Nelson and colleagues propose a neuropathological staging scheme for LATE, with TDP-43 pathology at stage 1 in the amygdala, spreading to the hippocampus at stage 2, and spreading to the middle frontal gyrus at stage 3. This staging scheme might differentiate LATE-NC from FTLD-TDP or Alzheimer's disease pathology. As the TDP-43 aggregates begin to spread from the limbic areas in LATE-NC, the clinical presentation of this disease is associated with an amnestic syndrome, whereas behavioural and aphasic syndromes are linked to FTLD-TDP because of neocortical involvement.[7] However, symptoms of Alzheimer's disease reflect both neocortical (ie, impaired verbal fluency) and hippocampal (ie, delayed word recall) involvement, rather than the severe hippocampal pathology leading to sclerosis, which is associated with LATE-NC.[8] Compared with patients with Alzheimer's disease, patients with LATE have a delayed onset of symptoms (typically over 80 years of age), predominant episodic memory impairment, and a more restricted involvement of limbic structures on imaging. Also, when PET scans for tau and amyloid β do not correlate with the clinical severity in a patient with episodic memory loss and prominent hippocampal sclerosis, these findings will be suggestive of LATE.

So what is the importance of these findings for clinical practice? By highlighting a relatively common and previously underreported pathology of TDP-43, and putting this pathology clearly within a clinical framework, the authors have reminded the dementia research community of the fundamental need to understand the diseases that they are trying to treat. By assuming that all amnestic syndromes in older patients are Alzheimer's disease, researchers and clinicians are missing potentially confounding co-pathologies and might actually be missing the key pathological driver of cognitive decline in these patients, thus identifying the wrong molecular pathway to target. Post-mortem confirmation of the key pathologies associated with cognitive decline for at least a proportion of clinical cohorts would provide an accurate assessment, rather than assuming the cohort's key pathology on the basis of clinical presentation. The neuropathology community has already developed detailed grading systems to standardise the assessment of pathologies, such as phosphorylated tau, amyloid β, α-synuclein, or cerebrovascular pathology, and the staging scheme of Nelson and colleagues can standardise the approach to TDP-43 assessment.

Their study stresses the fact that, although Alzheimer's disease is by far the most common cause of dementia, clinicians should also think of LATE, especially when the onset of symptoms occur in advanced age. It will be interesting to see how the dementia research community's understanding of this condition will evolve over time and how that will modify their approach to clinical trials.

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HK is funded by the European Academy of Neurology (Vienna, Austria). TS-S is a member of the scientific advisory board of Cognition Therapeutics and receives research grants from Autifony Therapeutics and an anonymous donor, outside the submitted work. The other authors declare no competing interests.

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The trinity of tau, trauma, and time

Published **Online**
June 11, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30219-4

Chronic traumatic encephalopathy (CTE) is, according to neuropathological diagnostic criteria, a progressive, neurodegenerative tauopathy associated with a history of repetitive head trauma. However, clinical diagnostic criteria have not been established. In a novel study,[1] the PET tracer flortaucipir was used to measure tau burden while florbetapir was used to measure amyloid-β burden in the brains of 26 former National Football League

