Spatial distribution of PET radiotracers may help in differentiating Alzheimer's disease and rare dementias

Sebastian Palmqvist, MD, PhD[1,2*], Arman Eshaghi, MD, PhD [3,4]

[1] Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Sweden.
[2] Memory Clinic, Skåne University Hospital, Sweden.
[3] Queen Square Multiple Sclerosis Centre, UCL Queen Square Institute of Neurology, University College London, United Kingdom

[4] Centre for Medical Image Computing (CMIC), Department of Computer Science University College London

*Corresponding author
Sebastian Palmqvist
Memory Clinic
Skåne University Hospital
205 02 Malmö
Sebastian Palmqvist
e-mail: ebastian.palmqvist@med.lu.se

**DISCLOSURES.** The authors report no disclosures concerning this work.

The full disclosure statement is as follows:

AE has received speaker's honoraria from Biogen and At The Limits educational programme. He has received travel support from the National Multiple Sclerosis Society and honorarium from the *Journal of Neurology, Neurosurgery and Psychiatry* for Editorial Commentaries.

Application of Positron Emission Tomography (PET) to Alzheimer's disease (AD) has enabled us to visualize beta-amyloid (Aβ) and tau pathologies *in vivo*. PET has advanced our understanding of how the disease develops over decades –from preclinical stages to the dementia syndrome. Biomarkers of Aβ and tau have already been implemented in the diagnostic framework of AD. However, in clinical practice, only Aβ-PET has been used to diagnose AD. Such may soon be the case for tau-PET too, because results are emerging on its potential importance in differentiating AD from its mimics.[1, 2] Aβ- and tau biomarkers can improve the diagnostic accuracy of the typical amnestic AD, which usually presents with gradual deterioration of memory and later dysfunction in other cognitive domains. These radiotracers can also enable us to identify more challenging AD cases: those with cognitive symptoms less typical of AD. These include for example a predominant impairment of either verbal performance (logopenic AD) or visuospatial performance (posterior cortical atrophy; PCA). Such cases would previously were only identified as AD at a very late disease stage or after a neuropathological assessment.

In this issue of *Neurology*, La Joi et al. have examined the relationship between the clinical AD phenotypes (including PCA, logopenic and more typical AD) and patterns of tau- and Aβ-PET. Besides, they examined how age and *APOE* genotype (specifically the presence of an *APOE* ε4 allele that is known to increase the risk of AD significantly), were associated with the PET measures. Overall, the study mostly confirms previous findings.[3-8] The strength and novelty of the study, however, lie in the impressive number of rare AD phenotypes, concomitant investigation of two PET radiotracers, and the relationship across regional radiotracer uptake and clinical symptoms. Further, a detailed analysis of *APOE* genotype carriers with tau- and Aβ-PET provides a comprehensive picture reported for the first time in the literature.

In summary, the authors found that there was no association between the pattern of the Aβ-PET signal and the AD phenotypes (or a negligible difference in PCA). For tau-PET, on the

other hand, they confirm that the regional signal was different across phenotypes such that a relative increase in the left temporal (language) region was seen in logopenic AD; a relative increase in the occipital region was seen in PCA; and a relative increase in the medial temporal lobe (MTL) was seen in the typical AD. The authors demonstrate an overarching "AD pattern" regardless of phenotype: an increased tau-PET signal in the temporoparietal region. Further, they found that the global tau-PET signal was lower in older persons with AD, irrespective of clinical phenotype. Presence of *APOE* ε4 allele was not associated with any Aβ-PET pattern, but with an increased tau-PET signal in the MTL regardless of the Aβ pathology.

This work characterizes the heterogeneity of AD and therefore may open new avenues for future research in precision drug targeting in AD. Some of the study findings may raise questions too. In near future anti-Aβ treatments may become available. An FDA decision is expected in March 2021 for the first anti-Aβ treatment. Potential anti-tau treatments, which are in earlier stages of development, may also become available in future. If MTL tau and memory impairment can appear due to the sole presence of the *APOE* ε4 genotype regardless of the Aβ burden as also shown in previous studies in those with and without Aβ pathology[3, 8], will anti-Aβ treatments have less of an effect on cognition in some *APOE* ε4 positive individuals? And does the correlation between high age and low tau-PET signal in AD (adjusted for clinical severity) mean that older people will have less effect of anti-tau and anti-Aβ treatments? Hopefully these concerns can be addressed in future studies.

