/s00429-017-1507-y. [Epub 2017 Sep 7].

Cope, T.E., Rittman, T., Borchert, R.J., Jones, P.S., Vatansever, D., Allinson, K., Passamonti, L., Vazquez Rodriguez, P., Bevan-Jones, W.R., O'Brien, J.T., Rowe, J.B., 2018. Tau burden and the functional connectome in Alzheimer's disease and progressive supranuclear palsy. Brain 141, 550–567.

Cummings, J., Lee, G., Ritter, A., Zhong, K., 2018. Alzheimer's disease drug development pipeline: 2018. Alzheimers Dement. (NY) 4, 195–214.

Das, S.R., Xie, L., Wisse, L.E.M., Ittyerah, R., Tustison, N.J., Dickerson, B.C., Yushkevich, P.A., Wolk, D.A., Alzheimer's Disease Neuroimaging, I., 2018. Longitudinal and cross-sectional structural magnetic resonance imaging correlates of AV-1451 uptake. Neurobiol. Aging 66, 49–58.

Devous Sr., M.D., Joshi, A.D., Navitsky, M., Southekal, S., Pontecorvo, M.J., Shen, H., Lu, M., Shankle, W.R., Seibyl, J.P., Marek, K., Mintun, M.A., 2018. Test-retest reproducibility for the tau PET imaging agent Flortaucipir F 18. J. Nucl. Med. 59, 937–943.

Dickson, D.W., Ahmed, Z., Algom, A.A., Tsuboi, Y., Josephs, K.A., 2010. Neuropathology of variants of progressive supranuclear palsy. Curr. Opin. Neurol. 23, 394–400.

Dickson, D.W., Kouri, N., Murray, M.E., Josephs, K.A., 2011. Neuropathology of frontotemporal lobar degeneration-tau (FTLD-tau). J. Mol. Neurosci. 45, 384–389.

Donohue, M.C., Sperling, R.A., Petersen, R., Sun, C.K., Weiner, M.W., Aisen, P.S., Alzheimer's Disease Neuroimaging, I., 2017. Association between elevated brain amyloid and subsequent cognitive decline among cognitively Normal persons. JAMA 317, 2305–2316.

Dubois, B., Epelbaum, S., Nyasse, F., Bakardjian, H., Gagliardi, G., Uspenskaya, O., Houot, M., Lista, S., Cacciamani, F., Potier, M.C., Bertrand, A., Lamari, F., Benali, H., Mangin, J.F., Colliot, O., Genthon, R., Habert, M.O., Hampel, H., Group IN-ps, 2018. Cognitive and neuroimaging features and brain beta-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study. Lancet Neurol. 17, 335–346.

Dubois, B., Feldman, H.H., Jacova, C., Hampel, H., Molinuevo, J.L., Blennow, K., Dekosky, S.T., Gauthier, S., Selkoe, D., Bateman, R., Cappa, S., Crutch, S., Engelborghs, S., Frisoni, G.B., Fox, N.C., Galasko, D., Habert, M.O., Jicha, G.A., Nordberg, A., Pasquier, F., et al., 2014. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 13, 614–629.

Engelborghs, S., Sleegers, K., Cras, P., Brouwers, N., Serneels, S., De Leenheir, E., Martin, J.J., Vanmechelen, E., Van Broeckhoven, C., De Deyn, P.P., 2007. No association of CSF biomarkers with APOEepsilon4, plaque and tangle burden in definite Alzheimer's disease. Brain 130, 2320–2326.

Fiandaca, M.S., Kapogiannis, D., Mapstone, M., Boxer, A., Eitan, E., Schwartz, J.B., Abner, E.L., Petersen, R.C., Federoff, H.J., Miller, B.L., Goetzl, E.J., 2015. Identification of preclinical Alzheimer's disease by a profile of pathogenic proteins in neurally derived blood exosomes: a case-control study. Alzheimers Dement. 11, 600–607 (e1).

Fitzpatrick, A.W.P., Falcon, B., He, S., Murzin, A.G., Murshudov, G., Garringer, H.J., Crowther, R.A., Ghetti, B., Goedert, M., Scheres, S.H.W., 2017. Cryo-EM structures of tau filaments from Alzheimer's disease. Nature 547, 185–190.

Fontaine, S.N., Sabbagh, J.J., Baker, J., Martinez-Licha, C.R., Darling, A., Dickey, C.A., 2015. Cellular factors modulating the mechanism of tau protein aggregation. Cell. Mol. Life Sci. 72, 1863–1879.

Fowler, J.S., Volkow, N.D., Wang, G.J., Logan, J., Pappas, N., Shea, C., MacGregor, R., 1997. Age-related increases in brain monoamine oxidase B in living healthy human subjects. Neurobiol. Aging 18, 431–435.

Gobbi, L.C., Knust, H., Korner, M., Honer, M., Czech, C., Belli, S., Muri, D., Edelmann, M.R., Hartung, T., Erbsmehl, I., Grall-Ulsemer, S., Koblet, A., Rueher, M., Steiner, S.,

Ravert, H.T., Mathews, W.B., Holt, D.P., Kuwabara, H., Valentine, H., Dannals, R.F., et al., 2017. Identification of three novel radiotracers for imaging aggregated tau in Alzheimer's disease with positron emission tomography. J. Med. Chem. 60, 7350–7370.

Goedert, M., Spillantini, M.G., Jakes, R., Rutherford, D., Crowther, R.A., 1989. Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. Neuron 3, 519–526.

Golla, S.S.V., Timmers, T., Ossenkoppele, R., Groot, C., Verfaillie, S., Scheltens, P., van der Flier, W.M., Schwarte, L., Mintun, M.A., Devous, M., Schuit, R.C., Windhorst, A.D., Lammertsma, A.A., Boellaard, R., van Berckel, B.N.M., Yaqub, M., 2017. Quantification of tau load using [^{18}F]AV1451 PET. Mol. Imaging Biol. 1–9.

Gordon, B.A., Friedrichsen, K., Brier, M., Blazey, T., Su, Y., Christensen, J., Aldea, P., McConathy, J., Holtzman, D.M., Cairns, N.J., Morris, J.C., Fagan, A.M., Ances, B.M., Benzinger, T.L., 2016. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. Brain 139, 2249–2260.

Gordon, B.A., McCullough, A., Mishra, S., Blazey, T.M., Su, Y., Christensen, J., Dincer, A., Jackson, K., Hornbeck, R.C., Morris, J.C., Ances, B.M., Benzinger, T.L.S., 2018. Cross-sectional and longitudinal atrophy is preferentially associated with tau rather than amyloid beta positron emission tomography pathology. Alzheimers Dement. (Amst) 10, 245–252.

Grothe, M.J., Teipel, S.J., Alzheimer's Disease Neuroimaging, I., 2016. Spatial patterns of atrophy, hypometabolism, and amyloid deposition in Alzheimer's disease correspond to dissociable functional brain networks. Hum. Brain Mapp. 37, 35–53.

Grundke-Iqbal, I., Iqbal, K., Quinlan, M., Tung, Y.C., Zaidi, M.S., Wisniewski, H.M., 1986a. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. J. Biol. Chem. 261, 6084–6089.

Grundke-Iqbal, I., Iqbal, K., Tung, Y.C., Quinlan, M., Wisniewski, H.M., Binder, L.I., 1986b. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc. Natl. Acad. Sci. U. S. A. 83, 4913–4917.

Hahn, A., Schain, M., Erlandsson, M., Sjölin, P., James, G.M., Strandberg, O.T., Hägerström, D., Lanzenberger, R., Jögi, J., Olsson, T.G., Smith, R., Hansson, O., 2017. Modeling strategies for quantification of in vivo ^{18}F-AV-1451 binding in patients with tau pathology. J. Nucl. Med. 58, 623–631.

Hall, S., Öhrfelt, A., Constantinescu, R., et al., 2012. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders. Arch. Neurol. 69, 1445–1452.

