Does early cognitive decline require the presence of both tau and amyloid-β?

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In vivo biomarkers of tau and amyloid-β pathology have become essential tools in research into preclinical Alzheimer's disease, as accumulation of both proteins begins many years before clinical symptoms emerge. In recent years, the first positron emission tomography (PET) imaging probes sensitive to tau aggregates, such as [^{18}F]-Flortaucipir ([^{18}F]AV1451), have been studied intensively in cohorts of cognitively unimpaired older adults. Overall, these studies have confirmed *in vivo* the neurofibrillary tau tangle topography described earlier by *post-mortem* studies. Elevated tau PET tracer retention is most frequently seen first in the entorhinal cortex, followed by the inferolateral temporal and medial parietal lobes, commonly in the presence of elevated cortical amyloid-β (Schöll, Maass et al., 2019). Greater tau ligand retention, particularly in the entorhinal cortex, is consistently related to poorer memory performance cross-sectionally and to memory decline over time, assessed retrospectively in most cases. More recently, a new generation of tau PET ligands has been introduced that allegedly show less "off-target" tracer retention and increased sensitivity to tau, presumably increasing the ability to detect very early tau aggregates during the preclinical stages of Alzheimer's disease. ~~Moreover, recently, PET-based biomarkers for amyloid-β and tau pathology have been incorporated into the NIA-AA Research Framework (Jack, Bennett et al., 2018) that aims to characterize Alzheimer's disease *in vivo* based on a dichotomized biomarker classification scheme (AT(N)).~~ In this issue of *Brain*, Betthauser and co-workers demonstrate that PET-biomarker evidence for both amyloid-β and tau pathology (A+/T+), the latter assessed with the novel tau PET tracer [^{18}F]MK-6240, is associated with accelerated cognitive decline, beginning in late middle-age (Betthauser et al., 2020).

In their longitudinal study, the authors studied 167 adults in their late fifties, who were cognitively unimpaired at study entry, over the course of eight years (Fig. 1). The participants were part of the Wisconsin Registry for Alzheimer's Prevention (WRAP) study and underwent neuropsychological testing approximately every second year. Cognitive ability was assessed using a composite score comprising measures of verbal learning, logical memory and executive function. PET scans for the assessment of Alzheimer's disease-related pathology were acquired at the end of the study, when the tau PET tracer [^{18}F]MK-6240 first became available (Hostetler, Walji et al., 2016). In accordance with the NIA-AA Research Framework AT(N) biomarker classification scheme for Alzheimer's disease (Jack, Bennett et al., 2018), Betthauser and colleagues stratified individuals into four groups based on their biomarker status for amyloid-β pathology (A+/-) using a global cortical composite measure of [^{11}C]PIB PET, and for tau pathology (T+/-) using [^{18}F]MK-6240 retention in the entorhinal cortex. A cutoff for T+ was established relative to [^{18}F]MK-6240 retention in the A- group (mean standardized

uptake value ratio (SUVR) + 2 SD ≈ 1.27). As summarised in Fig. 1, the majority of individuals (74%) were assigned a negative status for both biomarkers (A-/T-), whereas only 9% of the sample were classified as both A+ and T+, i.e., demonstrating categorical *in vivo* evidence of Alzheimer's disease. A very small proportion – 3% (5 individuals) – were classified as T+ in the absence of pathological levels of amyloid-β (A-/T+). The subgroups did not differ in cognitive performance at study baseline, and only small differences were seen in measures of general health. However, mixed effects models revealed that although all groups showed declining cognition, the A+/T+ group was declining about three times faster than the other three subgroups, which did not differ in their cognitive trajectories.

This is the first report on the association between [^{18}F]MK-6240 retention and cognitive decline, and one of the first to retrospectively assess cognitive decline in individuals of late-middle age. The results suggest that in this age group, cognitive decline is accelerated only in the presence of both elevated tau and amyloid-β PET signal (A+T+). While the subgroups with only one deviant biomarker (A+ or T+) were small, the authors were able to replicate their intriguing results using different (lower) thresholds for entorhinal [^{18}F]MK-6240 retention or by using [^{18}F]MK-6240 retention in the hippocampus to establish tau pathology status. Several previous studies have examined the association between [^{18}F]-Flortaucipir PET retention patterns and cognitive decline in various age groups. Findings of "synergistic" effects of tau and amyloid-β on cognition have been mixed, with some studies reporting accelerated cognitive decline only in the presence of both significantly increased amyloid-β and tau PET signal (for example (Sperling, Mormino et al., 2019)) while others demonstrated tau-related cognitive decline irrespective of the presence of elevated amyloid-β. These inconsistencies could be due in part to demographic differences (in addition to differing cut-points, cognitive measures, etc), as tau aggregation in the absence of elevated amyloid-β, also termed 'primary age-related tauopathy' (PART), is more prevalent in older individuals. Studies including a higher proportion of patients with PART are thus more likely to find medial temporal lobe tau-associated cognitive decline that is seemingly independent of amyloid-β status.