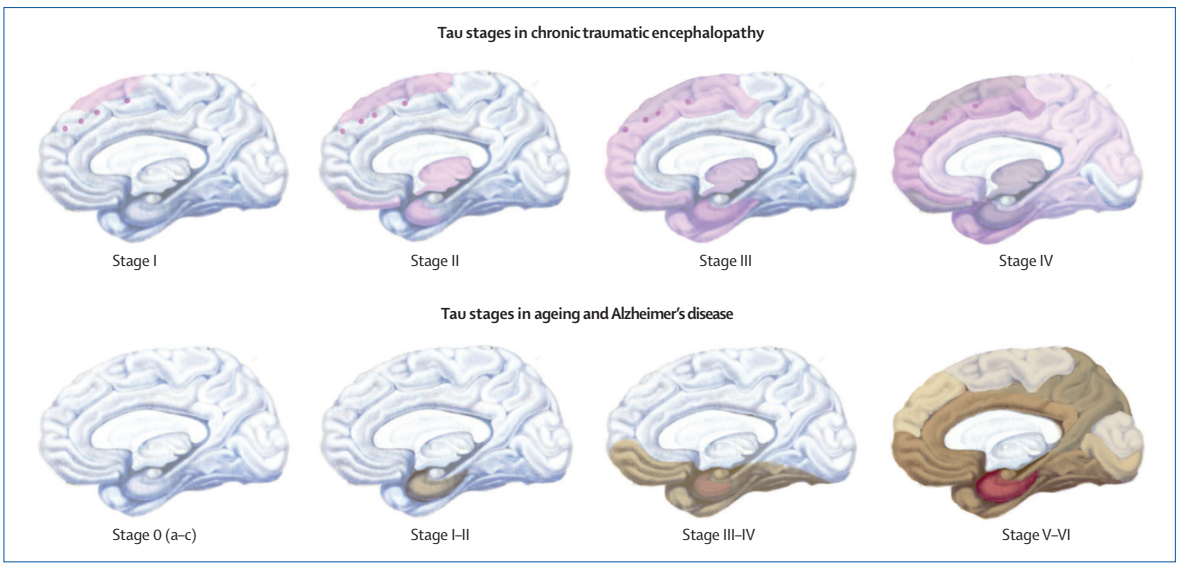

Figure: **Schematic representation of the stages of tau deposition in the brain in CTE and in Alzheimer's disease or ageing**
While tau deposition is predominantly anterior in symptomatic CTE, involving the superior frontal gyrus and the medial temporal lobe,[2] tau deposition is predominantly posterior in Alzheimer's disease dementia, involving the medial temporal lobe, temporoparietal cortices, and posterior cingulate gyrus.[4] These stereotypical patterns of tau deposition match the regional pattern of flortaucipir retention, particularly in stages III and IV of the McKee classification of CTE, observed in symptomatic former National Football League players,[1] as well as the pattern of flortaucipir retention, in particular in Braak stages V and VI, observed in Alzheimer's disease.[5,6] This matches the conclusions of a recent flortaucipir phase 3 study.[7] CTE=chronic traumatic encephalopathy.

players with cognitive and neuropsychiatric symptoms. Stern and colleagues[1] report that, at a group level, these ex-professional players had higher flortaucipir retention bilaterally in the superior frontal and medial temporal lobes, and in the left parietal cortex than 31 asymptomatic men with no history of traumatic brain injury. Higher flortaucipir retention was associated with more years of play, but no association was found between flortaucipir retention and scores on neuropsychiatric and cognitive tests. No substantial global or regional amyloid-β deposition, as measured by florbetapir PET, was detected, and no substantial differences were found between the groups.

This study is timely and prompts us to consider three different aspects: the pattern of tau deposition in CTE versus that in Alzheimer's disease; the role of tau imaging with flortaucipir PET; and the intrinsic characteristics of this report.

As described by McKee and colleagues,[2] repetitive trauma over time can lead to tau accumulation in the brain. In the study by Stern and colleagues, the pattern of flortaucipir retention in ex-football players who were symptomatic matched the known distribution of tau aggregates at stages 3 and 4 of the McKee classification of CTE (figure),[2,3] with high tau in superior frontal and medial temporal regions. This finding is in stark contrast with the regional distribution of tau observed in people with Alzheimer's disease dementia, particularly at stages V and VI as described by Braak and Braak[4] (figure). Tau imaging with flortaucipir allows the distinction of the predominantly anterior tau deposition in symptomatic football players from the predominantly posterior tau deposition observed in patients with Alzheimer's disease.[5] The study by Stern and colleagues,[1] along with two other reports by Ossenkoppele and colleagues,[6,7] constitute a trinity of papers that are crucial in defining the diagnostic role of tau imaging with flortaucipir in neurodegeneration.

In patients with Alzheimer's disease, the clinical presentation is associated with the distribution of tau, but not amyloid-β in the brain.[8] For example, in patients with posterior cortical atrophy, flortaucipir retention is mainly localised in the occipital lobe, in stark contrast with the temporoparietal and posterior cingulate distribution observed in the typical amnestic presentation of Alzheimer's disease.[5,8] These patterns, in turn, are different from the predominantly anterior flortaucipir retention pattern observed in symptomatic ex-football players.[1]

Tau imaging with flortaucipir has exquisite differential diagnostic accuracy at the advanced stages of Alzheimer's disease dementia.[6] Although the overwhelming majority of tau-positive individuals with Alzheimer's diseases

are amyloid-β-positive, not all people with amyloid-β-positive Alzheimer's disease are tau-positive, suggesting that, with the available tau tracers and PET scanners, detectable cortical amyloid-β deposition precedes detectable cortical tau accumulation. It also shows that cortical tau, as assessed by flortaucipir, is not a marker of pre-symptomatic disease, but is likely to be a robust diagnostic and predictive tool at the advanced symptomatic stages of 3R/4R tauopathies, namely typical and atypical presentations of Alzheimer's disease, and perhaps CTE too.[1,6]

Although tau deposition in the medial temporal lobes is frequently associated with memory impairment, it is cortical tau that is associated with multidomain cognitive impairment and clinical phenotype.[5]

These findings allow us to draw three conclusions. Firstly, that tau imaging with flortaucipir PET could be a very powerful tool for the differential diagnosis between different tauopathies, and between tauopathies and other neurodegenerative conditions.[1,6] Secondly, in individuals with advanced cognitive impairment or dementia, an MRI and a tau imaging study with flortaucipir PET should be enough to make a differential diagnosis of the underlying condition, with no amyloid imaging required. Thirdly, neocortical tau is not an early pre-symptomatic marker of Alzheimer's disease or CTE. Researchers and trial coordinators should be acutely aware of these issues when implementing the new amyloid, tau, and neurodegeneration biomarker classification framework.[9]

As a final note, we believe it is very important to highlight the exemplar characteristics of the report by Stern and colleagues.[1] By contrast with the hype in which this study had been advertised in the media, the paper is factual and elegant, detailing the findings and the limitations of both the technique and the study. The article is a stern reminder of how scientific reports should be written in this age of exaggeration, spin, and hype. Tau imaging with flortaucipir PET has come of age. Further studies with flortaucipir and other novel selective tau tracers will continue to aid in defining, revising, and refining the role of tau in neurodegenerative conditions.

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SB reports personal fees and other from Hoffmann-La Roche, outside the submitted work, and has a patent pending for a method for detection of a neurological disease. VLV and VD declare no competing interests.

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