Hampel, H., Buerger, K., Zinkowski, R., Teipel, S.J., Goernitz, A., Andreasen, N., Sjoegren, M., Debernardis, J., Kerkman, D., Ishiguro, K., Ohno, H., Vanmechelen, E., Vanderstichele, H., McCulloch, C., Moller, H.J., Davies, P., Blennow, K., 2004. Measurement of phosphorylated tau epitopes in the differential diagnosis of Alzheimer disease: a comparative cerebrospinal fluid study. Arch. Gen. Psychiatry 61, 95–102.

Hanseeuw, B.J., Betensky, R.A., Schultz, A.P., Papp, K.V., Mormino, E.C., Sepulcre, J., Bark, J.S., Cosio, D.M., LaPoint, M., Chhatwal, J.P., Rentz, D.M., Sperling, R.A., Johnson, K.A., 2017. Fluorodeoxyglucose metabolism associated with tau-amyloid interaction predicts memory decline. Ann. Neurol. 81, 583–596.

Hansen, A.K., Brooks, D.J., Borghammer, P., 2018. MAO-B inhibitors do not block in vivo flortaucipir([(18)F]-AV-1451) binding. Mol. Imaging Biol. 20, 356–360.

Hansen, A.K., Knudsen, K., Lillethorup, T.P., Landau, A.M., Parbo, P., Fedorova, T., Audrain, H., Bender, D., Ostergaard, K., Brooks, D.J., Borghammer, P., 2016. In vivo imaging of neuromelanin in Parkinson's disease using ^{18}F-AV-1451 PET. Brain 139, 2039–2049.

Hansson, O., Grothe, M.J., Strandberg TO, Ohlsson, T., Hagerstrom, D., Jogi, J., Smith, R., Schöll, M., 2017. Tau pathology distribution in Alzheimer's disease corresponds differentially to cognition-relevant functional brain networks. Front. Neurosci. 11, 167.

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., et al., 2018. Correlations of (18)F-THK5351 PET with postmortem burden of tau and astrogliosis in Alzheimer Disease. J. Nucl. Med. 59, 671–674.

Hashimoto, H., Kawamura, K., Igarashi, N., Takei, M., Fujishiro, T., Aihara, Y., Shiomi, S., Muto, M., Ito, T., Furutsuka, K., 2014. Radiosynthesis, photoisomerization, biodistribution, and metabolite analysis of 11C-PBB3 as a clinically useful PET probe for imaging of tau pathology. J. Nucl. Med. 55.

Hashimoto, H., Kawamura, K., Takei, M., Igarashi, N., Fujishiro, T., Shiomi, S., Watanabe, R., Muto, M., Furutsuka, K., Ito, T., Yamasaki, T., Yui, J., Nemoto, K., Kimura, Y., Higuchi, M., Zhang, M.-R., 2015. Identification of a major radiometabolite of [11C] PBB3. Nucl. Med. Biol. 42, 905–910.

Hedden, T., Oh, H., Younger, A.P., Patel, T.A., 2013. Meta-analysis of amyloid-cognition relations in cognitively normal older adults. Neurology 80, 1341–1348.

Hesse, C., Rosengren, L., Andreasen, N., Davidsson, P., Vanderstichele, H., Vanmechelen, E., Blennow, K., 2001. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neurosci. Lett. 297, 187–190.

Heurling, K., Smith, R., Strandberg, O.T., Schain, M., Ohlsson, T., Hansson, O., Scholl, M., 2018. Regional times to equilibria and their impact on semi-quantification of [(18)F]AV-1451 uptake. J. Cereb. Blood Flow Metab., 271678X18791430. https://doi.org/10.1177/0271678X18791430. [Epub ahead of print].

Hoenig, M.C., Bischof, G.N., Seemiller, J., Hammes, J., Kukolja, J., Onur, O.A., Jessen, F., Fliessbach, K., Neumaier, B., Fink, G.R., van Eimeren, T., Drzezga, A., 2018. Networks of tau distribution in Alzheimer's disease. Brain 141, 568–581.

Honer, M., Gobbi, L., Knust, H., Kuwabara, H., Muri, D., Koerner, M., Valentine, H., Dannals, R.F., Wong, D.F., Borroni, E., 2018. Preclinical evaluation of (18)F-RO6958948, (11)C-RO6931643, and (11)C-RO6924963 as novel PET radiotracers for imaging tau aggregates in Alzheimer disease. J. Nucl. Med. 59, 675–681.

Hostetler, E.D., Walji, A.M., Zeng, Z., Miller, P., Bennacef, I., Salinas, C., Connolly, B., Gantert, L., Haley, H., Holahan, M., Purcell, M., Riffel, K., Lohith, T.G., Coleman, P., Soriano, A., Ogawa, A., Xu, S., Zhang, X., Joshi, E., Della Rocca, J., et al., 2016. Preclinical characterization of ^{18}F-MK-6240, a promising PET tracer for in vivo quantification of human neurofibrillary tangles. J. Nucl. Med. 57, 1599–1606.

Hu, Y.Y., He, S.S., Wang, X., Duan, Q.H., Grundke-Iqbal, I., Iqbal, K., Wang, J., 2002. Levels of nonphosphorylated and phosphorylated tau in cerebrospinal fluid of Alzheimer's disease patients: an ultrasensitive bienzyme-substrate-recycle enzyme-linked immunosorbent assay. Am. J. Pathol. 160, 1269–1278.

Hyman, B.T., Phelps, C.H., Beach, T.G., Bigio, E.H., Cairns, N.J., Carrillo, M.C., Dickson, D.W., Duyckaerts, C., Frosch, M.P., Masliah, E., Mirra, S.S., Nelson, P.T., Schneider, J.A., Thal, D.R., Thies, B., Trojanowski, J.Q., Vinters, H.V., Montine, T.J., 2012. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. 8, 1–13.

Iaccarino, L., Tammewar, G., Ayakta, N., Baker, S.L., Bejanin, A., Boxer, A.L., Gorno-Tempini, M.L., Janabi, M., Kramer, J.H., Lazaris, A., Lockhart, S.N., Miller, B.L., Miller, Z.A., O'Neil, J.P., Ossenkoppele, R., Rosen, H.J., Schonhaut, D.R., Jagust, W.J., Rabinovici, G.D., 2018. Local and distant relationships between amyloid, tau and neurodegeneration in Alzheimer's Disease. Neuroimage Clin. 17, 452–464.

Ihara, Y., Nukina, N., Miura, R., Ogawara, M., 1986. Phosphorylated tau protein is integrated into paired helical filaments in Alzheimer's disease. J. Biochem. 99, 1807–1810.

Ikonomovic, M.D., Uryu, K., Abrahamson, E.E., Ciallella, J.R., Trojanowski, J.Q., Lee, V.M., Clark, R.S., Marion, D.W., Wisniewski, S.R., Dekosky, S.T., 2004. Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. Exp. Neurol. 190, 192–203.

Iqbal, K., Liu, F., Gong, C.X., 2016. Tau and neurodegenerative disease: the story so far. Nat. Rev. Neurol. 12, 15–27.

Irwin, D.J., Brettschneider, J., McMillan, C.T., Cooper, F., Olm, C., Arnold, S.E., Van Deerlin, V.M., Seeley, W.W., Miller, B.L., Lee, E.B., Lee, V.M., Grossman, M., Trojanowski, J.Q., 2016. Deep clinical and neuropathological phenotyping of Pick disease. Ann. Neurol. 79, 272–287.

Ishiguro, K., Ohno, H., Arai, H., Yamaguchi, H., Urakami, K., Park, J.M., Sato, K., Kohno, H., Imahori, K., 1999. Phosphorylated tau in human cerebrospinal fluid is a diagnostic marker for Alzheimer's disease. Neurosci. Lett. 270, 91–94.

