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GUEST EDITORIAL

Tau PET: the next frontier in molecular imaging of dementia

We have arrived at an exciting juncture in dementia research: the second major pathological hallmark of Alzheimer's disease (AD)–tau–can now be seen for the first time in the living human brain. The major proteinopathies in AD include amyloid-β plaques and neurofibrillary tangles (NFTs) made of hyperphosphorylated paired helical filament (PHF) tau. Since its advent more than a decade ago, amyloid PET imaging has revolutionized the field of dementia research, enabling more confident diagnosis of the likely pathology in patients with a variety of clinical dementia syndromes, paving the way for the identification of people with preclinical or prodromal AD pathology, and serving as a minimally invasive molecular readout in clinical trials of putative disease-modifying interventions. Now that we are on the brink of a second revolution in molecular imaging in dementia, it is worth considering the likely potential impact of this development on the field.

More than two decades of post-mortem studies of AD demonstrate a close relationship between the topography and severity of hyperphosphorylated tau protein accumulation and the types and severity of clinical symptoms, in contrast to amyloid, which does not relate very strongly to symptoms (Nelson *et al.*, 2012). In the past 10 years, we have learned a tremendous amount about pathological tau proteins in living people from cerebrospinal fluid (CSF) biomarkers of AD neurofibrillary tau pathology. However, despite its value as a biomarker and outcome measure in clinical therapeutic trials, CSF tau measures require lumbar puncture and, most importantly, cannot provide topographical information. Knowledge of the localization and magnitude of tau pathology in the living human brain will likely shed new light on the neurobiology of disease as well as having important clinical utility.

To date, three main chemical classes of putative tau PET tracers have been validated *in vitro* as showing relatively selective binding to PHF tau pathology: (1) quinolone derivatives such as [^{18}F]THK523, [^{18}F]THK5117, [^{18}F]THK5105; (2) benzothiazole derivatives such as [^{11}C]PBB3; and (3) benzimidazole pyrimidines such as [^{18}F]AV-1451 (previously known as [^{18}F]T807) and [^{18}F]T808 (Villemagne *et al.*, 2015). Multiple studies have now reported *in vivo* results of these tracers in healthy aging and AD. Chien *et al.* showed the first *in vivo* images and kinetic analyses of the benzimidazole pyrimidine [^{18}F]AV-1451 (Chien *et al.*, 2013), demonstrating the expected uptake in temporal and parietal regions in patients with amnesic mild cognitive impairment (MCI) and AD dementia. Our group recently examined [^{18}F]AV-1451 in normal aging (cognitively normal subjects across the age spectrum) and in patients with amnesic MCI or AD (Johnson *et al.*, 2016). The spatial topography was consistent with Braak staging, with more prominent [^{18}F]AV-1451 binding in inferior and lateral temporoparietal, parieto-occipital, posterior cingulate, and precuneus, in contrast to less prominent binding in frontal regions and primary sensorimotor cortices. Moreover, [^{18}F]AV-1451 binding in the inferior temporal gyrus correlated better than [^{11}C]PiB with clinical impairment, suggesting a relationship between *in vivo* tau pathology and clinical symptoms as predicted by previous post-mortem studies. Schöll *et al.* (2016) similarly found the topography of [^{18}F]AV-1451 to follow Braak staging in a group of 15 AD dementia patients. Focusing on quinolone derivatives, Villemagne *et al.* (2014) found [^{18}F]THK523 binding followed Braak staging and did not correlate with [^{11}C]PiB, indicating its specificity to tau pathology. Furthermore, [^{18}F]THK523 binding in the hippocampus correlated with clinical impairment and atrophy. Unfortunately, despite these promising initial findings, [^{18}F]THK523 demonstrated high binding in subcortical white matter, precluding proper visual inspection, hence limiting its potential as a tau PET tracer. [^{18}F]THK5105 and [^{18}F]THK5117, compounds similar to [^{18}F]THK523, showed higher binding affinity to tau in AD brain aggregates and homogenates (Okamura *et al.*, 2013). Most recently, [^{18}F]THK5351, the newest candidate in the same chemical family, showed prominent binding in temporal lobes as expected, and other favorable characteristics supporting its potential value moving forward (Harada *et al.*, 2015). Finally, *in vivo* binding of the benzothiazole derivative [^{11}C]PBB3 was assessed in three AD patients and three healthy controls (Maruyama *et al.*, 2013). [^{11}C]PBB3 binding was localized distinctly from [^{11}C]PiB,