PART has been said to reflect tauopathy predominantly in the medial temporal lobe (entorhinal and parahippocampal cortex and the hippocampus) that is distinct from Alzheimer's disease in clinical and pathological features (Bell, An et al., 2019). Whether PART constitutes a distinct pathological or clinical entity remains controversial (Duyckaerts, Braak et al., 2015). However, basing tau pathology status on elevated tau PET ligand retention in these brain regions hypothetically entails classifying both individuals with PART and Alzheimer's disease as T+. While there are clear implicationss ~~[ok?]~~ for clinical research, trial recruitment and

patient assessment of defining pathological states using categories – as proposed by the NIA-AA Research Framework – doing so lowers the diagnostic and prognostic resolution of any given biomarker for describing stages within the Alzheimer's disease continuum (Aisen, Cummings et al., 2017). A discrete definition of tau pathology status (T+/-) can, for example, be established by applying pre-defined cut-offs to the level of phosphorylated tau in cerebrospinal fluid, thus basing the definition on a single variable. When tau PET-derived measures are used instead, many more potentially unknown variables are introduced to the equation. Strong diagnostic performance for Alzheimer's disease has been reported for [^{18}F]-Flortaucipir PET using similar pre-defined brain regions and region-specific cut-points (see for example (Jack, Wiste et al., 2017, Ossenkoppele, Rabinovici et al., 2018)). However, no consistent cut-points have yet been established for any single tau PET ligand or brain region (due to differing imaging protocols, cohorts, scanner types, image processing pipelines, etc), nor is there any consensus on which brain regions (or combinations thereof) yield maximum prognostic or diagnostic value for establishing a discrete tau pathology status. Future research will have to validate the prognostic and diagnostic performance of "T+/-" and its value in describing the pathological and clinical continuum that is Alzheimer's disease.

In the current study, Betthauser *et al.* also examined regional associations of [^{18}F]MK-6240 retention with global cortical amyloid-β PET measures and age. In accordance with previous studies, the strongest associations of a global [^{11}C]PiB PET measure with [^{18}F]MK-6240 retention were observed in the medial and lateral temporal lobe, peaking in the entorhinal cortex, while weaker associations were observed in frontal and parietal regions (Fig. 1). In contrast, associations between [^{18}F]MK-6240 retention and age were weak and disappeared when global amyloid-β burden was accounted for. These results are of particular interest as [^{18}F]MK-6240 has been suggested to exhibit less "off-target" binding specifically in the choroid plexus and the basal ganglia than, for instance, [^{18}F]-Flortaucipir, thereby enabling improved assessment of meaningful tracer signal in the hippocampus and thus detection of early age-related tau burden in the medial temporal lobe. However, Betthauser *et al*. pointed out that individuals needed increased levels of global [^{11}C]PiB to exhibit elevated [^{18}F]MK-6240 signal in the hippocampus, and that no age-association was observed with [^{18}F]MK-6240 in the hippocampus or the entorhinal cortex when accounting for global [^{11}C]PiB. Moreover, average SUVRs of entorhinal [^{18}F]MK-6240 in the whole cohort were close to 1 and thus not different from tracer retention in the reference region. Overall, this observation does not confirm *post-mortem* data according to which entorhinal tau tangle pathology can be detected in the majority of elderly individuals at age 60, also in the absence of amyloid-β (Braak stages

I/II). Finally, based on their findings, the authors suggest that PET-detectable amyloid-β plaque pathology generally precedes PET-detectable tau aggregates. This holds implications for the sensitivity of existing tau PET tracers for detecting the early stages of tau pathology common in individuals of late middle-age.

Glossary

AT(N) system: Biomarker classification system for the *in vivo* staging of Alzheimer's disease pathology. Amyloid-β, tau, and neurodegeneration are each categorised in a dichotomous manner as positive or negative to classify pathology status. The system was proposed as part of the 2018 NIA-AA Research Framework (Jack et al., 2018). A biomarker-based definition of Alzheimer's disease requires evidence of both pathological levels of amyloid-β and tau (A+/T+), whereas abnormal amyloid-β alone represents "Alzheimer's disease pathological change".

[^{18}F]MK-6240: PET tracer sensitive to neurofibrillary tau tangle pathology that has shown favourable imaging characteristics and spatial retention patterns consistent with neuropathological staging of Alzheimer's disease tau pathology in previous studies. The tracer presumably shares the same binding site as the well-described tau PET tracer [^{18}F]-Flortaucipir, and is thus likely to be sensitive predominantly to Alzheimer's disease-type tau pathology. However, less [^{18}F]MK-6240 binding in "off-target" brain regions such as the choroid plexus or the basal ganglia has been reported.

PART

Neurofibrillary tau tangle pathology mainly confined to the temporal lobe in the absence, or presence of only a few, amyloid-β plaques has been described as primary age-related tauopathy (PART) (Crary, Trojanowski et al., 2014). Neuropathological results indicate that a higher Braak stage of tau pathology is related to higher age, worse cognition, and hippocampal atrophy in cases with PART. However, there is an ongoing debate about whether PART represents an independent entity or is part of the Alzheimer's disease continuum (Duyckaerts et al., 2015). Recent data indicate similar pathology seeding activities in both Alzheimer's disease and PART, beginning in the transentorhinal cortex.

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Figure legend

Figure 1. **Study overview and main results from Betthauser *et al*.** Initially cognitively normal adults in late middle-age were followed over approximately eight years leading up to PET imaging of Alzheimer's disease-associated pathology. Participants completed a neuropsychological battery at their first visit, two or four years later at their second visit and approximately every two years thereafter. The three-test preclinical Alzheimer's cognitive composite (PACC-3) score was used for cognitive assessment. Participants were classified based on abnormal PET biomarkers for global amyloid-β or regional tau burden, and cognitive trajectories between biomarker-defined groups were compared. The group with abnormal amyloid-β (A+) and tau (T+) PET biomarkers showed accelerated retrospective cognitive decline when compared to the other biomarker-defined subgroups.