Ishiki, A., Harada, R., Okamura, N., Tomita, N., Rowe, C.C., Villemagne, V.L., Yanai, K., Kudo, Y., Arai, H., Furumoto, S., Tashiro, M., Furukawa, K., 2017. Tau imaging with [(18) F]THK-5351 in progressive supranuclear palsy. Eur. J. Neurol. 24, 130–136.

Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., et al., 2018a. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 14, 535–562.

Jack Jr., C.R., Wiste, H.J., Schwarz, C.G., Lowe, V.J., Senjem, M.L., Vemuri, P., Weigand, S.D., Therneau, T.M., Knopman, D.S., Gunter, J.L., Jones, D.T., Graff-Radford, J., Kantarci, K., Roberts, R.O., Mielke, M.M., Machulda, M.M., Petersen, R.C., 2018b. Longitudinal tau PET in ageing and Alzheimer's disease. Brain 141 (5), 1517–1528.

Jack Jr., C.R., Wiste, H.J., Weigand, S.D., Therneau, T.M., Lowe, V.J., Knopman, D.S., Gunter, J.L., Senjem, M.L., Jones, D.T., Kantarci, K., Machulda, M.M., Mielke, M.M., Roberts, R.O., Vemuri, P., Reyes, D.A., Petersen, R.C., 2017. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimers Dement. 13, 205–216.

Jacobs, H.L.L., Hedden, T., Schultz, A.P., Sepulcre, J., Perea, R.D., Amariglio, R.E., Papp, K.V., Rentz, D.M., Sperling, R.A., Johnson, K.A., 2018. Structural tract alterations predict down-stream tau accumulation in amyloid positive older individuals. Nat. Neurosci. 21, 424–431.

Jansen, W.J., Ossenkoppele, R., Tijms, B.M., Fagan, A.M., Hansson, O., Klunk, W.E., van der Flier, W.M., Villemagne, V.L., Frisoni, G.B., Fleisher, A.S., Lleo, A., Mintun, M.A., Wallin, A., Engelborghs, S., Na, D.L., Chetelat, G., Molinuevo, J.L., Landau, S.M., Mattsson, N., Kornhuber, J., et al., 2018. Association of cerebral amyloid-beta aggregation with cognitive functioning in persons without dementia. JAMA Psychiat. 75, 84–95.

Johnson, K.A., Schultz, A., Betensky, R.A., Becker, J.A., Sepulcre, J., Rentz, D., Mormino, E., Chhatwal, J., Amariglio, R., Papp, K., Marshall, G., Albers, M., Mauro, S., Pepin, L., Alverio, J., Judge, K., Philiossaint, M., Shoup, T., Yokell, D., Dickerson, B., et al., 2016. Tau positron emission tomographic imaging in aging and early Alzheimer disease. Ann. Neurol. 79, 110–119.

Jonasson, M., Wall, A., Chiotis, K., Saint-Aubert, L., Wilking, H., Sprycha, M., Borg, B., Thibblin, A., Eriksson, J., Sörensen, J., Antoni, G., Nordberg, A., Lubberink, M., 2016. Tracer kinetic analysis of (S)-^{18}F-THK5117 as a PET tracer for assessing tau pathology. J. Nucl. Med. 57, 574–581.

Jones, D.T., Graff-Radford, J., Lowe, V.J., Wiste, H.J., Gunter, J.L., Senjem, M.L., Botha, H., Kantarci, K., Boeve, B.F., Knopman, D.S., Petersen, R.C., Jack Jr., C.R., 2017. Tau, amyloid, and cascading network failure across the Alzheimer's disease spectrum. Cortex 97, 143–159.

Jones, D.T., Knopman, D.S., Gunter, J.L., Graff-Radford, J., Vemuri, P., Boeve, B.F., Petersen, R.C., Weiner, M.W., Jack Jr., C.R., Alzheimer's Disease Neuroimaging, I., 2016. Cascading network failure across the Alzheimer's disease spectrum. Brain 139, 547–562.

Josephs, K.A., Whitwell, J.L., Tacik, P., Duffy, J.R., Senjem, M.L., Tosakulwong, N., Jack, C.R., Lowe, V., Dickson, D.W., Murray, M.E., 2016. [^{18}F]AV-1451 tau-PET uptake does correlate with quantitatively measured 4R-tau burden in autopsy-confirmed corticobasal degeneration. Acta Neuropathol. 132, 931–933.

Khanna, M.R., Kovalevich, J., Lee, V.M., Trojanowski, J.Q., Brunden, K.R., 2016. Therapeutic strategies for the treatment of tauopathies: hopes and challenges. Alzheimers Dement. 12, 1051–1065.

Klunk, W.E., Koeppe, R.A., Price, J.C., Benzinger, T.L., Devous Sr., M.D., Jagust, W.J., Johnson, K.A., Mathis, C.A., Minhas, D., Pontecorvo, M.J., Rowe, C.C., Skovronsky, D.M., Mintun, M.A., 2015. The centiloid project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement. 11 (1–15.e4).

Kohnken, R., Buerger, K., Zinkowski, R., Miller, C., Kerkman, D., Debernardis, J., Shen, J., Moller, H.J., Davies, P., Hampel, H., 2000. Detection of tau phosphorylated at threonine 231 in cerebrospinal fluid of Alzheimer's disease patients. Neurosci. Lett. 287, 187–190.

Kosik, K.S., Joachim, C.L., Selkoe, D.J., 1986. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 83, 4044–4048.

La Joie, R., Bejanin, A., Fagan, A.M., Ayakta, N., Baker, S.L., Bourakova, V., Boxer, A.L., Cha, J., Karydas, A., Jerome, G., Maass, A., Mensing, A., Miller, Z.A., O'Neil, J.P., Pham, J., Rosen, H.J., Tsai, R., Visani, A.V., Miller, B.L., Jagust, W.J., et al., 2018. Associations between [(18)F]AV1451 tau PET and CSF measures of tau pathology in a clinical sample. Neurology 90, e282–e290.

LaPoint, M.R., Chhatwal, J.P., Sepulcre, J., Johnson, K.A., Sperling, R.A., Schultz, A.P., 2017. The association between tau PET and retrospective cortical thinning in clinically normal elderly. NeuroImage 157, 612–622.

Leal, S.L., Lockhart, S.N., Maass, A., Bell, R.K., Jagust, W.J., 2018. Subthreshold amyloid predicts tau deposition in aging. J. Neurosci. 38, 4482–4489.

Lee, C.M., Jacobs, H.I.L., Marquie, M., Becker, J.A., Andrea, N.V., Jin, D.S., Schultz, A.P., Frosch, M.P., Gomez-Isla, T., Sperling, R.A., Johnson, K.A., 2018. ^{18}F-Flortaucipir binding in choroid plexus: related to race and hippocampus signal. J. Alzheimers Dis. 62, 1691–1702.

Lemoine, L., Gillberg, P.G., Svedberg, M., Stepanov, V., Jia, Z., Huang, J., Nag, S., Tian, H., Ghetti, B., Okamura, N., Higuchi, M., Halldin, C., Nordberg, A., 2017. Comparative binding properties of the tau PET tracers THK5117, THK5351, PBB3, and T807 in postmortem Alzheimer brains. Alzheimers Res. Ther. 9, 96.

Lemoine, L., Leuzy, A., Chiotis, K., Rodriguez-Vieitez, E., Nordberg, A., 2018. Tau positron emission tomography imaging in tauopathies: the added hurdle of off-target binding. Alzheimers Dement. (Amst) 10, 232–236.

Lockhart, S.N., Ayakta, N., Winer, J.R., La Joie, R., Rabinovici, G.D., Jagust, W.J., 2017a. Elevated (18)F-AV-1451 PET tracer uptake detected in incidental imaging findings. Neurology 88, 1095–1097.