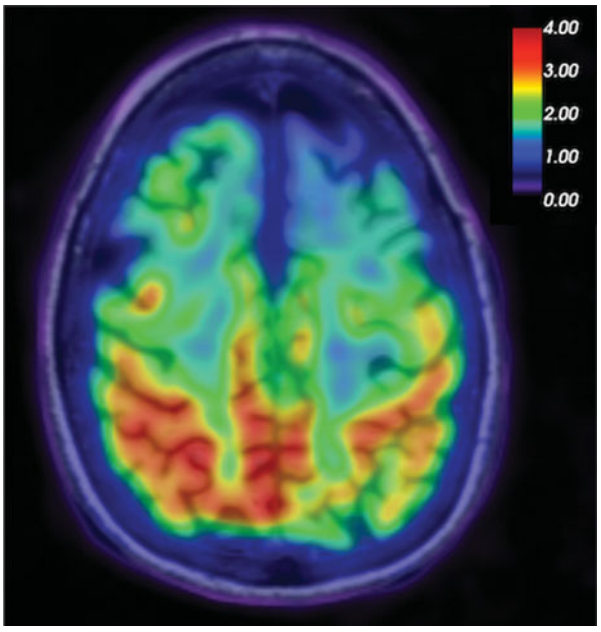

Figure 1. [^{18}F]AV-1451 PET co-registered with MRI in a case of corticobasal syndrome with underlying Alzheimer's disease pathology; color bar displays legend for [^{18}F]AV-1451 SUVR (standard uptake value ratios) values.

including in the atrophic medial temporal lobe.

In addition to amnesic MCI and typical AD dementia, tau PET imaging is also an attractive new imaging tool for the study of non-amnesic clinical MCI/dementia syndromes which can now be established using molecular biomarkers as atypical subtypes of AD. These syndromes include Primary Progressive Aphasia (PPA), Posterior Cortical Atrophy (PCA), a behavioral/dysexecutive syndrome, and Corticobasal Syndrome (CBS). In a cohort of patients with atypical subtypes of AD, tau accumulation measured by [^{18}F]AV-1451 closely linked to clinical phenotype and better co-localized with hypometabolism compared to [^{11}C]PiB (Ossenkoppele *et al.*, 2016). These findings are consistent with findings in our own cohort, where topography of [^{18}F]AV-1451 binding co-localized closely with atrophy in a distribution expected based on clinical phenotype. For example, a 60 year-old right-handed woman initially presented with symptoms consistent with CBS (asymmetric alien limb syndrome, limb apraxia with rigidity, and progressive myoclonus with visuospatial, executive, and language deficits). CSF and amyloid PET imaging were consistent with underlying AD pathology. Tau PET imaging showed peri-Rolandic signal closely related to clinical symptoms that also co-localized with atrophy (Figure 1). Echoing what has already been observed in amnesic MCI and clinically typical AD, these initial findings support predictions from post-mortem studies of the close association between tau pathology and neurodegeneration, a relationship not clearly present with amyloid pathology.

These initial findings demonstrate that we have now entered an era in which it is possible to visualize and quantify both major molecular pathological hallmarks of AD in the brains of living people. How will this be useful? First, tau PET imaging will advance our understanding of the neurobiology of disease. For example, we will be able to further investigate and refine ideas regarding the typical and atypical localization of tau pathology in people with cognitive impairment and dementia. Questions regarding the spread of tau pathology along neural networks will be possible to examine. The localization and magnitude of tau pathology in aging will be much more readily investigated. We will be able to study relationships between tau and amyloid, as well as between tau and other biomarkers of neurodegeneration such as regional brain atrophy and hypometabolism. Finally, it will be possible to ask very interesting questions about the effects of tau on functional brain activation (e.g. task-related fMRI) and structural and functional neural connectivity (e.g. functional connectivity MRI and diffusion tensor imaging). Second, since PHF tau is the molecular pathology that appears more proximal than amyloid to the neurodegenerative lesions associated with symptoms, the identification of tau pathology in regions of atrophy and hypometabolism in a person with MCI or dementia would strongly support the diagnosis of AD, regardless of whether symptoms are typical or atypical (Dickerson *et al.*, in press). In contrast, it is well-known that some individuals with Frontotemporal Lobar Degeneration (FTLD) or other non-AD dementias may have co-occurring AD pathology which may or may not contribute to the clinical phenotype (Naasan *et al.*, 2016). Tau PET imaging may help clarify contributions. For example, if a patient has PPA or another clinical phenotype often associated with non-AD pathology, but has a positive amyloid PET scan accompanied by low signal on tau PET, the clinician might suspect that the AD pathology is a secondary, possibly non-contributory, pathology. In contrast, if the tau PET signal is robust and co-localized with hypometabolism or atrophy, it would be more likely that AD pathology is an important contributor to the clinical phenotype. Beyond its potential diagnostic use, tau PET imaging will likely be valuable in clinical trials as an inclusion criterion for putative tau therapeutics, and as an outcome measure in disease-modifying trials targeting tau directly or indirectly through amyloid or neuroprotective or other strategies.