Lockhart, S.N., Schöll, M., Baker, S.L., Ayakta, N., Swinnerton, K.N., Bell, R.K., Mellinger, T.J., Shah, V.D., O'Neil, J.P., Janabi, M., Jagust, W.J., 2017b. Amyloid and tau PET demonstrate region-specific associations in normal older people. NeuroImage 150, 191–199.

Lohith, T.G., Bennacef, I., Vandenberghe, R., Vandenbulcke, M., Salinas-Valenzuela, C., Declercq, R., Reynders, T., Telan-Choing, F., Riffel, K., Celen, S., Serdons, K., Bormans, G., Tsai, K., Walji, A., Hostetler, E.D., Evelhoch, J.L., Van Laere, K., Forman, M., Stoch, A., Sur, C., et al., 2018. First-in-human brain imaging of Alzheimer dementia patients and elderly controls with (18)F-MK-6240, a PET tracer targeting neurofibrillary tangle pathology. J. Nucl. Med. https://doi.org/10.2967/jnumed.118.208215. pii: jnumed.118.208215 [Epub ahead of print].

Lois, C., Gonzalez, I., Johnson, K.A., Price, J.C., 2018. PET imaging of tau protein targets: a methodology perspective. Brain Imaging Behav. https://doi.org/10.1007/s11682-018-9847-7. [Epub ahead of print].

Lowe, V.J., Bruinsma, T.J., Min, H.K., Lundt, E.S., Fang, P., Senjem, M.L., Boeve, B.F., Josephs, K.A., Pandey, M.K., Murray, M.E., Kantarci, K., Jones, D.T., Schwarz, C.G., Knopman, D.S., Petersen, R.C., Jack Jr., C.R., 2018a. Elevated medial temporal lobe and pervasive brain tau-PET signal in normal participants. Alzheimers Dement. (Amst) 10, 210–216.

Lowe, V.J., Curran, G., Fang, P., Liesinger, A.M., Josephs, K.A., Parisi, J.E., Kantarci, K., Boeve, B.F., Pandey, M.K., Bruinsma, T., Knopman, D.S., Jones, D.T., Petrucelli, L., Cook, C.N., Graff-Radford, N.R., Dickson, D.W., Petersen, R.C., Jack Jr., C.R., Murray, M.E., 2016. An autoradiographic evaluation of AV-1451 tau PET in dementia. Acta Neuropathol. Commun. 4, 58.

Lowe, V.J., Wiste, H.J., Senjem, M.L., Weigand, S.D., Therneau, T.M., Boeve, B.F., Josephs, K.A., Fang, P., Pandey, M.K., Murray, M.E., Kantarci, K., Jones, D.T., Vemuri, P., Graff-Radford, J., Schwarz, C.G., Machulda, M.M., Mielke, M.M., Roberts, R.O., Knopman, D.S., Petersen, R.C., et al., 2018b. Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. Brain 141, 271–287.

Maass, A., Landau, S., Baker, S.L., Horng, A., Lockhart, S.N., La Joie, R., Rabinovici, G.D., Jagust, W.J., Alzheimer's Disease Neuroimaging, I., 2017. Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. NeuroImage 157, 448–463.

Maass, A., Lockhart, S.N., Harrison, T.M., Bell, R.K., Mellinger, T., Swinnerton, K., Baker, S.L., Rabinovici, G.D., Jagust, W.J., 2018. Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging. J. Neurosci. 38, 530–543.

Mackenzie, I.R., Neumann, M., 2016. Molecular neuropathology of frontotemporal dementia: insights into disease mechanisms from postmortem studies. J. Neurochem. 138 (Suppl. 1), 54–70.

Maia, L.F., Kaeser, S.A., Reichwald, J., Hruscha, M., Martus, P., Staufenbiel, M., Jucker, M., 2013. Changes in amyloid-beta and tau in the cerebrospinal fluid of transgenic mice overexpressing amyloid precursor protein. Sci. Transl. Med. 5 (194re2).

Marquie, M., Normandin, M.D., Meltzer, A.C., Siao Tick Chong, M., Andrea, N.V., Anton-Fernandez, A., Klunk, W.E., Mathis, C.A., Ikonomovic, M.D., Debnath, M., Bien, E.A., Vanderburg, C.R., Costantino, I., Makaretz, S., Devos, S.L., Oakley, D.H., Gomperts, S.N., Growdon, J.H., Domoto-Reilly, K., Lucente, D., et al., 2017a. Pathological correlations of [F-18]-AV-1451 imaging in non-alzheimer tauopathies. Ann. Neurol. 81, 117–128.

Marquie, M., Normandin, M.D., Vanderburg, C.R., Costantino, I.M., Bien, E.A., Rycyna, L.G., Klunk, W.E., Mathis, C.A., Ikonomovic, M.D., Debnath, M.L., Vasdev, N., Dickerson, B.C., Gomperts, S.N., Growdon, J.H., Johnson, K.A., Frosch, M.P., Hyman, B.T., Gomez-Isla, T., 2015. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann. Neurol. 78, 787–800.

Marquie, M., Siao Tick Chong, M., Anton-Fernandez, A., Verwer, E.E., Saez-Calveras, N., Meltzer, A.C., Ramanan, P., Amaral, A.C., Gonzalez, J., Normandin, M.D., Frosch, M.P., Gomez-Isla, T., 2017b. [F-18]-AV-1451 binding correlates with postmortem neurofibrillary tangle Braak staging. Acta Neuropathol. 134, 619–628.

Marquie, M., Verwer, E.E., Meltzer, A.C., Kim, S.J.W., Aguero, C., Gonzalez, J., Makaretz, S.J., Siao Tick Chong, M., Ramanan, P., Amaral, A.C., Normandin, M.D., Vanderburg, C.R., Gomperts, S.N., Johnson, K.A., Frosch, M.P., Gomez-Isla, T., 2017c. Lessons learned about [F-18]-AV-1451 off-target binding from an autopsy-confirmed Parkinson's case. Acta Neuropathol. Commun. 5, 75.

Maruyama, M., Shimada, H., Suhara, T., Shinotoh, H., Ji, B., Maeda, J., Zhang, M.R., Trojanowski, J., Lee, V.Y., Ono, M., Masamoto, K., Takano, H., Sahara, N., Iwata, N., Okamura, N., Furumoto, S., Kudo, Y., Chang, Q., Saido, T., Takashima, A., et al., 2013. Imaging of tau pathology in a tauopathy mouse model and in alzheimer patients compared to normal controls. Neuron 79, 1094–1108.

Mattsson, N., Andreasson, U., Zetterberg, H., Blennow, K., Alzheimer's Disease Neuroimaging, I., 2017a. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. JAMA Neurol. 74, 557–566.

Mattsson, N., Insel, P.S., Palmqvist, S., Portelius, E., Zetterberg, H., Weiner, M., Blennow, K., Hansson, O., Alzheimer's Disease Neuroimaging, I., 2016a. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. EMBO Mol. Med. 8, 1184–1196.

Mattsson, N., Ossenkoppele, R., Smith, R., Strandberg, O., Ohlsson, T., Jogi, J., Palmqvist, S., Stomrud, E., Hansson, O., 2018a. Greater tau load and reduced cortical thickness in APOE epsilon4-negative Alzheimer's disease: a cohort study. Alzheimers Res. Ther. 10, 77.

Mattsson, N., Schöll, M., Strandberg, O., Smith, R., Palmqvist, S., Insel, P.S., Hagerstrom, D., Ohlsson, T., Zetterberg, H., Jogi, J., Blennow, K., Hansson, O., 2017b. (18)F-AV-1451 and CSF T-tau and P-tau as biomarkers in Alzheimer's disease. EMBO Mol. Med. 9, 1212–1223.

Mattsson, N., Smith, R., Strandberg, O., Palmqvist, S., Schöll, M., Insel, P.S., Hagerstrom, D., Ohlsson, T., Zetterberg, H., Blennow, K., Jogi, J., Hansson, O., 2018b. Comparing (18)F-AV-1451 with CSF t-tau and p-tau for diagnosis of Alzheimer disease. Neurology 90, e388–e395.

Mattsson, N., Zetterberg, H., Janelidze, S., Insel, P.S., Andreasson, U., Stomrud, E., Palmqvist, S., Baker, D., Tan Hehir, C.A., Jeromin, A., Hanlon, D., Song, L., Shaw, L.M., Trojanowski, J.Q., Weiner, M.W., Hansson, O., Blennow, K., Investigators, A., 2016b. Plasma tau in Alzheimer disease. Neurology 87, 1827–1835.

Mattsson, N., Zetterberg, H., Nielsen, N., Blennow, K., Dankiewicz, J., Friberg, H., Lilja, G., Insel, P.S., Rylander, C., Stammet, P., Aneman, A., Hassager, C., Kjaergaard, J., Kuiper, M., Pellis, T., Wetterslev, J., Wise, M., Cronberg, T., 2017c. Serum tau and neurological outcome in cardiac arrest. Ann. Neurol. 82, 665–675.

Meeter, L.H.H., Vijverberg, E.G., Del Campo, M., Rozemuller, A.J.M., Donker Kaat, L., de Jong, F.J., van der Flier, W.M., Teunissen, C.E., van Swieten, J.C., Pijnenburg, Y.A.L., 2018. Clinical value of neurofilament and phospho-tau/tau ratio in the frontotemporal dementia spectrum. Neurology 90, e1231–e1239.

Meredith Jr., J.E., Sankaranarayanan, S., Guss, V., Lanzetti, A.J., Berisha, F., Neely, R.J., Slemmon, J.R., Portelius, E., Zetterberg, H., Blennow, K., Soares, H., Ahlijanian, M., Albright, C.F., 2013. Characterization of novel CSF tau and ptau biomarkers for Alzheimer's disease. PLoS One 8, e76523.

Mielke, M.M., Hagen, C.E., Wennberg, A.M.V., Airey, D.C., Savica, R., Knopman, D.S., Machulda, M.M., Roberts, R.O., Jack Jr., C.R., Petersen, R.C., Dage, J.L., 2017. Association of plasma total tau level with cognitive decline and Risk of mild cognitive impairment or dementia in the Mayo Clinic study on aging. JAMA Neurol. 74, 1073–1080.

Mielke, M.M., Hagen, C.E., Xu, J., Chai, X., Vemuri, P., Lowe, V.J., Airey, D.C., Knopman, D.S., Roberts, R.O., Machulda, M.M., Jack Jr., C.R., Petersen, R.C., Dage, J.L., 2018. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimers Dement. 14, 989–997.

Mishra, S., Gordon, B.A., Su, Y., Christensen, J., Friedrichsen, K., Jackson, K., Hornbeck, R., Balota, D.A., Cairns, N.J., Morris, J.C., Ances, B.M., Benzinger, T.L.S., 2017. AV-1451 PET imaging of tau pathology in preclinical Alzheimer disease: defining a summary measure. NeuroImage 161, 171–178.

Murugan, N.A., Nordberg, A., Agren, H., 2018. Different positron emission tomography tau tracers bind to multiple binding sites on the tau fibril: insight from computational modeling. ACS Chem. Neurosci. 9, 1757–1767.

Nelson, P.T., Alafuzoff, I., Bigio, E.H., Bouras, C., Braak, H., Cairns, N.J., Castellani, R.J., Crain, B.J., Davies, P., Del Tredici, K., Duyckaerts, C., Frosch, M.P., Haroutunian, V., Hof, P.R., Hulette, C.M., Hyman, B.T., Iwatsubo, T., Jellinger, K.A., Jicha, G.A., Kovari, E., et al., 2012. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J. Neuropathol. Exp. Neurol. 71, 362–381.

Ng, K.P., Pascoal, T.A., Mathotaarachchi, S., Therriault, J., Kang, M.S., Shin, M., Guiot, M.C., Guo, Q., Harada, R., Comley, R.A., Massarweh, G., Soucy, J.P., Okamura, N., Gauthier, S., Rosa-Neto, P., 2017b. Monoamine oxidase B inhibitor, selegiline, reduces (18)F-THK5351 uptake in the human brain. Alzheimers Res. Ther. 9, 25.

Ng, K.P., Pascoal, T.A., Mathotaarachchi, S., Therriault, J., Kang, M.S., Shin, M., Guiot, M.-C., Guo, Q., Harada, R., Comley, R.A., Massarweh, G., Soucy, J.-P., Okamura, N., Gauthier, S., Rosa-Neto, P., 2017a. Monoamine oxidase B inhibitor, selegiline, reduces ^{18}F-THK5351 uptake in the human brain. Alzheimers Res. Ther. 9, 25.

Okamura, N., Furumoto, S., Harada, R., Tago, T., Yoshikawa, T., Fodero-Tavoletti, M., Mulligan, R.S., Villemagne, V.L., Akatsu, H., Yamamoto, T., 2013. Novel ^{18}F-labeled arylquinoline derivatives for noninvasive imaging of tau pathology in Alzheimer disease. J. Nucl. Med. 54.

Olsson, B., Lautner, R., Andreasson, U., Ohrfelt, A., Portelius, E., Bjerke, M., Holtta, M., Rosen, C., Olsson, C., Strobel, G., Wu, E., Dakin, K., Petzold, M., Blennow, K., Zetterberg, H., 2016. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 15, 673–684.

Ono, M., Kitamura, S., Shimada, H., Sahara, N., Takuwa, H., Yoshiyama, Y., Trojanowski, J.Q., Lee, V., Suhara, T., Zhang, M.-R., Jang, M.K., Tamagnan, G., Marek, K., Higuchi, M., 2017a. Development of novel tau PET tracers, [^{18}F]AM-PPB3 and [^{18}F]PM-PPB3. In: Human Amyloid Imaging Meeting, pp. 34.

Ono, M., Sahara, N., Kumata, K., Ji, B., Ni, R., Koga, S., Dickson, D.W., Trojanowski, J.Q., Lee, V.M.-Y., Yoshida, M., Hozumi, I., Yoshiyama, Y., van Swieten, J.C., Nordberg, A., Suhara, T., Zhang, M.-R., Higuchi, M., 2017b. Distinct binding of PET ligands PBB3 and AV-1451 to tau fibril strains in neurodegenerative tauopathies. Brain 140, 764–780.

Ossenkoppele, R., Rabinovici, G., Smith, R., Cho, H., Schöll, M., Strandberg, O., Palmqvist, S., Mattsson, N., Janelidze, S., Santillo, A., Ohlsson, T., Jögi, J., Tsai, R., La Joie, R., Kramer, J., Boxer, A., Gorno-Tempini, M., Choi, J., Ryu, Y., Lyoo, C., et al., 2018. Discriminative accuracy of [^{18}F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. JAMA 320 (11), 1151–1162.

Ossenkoppele, R., Schonhaut, D.R., Schöll, M., Lockhart, S.N., Ayakta, N., Baker, S.L., O'Neil, J.P., Janabi, M., Lazaris, A., Cantwell, A., Vogel, J., Santos, M., Miller, Z.A., Bettcher, B.M., Vossel, K.A., Kramer, J.H., Gorno-Tempini, M.L., Miller, B.L., Jagust, W.J., Rabinovici, G.D., 2016. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139, 1551–1567.

Ouchi, H., Toyoshima, Y., Tada, M., Oyake, M., Aida, I., Tomita, I., Satoh, A., Tsujihata, M., Takahashi, H., Nishizawa, M., Shimohata, T., 2014. Pathology and sensitivity of current clinical criteria in corticobasal syndrome. Mov. Disord. 29, 238–244.