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Tau PET imaging also holds enormous potential as a biomarker to enhance diagnostic confidence and pathophysiological understanding for non-AD tauopathies, including FTLD-spectrum tauopathies such as Pick's disease, progressive supranuclear palsy (PSP), or corticobasal degeneration (CBD). The FTLD field desperately needs imaging or fluid biomarkers to distinguish tauopathies from TDP-43 proteinopathies or less common pathologies. Tau PET imaging will likely be a cornerstone of the diagnostic evaluation of patients with suspected FTLD in the future. Initial efforts to evaluate tau PET ligands *in vivo* in FTLD have shown increased [^{18}F]AV-1451 uptake in frontal and temporal cortices (Ghetti *et al.*, 2015). However, autoradiographic investigations of post-mortem tracer binding has produced conflicting data, with some studies showing low-level binding to some types of FTLD (Sander *et al.*, 2016) and others, including our own, showing no appreciable binding (Marquié *et al.*, 2015). One particular hurdle to generalizing the use of tau PET imaging to non-AD tauopathies is that NFTs in AD and non-AD tauopathies are biochemically distinct. The histological and ultrastructural distinctions between these different tau deposits found in different tauopathies may be crucially relevant to tau ligands development as it has so far mainly focused on optimizing affinity for the specific PHF tau found in AD. The development of tracers targeted toward these non-AD tauopathies will likely require extensive tissue-based screening against other specific tau pathologies, such as PSP or CBD.

In parallel to efforts devoted to exploring the potential of tau PET imaging in AD and non-AD tauopathies, some have also begun investigating its use in cognitively normal individuals. Normal aging is increasingly being thought of as being accompanied by a tauopathy. In cognitively intact older adults, tau tracer binding localizes to medial and inferior temporal regions, consistent with Braak stage III/IV (Johnson *et al.*, 2016). Further studies using tau PET imaging in different age groups of cognitively normal individuals, or perhaps even following them longitudinally, will be needed to understand how tau accumulation progresses during life independent of pathological neurodegenerative processes. This differentiation between normal and abnormal tau accumulation will be crucial for defining the parameters of a "positive" (i.e. pathological) scan, and how these parameters may differ between AD versus non-AD tauopathies introduces an additional layer of complexity. Clarifying binding patterns in healthy aging (especially in conjunction with *ex vivo* validation studies) may also illuminate the origin of instances of off-target binding. These binding patterns may either be due to ligand affinity to a substance other than hyperphosphorylated tau (Marquié *et al.*, 2015) or to yet incompletely understood *in vivo* ligand kinetics, a topic of considerable interest at present.

Several issues regarding sensitivity, specificity, and ante-mortem/post-mortem validation of tau PET ligands remain to be resolved. One of the first challenges encountered in tau PET tracer development was ensuring that the tracer display high binding-specificity to tau as opposed to other pathological proteins such as TDP-43, alpha-synuclein, and of course amyloid, which not only co-localizes with tau but is also found in higher concentrations. And as outlined above, another pivotal challenge we have yet to meet is to further probe various tracers' respective specificity to AD and non-AD tauopathies. Furthermore, most of the *in vivo* or *ex vivo* studies have not been done with the same patients; we desperately need more end-of-life tau PET studies to validate the tracers. Finally, we need head-to-head comparisons of the various tau PET tracers currently in development.

In conclusion, developments in the new field of tau PET imaging are rapidly evolving. Tau PET tracers appear to be "ready for prime time" for use in clinical research studies of AD, including as add-on measures in clinical trials. New chemical entities are still desperately needed for the FTD and other non-AD tauopathies. Whether there is a consistent primary age-related tauopathy in the absence of amyloid deserves intense *in vivo* study. And the relation of tau measured by PET to CSF tau and to atrophy and hypometabolism is a very ripe topic of study beginning to yield interesting fruit. Once more fully validated, we hope that tau PET imaging will further accelerate clinical therapeutic development for AD and non-AD tauopathies.

Conflicts of interest

None.

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Chenjie Xia[1] and Bradford C. Dickerson[1,2]

[1]Department of Neurology, Frontotemporal Disorders Unit, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts, USA
[2]Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts, USA
Email: brad.dickerson@mgh.harvard.edu

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