Pascoal, T.A., Shin, M., Kang, M.S., Chamoun, M., Chartrand, D., Mathotaarachchi, S., Bennacef, I., Therriault, J., Ng, K.P., Hopewell, R., Bouhachi, R., Hsiao, H.H., Benedet, A.L., Soucy, J.P., Massarweh, G., Gauthier, S., Rosa-Neto, P., 2018. In vivo quantification of neurofibrillary tangles with [(18)F]MK-6240. Alzheimers Res. Ther. 10, 74.

Plog, B.A., Nedergaard, M., 2018. The glymphatic system in central nervous system health and disease: past, present, and future. Annu. Rev. Pathol. 13, 379–394.

Pontecorvo, M.J., Devous Sr., M.D., Navitsky, M., Lu, M., Salloway, S., Schaerf, F.W., Jennings, D., Arora, A.K., McGeehan, A., Lim, N.C., Xiong, H., Joshi, A.D., Siderowf, A., Mintun, M.A., Investigators FA-A, 2017. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain 140, 748–763.

Quiroz, Y.T., Sperling, R.A., Norton, D.J., Baena, A., Arboleda-Velasquez, J.F., Cosio, D., Schultz, A., LaPoint, M., Guzman-Velez, E., Miller, J.B., Kim, L.A., Chen, K., Tariot, P.N., Lopera, F., Reiman, E.M., Johnson, K.A., 2018. Association between amyloid and tau accumulation in young adults with Autosomal dominant Alzheimer disease. JAMA Neurol. 75, 548–556.

Rabinovici, G.D., Furst, A.J., Alkalay, A., Racine, C.A., O'Neil, J.P., Janabi, M., Baker, S.L., Agarwal, N., Bonasera, S.J., Mormino, E.C., Weiner, M.W., Gorno-Tempini, M.L., Rosen, H.J., Miller, B.L., Jagust, W.J., 2010. Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. Brain 133, 512–528.

Ren, R.J., Dammer, E.B., Wang, G., Seyfried, N.T., Levey, A.I., 2014. Proteomics of protein post-translational modifications implicated in neurodegeneration. Transl. Neurodegener. 3, 23.

Rissin, D.M., Kan, C.W., Campbell, T.G., Howes, S.C., Fournier, D.R., Song, L., Piech, T., Patel, P.P., Chang, L., Rivnak, A.J., Ferrell, E.P., Randall, J.D., Provuncher, G.K., Walt, D.R., Duffy, D.C., 2010. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. Nat. Biotechnol. 28, 595–599.

Rubenstein, R., Chang, B., Yue, J.K., Chiu, A., Winkler, E.A., Puccio, A.M., Diaz-Arrastia, R., Yuh, E.L., Mukherjee, P., Valadka, A.B., Gordon, W.A., Okonkwo, D.O., Davies, P., Agarwal, S., Lin, F., Sarkis, G., Yadikar, H., Yang, Z., Manley, G.T., Wang, K.K.W., et al., 2017. Comparing plasma phospho tau, total tau, and phospho tau-total tau ratio as acute and chronic traumatic brain injury biomarkers. JAMA Neurol. 74, 1063–1072.

Sanabria Bohorquez, S., Barret, O., Tamagnan, G., Alagille, D., Marik, J., Ayalon, G., Bengtsson, T., de Crespigny, A., Jennings, D., Seibyl, J.P., Marek, K., Weimer, R., Kerchner, G.A., 2016. Evaluation of tau burden in a cross-sectional cohort of Alzheimer's disease subjects using [^{18}F]GTP1 (Genentech tau probe 1). Alzheimer's & Dementia: The Journal of the Alzheimer's Association 12, P1172.

Sanabria Bohorquez, S., Bengtsson, T., Barrett, O., Tamagnan, G., Alagille, D., de Crespigny, A., Ayalon, G., Ward, M., Kerchner, G., Jennings, D., Seibyl, J., Marek, K., Weimer, R., Marik, J., 2017. Kinetics of [^{18}F]GTP (Genentech tau probe 1) in the basal ganglia of Alzheimer's disease patients and healthy controls. In: Human Amyloid Imaging Meeting, pp. 32.

Sander, K., Lashley, T., Gami, P., Gendron, T., Lythgoe, M.F., Rohrer, J.D., Schott, J.M., Revesz, T., Fox, N.C., Arstad, E., 2016. Characterization of tau positron emission tomography tracer [(18)F]AV-1451 binding to postmortem tissue in Alzheimer's disease, primary tauopathies, and other dementias. Alzheimers Dement. 12, 1116–1124.

Sato, C., Barthelemy, N.R., Mawuenyega, K.G., Patterson, B.W., Gordon, B.A., Jockel-Balsarotti, J., Sullivan, M., Crisp, M.J., Kasten, T., Kirmess, K.M., Kanaan, N.M., Yarasheski, K.E., Baker-Nigh, A., Benzinger, T.L.S., Miller, T.M., Karch, C.M., Bateman, R.J., 2018. Tau kinetics in neurons and the human central nervous system. Neuron 98, 861–864.

Schöll, M., Lockhart, S.N., Schonhaut, D.R., O'Neil, J.P., Janabi, M., Ossenkoppele, R., Baker, S.L., Vogel, J.W., Faria, J., Schwimmer, H.D., Rabinovici, G.D., Jagust, W.J., 2016. PET imaging of tau deposition in the aging human brain. Neuron 89, 971–982.

Schöll, M., Ossenkoppele, R., Strandberg, O., Palmqvist, S., Jögi, J., Ohlsson, T., Smith, R., Hansson, O., 2017a. Distinct ^{18}F-AV-1451 tau PET retention patterns in early- and late-onset Alzheimer's disease. Brain 140, 2286–2294.

Schöll, M., Ossenkoppele, R., Strandberg, O., Palmqvist, S., Swedish Bio, F.S., Jogi, J., Ohlsson, T., Smith, R., Hansson, O., 2017b. Distinct ^{18}F-AV-1451 tau PET retention patterns in early- and late-onset Alzheimer's disease. Brain 140, 2286–2294.

Schultz, A.P., Chhatwal, J.P., Hedden, T., Mormino, E.C., Hanseeuw, B.J., Sepulcre, J., Huijbers, W., LaPoint, M., Buckley, R.F., Johnson, K.A., Sperling, R.A., 2017. Phases of hyperconnectivity and hypoconnectivity in the default mode and salience networks track with amyloid and tau in clinically normal individuals. J. Neurosci. 37, 4323–4331.

Schwarz, A.J., Yu, P., Miller, B.B., Shcherbinin, S., Dickson, J., Navitsky, M., Joshi, A.D., Devous Sr., M.D., Mintun, M.S., 2016. Regional profiles of the candidate tau PET ligand ^{18}F-AV-1451 recapitulate key features of Braak histopathological stages. Brain 139, 1539–1550.

Seibyl, J., Barret, O., Stephens, A., Madonia, J., Alagille, D., Mueller, A., Bendt, M., Kroth, H., Muhs, A., Pfeifer, A., Tamagnan, G., Dinkelborg, L., Marek, K., 2017. First in human characterization of PI-2620, a next generation PET tracer for assessing tau in Alzheimer's disease and other tauopathies. In: International Conference of Alzheimers and Parkinsons Disease, pp. 224.

Seppala, T.T., Nerg, O., Koivisto, A.M., Rummukainen, J., Puli, L., Zetterberg, H., Pyykko, O.T., Helisalmi, S., Alafuzoff, I., Hiltunen, M., Jaaskelainen, J.E., Rinne, J., Soininen, H., Leinonen, V., Herukka, S.K., 2012. CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings. Neurology 78, 1568–1575.

Sepulcre, J., Grothe, M.J., Sabuncu, M., Chhatwal, J., Schultz, A.P., Hanseeuw, B., El Fakhri, G., Sperling, R., Johnson, K.A., 2017a. Hierarchical organization of tau and amyloid deposits in the cerebral cortex. JAMA Neurol. 74, 813–820.

Sepulcre, J., Sabuncu, M.R., Li, Q., El Fakhri, G., Sperling, R., Johnson, K.A., 2017b. Tau and amyloid beta proteins distinctively associate to functional network changes in the aging brain. Alzheimers Dement. 13, 1261–1269.

Sepulcre, J., Schultz, A.P., Sabuncu, M., Gomez-Isla, T., Chhatwal, J., Becker, A., Sperling, R., Johnson, K.A., 2016. In vivo tau, amyloid, and gray matter profiles in the aging brain. J. Neurosci. 36, 7364–7374.

Shimada, H., Kitamura, S., Ono, M., Kimura, Y., Ichise, M., Takahata, K., Moriguchi, S., Kubota, M., Ishii, T., Takado, Y., Seki, C., Hirano, S., Shinotoh, H., Sahara, N., Tempest, P., Tamagnan, G., Seibyl, J., Barrett, O., Alagille, D., Zhang, M.-R., et al., 2017a. First-in-Human PET Study with ^{18}F-AM-PBB3 and ^{18}F-PM-PBB3. Alzheimer's Association International Conference (pp IC-P-198).

Shimada, H., Kitamura, S., Shinotoh, H., Endo, H., Niwa, F., Hirano, S., Kimura, Y., Zhang, M.R., Kuwabara, S., Suhara, T., Higuchi, M., 2017b. Association between Abeta and tau accumulations and their influence on clinical features in aging and Alzheimer's disease spectrum brains: a [(11)C]PBB3-PET study. Alzheimers Dement. (Amst) 6, 11–20.

Shoghi-Jadid, K., Small, G.W., Agdeppa, E.D., Kepe, V., Ercoli, L.M., Siddarth, P., Read, S., Satamurthy, N., Petric, A., Huang, S.-C., Barrio, J.R., 2002. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with alzheimer disease. Am. J. Geriatr. Psychiatry 10, 24–35.

Sipe, J.D., Benson, M.D., Buxbaum, J.N., Ikeda, S.I., Merlini, G., Saraiva, M.J., Westermark, P., 2016. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. Amyloid 23, 209–213.

Skillback, T., Farahmand, B.Y., Rosen, C., Mattsson, N., Nagga, K., Kilander, L., Religa, D., Wimo, A., Winblad, B., Schott, J.M., Blennow, K., Eriksdotter, M., Zetterberg, H., 2015. Cerebrospinal fluid tau and amyloid-beta1-42 in patients with dementia. Brain 138, 2716–2731.

Skillback, T., Rosen, C., Asztely, F., Mattsson, N., Blennow, K., Zetterberg, H., 2014. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 71, 476–483.

Smith, R., Puschmann, A., Scholl, M., Ohlsson, T., van Swieten, J., Honer, M., Englund, E., Hansson, O., 2016. ^{18}F-AV-1451 tau PET imaging correlates strongly with tau neuropathology in MAPT mutation carriers. Brain 139, 2372–2379.

Smith, R., Schain, M., Nilsson, C., Strandberg, O., Olsson, T., Hagerstrom, D., Jogi, J., Borroni, E., Scholl, M., Honer, M., Hansson, O., 2017a. Increased basal ganglia binding of (18) F-AV-1451 in patients with progressive supranuclear palsy. Mov. Disord. 32, 108–114.

Smith, R., Schöll, M., Honer, M., Nilsson, C.F., Englund, E., Hansson, O., 2017b. Tau neuropathology correlates with FDG-PET, but not AV-1451-PET, in progressive supranuclear palsy. Acta Neuropathol. 133, 149–151.

Smith, R., Schöll, M., Londos, E., Ohlsson, T., Hansson, O., 2018. (18)F-AV-1451 in Parkinson's Disease with and without dementia and in dementia with Lewy bodies. Sci. Rep. 8, 4717.

Smith, R., Schöll, M., Widner, H., van Westen, D., Svenningsson, P., Hagerstrom, D., Ohlsson, T., Jogi, J., Nilsson, C., Hansson, O., 2017c. In vivo retention of (18)F-AV-1451 in corticobasal syndrome. Neurology 89, 845–853.

Southekal, S., Devous Sr., M.D., Kennedy, I., Navitsky, M., Lu, M., Joshi, A.D., Pontecorvo, M.J., Mintun, M.A., 2018. Flortaucipir F 18 quantitation using parametric estimation of reference signal intensity. J. Nucl. Med. 59, 944–951.

Sperling, R.A., Laviolette, P.S., O'Keefe, K., O'Brien, J., Rentz, D.M., Pihlajamaki, M., Marshall, G., Hyman, B.T., Selkoe, D.J., Hedden, T., Buckner, R.L., Becker, J.A., Johnson, K.A., 2009. Amyloid deposition is associated with impaired default network function in older persons without dementia. Neuron 63, 178–188.

Stephens, A., Seibyl, J.P., Mueller, A., Barret, O., Berndt, M., Madonia, J., Kroth, H., Bullich, S., Pfeifer, A., Muhs, A., Tamagnan, G.D., Marek, K., Dinkelborg, L., 2018. Clinical Update: [^{18}F]PI-2620, a next generation Tau PET agent evaluated in subjects with Alzheimer's disease and progressive supranuclear palsy. In: Alzheimer's Association International Conferencepp. 24827.

Tapiola, T., Alafuzoff, I., Herukka, S.K., Parkkinen, L., Hartikainen, P., Soininen, H.,

Pirttila, T., 2009. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch. Neurol. 66, 382–389.
Tatebe, H., Kasai, T., Ohmichi, T., Kishi, Y., Kakeya, T., Waragai, M., Kondo, M., Allsop, D., Tokuda, T., 2017. Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome. Mol. Neurodegener. 12, 63.
Tosun, D., Landau, S., Aisen, P.S., Petersen, R.C., Mintun, M., Jagust, W., Weiner, M.W., Alzheimer's Disease Neuroimaging, I., 2017. Association between tau deposition and antecedent amyloid-beta accumulation rates in normal and early symptomatic individuals. Brain 140, 1499–1512.
Tzen, K.Y., Yang, S.Y., Chen, T.F., Cheng, T.W., Horng, H.E., Wen, H.P., Huang, Y.Y., Shiue, C.Y., Chiu, M.J., 2014. Plasma Abeta but not tau is related to brain PiB retention in early Alzheimer's disease. ACS Chem. Neurosci. 5, 830–836.
Vemuri, P., Lowe, V.J., Knopman, D.S., Senjem, M.L., Kemp, B.J., Schwarz, C.G., Przybelski, S.A., Machulda, M.M., Petersen, R.C., Jack Jr., C.R., 2017. Tau-PET uptake: regional variation in average SUVR and impact of amyloid deposition. Alzheimers Dement. (Amst) 6, 21–30.
Vermeiren, C., Motte, P., Viot, D., Mairet-Coello, G., Courade, J.P., Citron, M., Mercier, J., Hannestad, J., Gillard, M., 2018. The tau positron-emission tomography tracer AV-1451 binds with similar affinities to tau fibrils and monoamine oxidases. Mov. Disord. 33, 273–281.
Wagshal, D., Sankaranarayanan, S., Guss, V., Hall, T., Berisha, F., Lobach, I., Karydas, A., Voltarelli, L., Scherling, C., Heuer, H., Tartaglia, M.C., Miller, Z., Coppola, G., Ahlijanian, M., Soares, H., Kramer, J.H., Rabinovici, G.D., Rosen, H.J., Miller, B.L., Meredith, J., et al., 2015. Divergent CSF tau alterations in two common tauopathies: Alzheimer's disease and progressive supranuclear palsy. J. Neurol. Neurosurg. Psychiatry 86, 244–250.
Walji, A.M., Hostetler, E.D., Selnick, H., Zeng, Z., Miller, P., Bennacef, I., Salinas, C., Connolly, B., Gantert, L., Holahan, M., O'Malley, S., Purcell, M., Riffel, K., Li, J., Balsells, J., Ja, O.B., Melquist, S., Soriano, A., Zhang, X., Ogawa, A., et al., 2016. Discovery of 6-(fluoro-(18)F)-3-(1H-pyrrolo[2,3-c]pyridin-1-yl)isoquinolin-5-amine ([(18)F]-MK-6240): a positron emission tomography (PET) imaging agent for quantification of neurofibrillary tangles (NFTs). J. Med. Chem. 59, 4778–4789.
Walker, L.C., LeVine 3rd, H., 2012. Corruption and spread of pathogenic proteins in neurodegenerative diseases. J. Biol. Chem. 287, 33109–33115.
Wallin, A.K., Blennow, K., Zetterberg, H., Londos, E., Minthon, L., Hansson, O., 2010. CSF biomarkers predict a more malignant outcome in Alzheimer disease. Neurology 74, 1531–1537.
Wang, L., Benzinger, T.L., Su, Y., Christensen, J., Friedrichsen, K., Aldea, P., McConathy, J., Cairns, N.J., Fagan, A.M., Morris, J.C., Ances, B.M., 2016. Evaluation of tau imaging in staging Alzheimer disease and revealing interactions between beta-amyloid and tauopathy. JAMA Neurol. 73, 1070–1077.
Weimer, R., Barrett, O., Tamagnan, G., Alagille, D., Marik, J., Ayalon, G., Bengtsson, T., Ward, M., Kerchner, G., Jennings, D., Seibyl, J.P., Marek, K., Sanabria Bohorquez, S., 2017. Evaluation of baseline and longitudinal tau burden in Alzheimer's disease using [^{18}F]GTP1 (Genentech Tau Probe 1) PET imaging. In: Human Amyloid Imaging Meeting, pp. 91.
Whitwell, J.L., Ahlskog, J.E., Tosakulwong, N., Senjem, M.L., Spychalla, A.J., Petersen, R.C., Jack Jr., C.R., Lowe, V.J., Josephs, K.A., 2018a. Pittsburgh compound B and AV-1451 positron emission tomography assessment of molecular pathologies of Alzheimer's disease in progressive supranuclear palsy. Parkinsonism Relat. Disord. 48, 3–9.
Whitwell, J.L., Graff-Radford, J., Tosakulwong, N., Weigand, S.D., Machulda, M., Senjem, M.L., Schwarz, C.G., Spychalla, A.J., Jones, D.T., Drubach, D.A., Knopman, D.S., Boeve, B.F., Ertekin-Taner, N., Petersen, R.C., Lowe, V.J., Jack Jr., C.R., Josephs, K.A., 2018b. [(18) F]AV-1451 clustering of entorhinal and cortical uptake in Alzheimer's disease. Ann. Neurol. 83, 248–257.
Wiepert, D.A., Lowe, V.J., Knopman, D.S., Boeve, B.F., Graff-Radford, J., Petersen, R.C., Jack Jr., C.R., Jones, D.T., 2017. A robust biomarker of large-scale network failure in Alzheimer's disease. Alzheimers Dement. (Amst) 6, 152–161.
Winer, J.R., Maass, A., Pressman, P., Stiver, J., Schonhaut, D.R., Baker, S.L., Kramer, J., Rabinovici, G.D., Jagust, W.J., 2018. Associations between tau, beta-amyloid, and cognition in Parkinson disease. JAMA Neurol. 75, 227–235.
Winston, C.N., Goetzl, E.J., Akers, J.C., Carter, B.S., Rockenstein, E.M., Galasko, D., Masliah, E., Rissman, R.A., 2016. Prediction of conversion from mild cognitive impairment to dementia with neuronally derived blood exosome protein profile. Alzheimers Dement. (Amst) 3, 63–72.
Wolters, E.E., Golla, S.S.V., Timmers, T., Ossenkoppele, R., van der Weijden, C.W.J., Scheltens, P., Schwarte, L., Schuit, R.C., Windhorst, A.D., Barkhof, F., Yaqub, M., Lammertsma, A.A., Boellaard, R., van Berckel, B.N.M., 2018. A novel partial volume correction method for accurate quantification of [(18)F] flortaucipir in the hippocampus. EJNMMI Res. 8, 79.
Wong, D., Kuwabara, H., Comley, R., Klein, G., Vozzi, C., Honer, M., Roberts, J., Kitzmiller, K., Gapasin, L., Borroni, E., 2017. Longitudinal changes in [^{18}F]-RO6958948 tau PET signal in four Alzheimer's subjects. In: Human Amyloid Imaging Meeting, pp. 70.
Wong, D.F., Comley, R., Kuwabara, H., Rosenberg, P.B., Resnick, S.M., Ostrowitzki, S., Vozzi, C., Boess, F., Oh, E., Lyketsos, C.G., Honer, M., Gobbi, L., Klein, G., George, N., Gapasin, L., Kitzmiller, K., Roberts, J., Sevigny, J., Nandi, A., Brasic, J.R., et al., 2018. First in-human PET study of 3 novel tau radiopharmaceuticals: [(11)C]RO6924963, [(11)C]RO6931643, and [(18)F]RO6958948. J. Nucl. Med. 59 (12), 1869–1876.
Wood, J.G., Mirra, S.S., Pollock, N.J., Binder, L.I., 1986. Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). Proc. Natl. Acad. Sci. U. S. A. 83, 4040–4043.
Wooten, D.W., Guehl, N.J., Verwer, E.E., Shoup, T.M., Yokell, D.L., Zubcevik, N., Vasdev, N., Zafonte, R.D., Johnson, K.A., El Fakhri, G., Normandin, M.D., 2017. Pharmacokinetic evaluation of the tau PET radiotracer ^{18}F-T807 (^{18}F-AV-1451) in human subjects. J. Nucl. Med. 58, 484–491.
Wren, M.C., Lashley, T., Arstad, E., Sander, K., 2018. Large inter- and intra-case variability of first generation tau PET ligand binding in neurodegenerative dementias. Acta Neuropathol. Commun. 6, 34.
Xia, C., Makaretz, S.J., Caso, C., McGinnis, S., Gomperts, S.N., Sepulcre, J., Gomez-Isla, T., Hyman, B.T., Schultz, A., Vasdev, N., Johnson, K.A., Dickerson, B.C., 2017. Association of in vivo [^{18}F]AV-1451 tau PET imaging results with cortical atrophy and symptoms in typical and atypical Alzheimer disease. JAMA Neurol. 74, 427–436.
Zetterberg, H., 2017. Applying fluid biomarkers to Alzheimer's disease. Am. J. Phys. Cell Phys. 313, C3–C10.
Zetterberg, H., Blennow, K., 2018. From cerebrospinal fluid to blood: the third wave of fluid biomarkers for Alzheimer's disease. J. Alzheimers Dis. 64, S271–S279.
Zetterberg, H., Hietala, M.A., Jonsson, M., Andreasen, N., Styrud, E., Karlsson, I., Edman, A., Popa, C., Rasulzada, A., Wahlund, L.O., Mehta, P.D., Rosengren, L., Blennow, K., Wallin, A., 2006. Neurochemical aftermath of amateur boxing. Arch. Neurol. 63, 1277–1280.
Zetterberg, H., Wilson, D., Andreasson, U., Minthon, L., Blennow, K., Randall, J., Hansson, O., 2013. Plasma tau levels in Alzheimer's disease. Alzheimers Res. Ther. 5, 9.
Zhang, Z., Song, M., Liu, X., Kang, S.S., Kwon, I.S., Duong, D.M., Seyfried, N.T., Hu, W.T., Liu, Z., Wang, J.Z., Cheng, L., Sun, Y.E., Yu, S.P., Levey, A.I., Ye, K., 2014. Cleavage of tau by asparagine endopeptidase mediates the neurofibrillary pathology in Alzheimer's disease. Nat. Med. 20, 1254–1262.