Although not the primary aim of the study, the findings may provide some considerations for clinical practice. *APOE* genotyping is sometimes used as part of the clinical work-up of AD. In the absence of Aβ PET radiotracers, the presence of one or especially two ε4 alleles may increase the likelihood of an AD diagnosis. According to the present and previous works[8], the ε4 positivity is associated with MTL tau accumulation which results in an amnestic phenotype. In individuals with a non-amnestic presentation, the ε4 negativity may therefore

not decrease the probability of an AD diagnosis as would be the case in an amnestic presentation.

When visually inspecting an Aβ-PET scan it is mostly just of interest to assess whether there is an increased global signal or not, as the pattern provides no or very little information. However, in preclinical stages, zooming in on certain regions may contribute to an earlier identification of accumulating Aβ.[9, 10]

Although the results of this study cannot be used for decision making at an individual level, it can have implications for future research in clinical practice. Associations between the tau-PET pattern and clinical symptoms could provide complementary information about the diagnosis in addition to an Aβ-PET scan, which is less specific for AD. For example, it may be difficult to say if an 83-year old patient with memory impairment and a positive Aβ-PET scan has a symptomatic AD. It could very well be a preclinical asymptomatic amyloidosis (present in 40% of cognitively unimpaired at this age[11]) with symptomatic cerebrovascular lesions, TDP-43 pathology in limbic regions (LATE) or some other cause of memory impairment. But with a tau-PET that shows increased signal the medial temporal lobe, the diagnosis is almost 100% certain: amnestic AD. Conversely, a discrepancy between regional tau-PET uptake and phenotype may increase the likelihood of other diagnoses. For example, a pronounced and progressive verbal impairment in combination with no or a weak tau-PET signal restricted to the MTL may increase the likelihood that a language variant of frontotemporal dementia is causing the symptoms instead of logopenic AD. Future research with a focus on individual outcomes will clarify these speculations.

REFERENCES

1. Ossenkoppele R, Rabinovici GD, Smith R, et al. Discriminative Accuracy of [18F]flortaucipir Positron Emission Tomography for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA 2018;320:1151-1162.
2. Leuzy A, Smith R, Ossenkoppele R, et al. Diagnostic Performance of RO948 F18 Tau Positron Emission Tomography in the Differentiation of Alzheimer Disease From Other Neurodegenerative Disorders. JAMA Neurol 2020.
3. Weigand AJ, Thomas KR, Bangen KJ, et al. APOE interacts with tau PET to influence memory independently of amyloid PET in older adults without dementia. Alzheimers Dement 2020.

4. Mattsson N, Ossenkoppele R, Smith R, et al. Greater tau load and reduced cortical thickness in APOE epsilon4-negative Alzheimer's disease: a cohort study. Alzheimers Res Ther 2018;10:77.
5. Ossenkoppele R, Schonhaut DR, Scholl M, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 2016;139:1551-1567.
6. Pontecorvo MJ, Devous MD, Sr., Navitsky M, et al. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain 2017;140:748-763.
7. Scholl M, Ossenkoppele R, Strandberg O, et al. Distinct 18F-AV-1451 tau PET retention patterns in early- and late-onset Alzheimer's disease. Brain 2017;140:2286-2294.
8. Therriault J, Benedet AL, Pascoal TA, et al. Association of Apolipoprotein E epsilon4 With Medial Temporal Tau Independent of Amyloid-beta. JAMA Neurol 2020;77:470-479.
9. Mattsson N, Palmqvist S, Stomrud E, Vogel J, Hansson O. Staging beta-Amyloid Pathology With Amyloid Positron Emission Tomography. JAMA Neurol 2019.
10. Palmqvist S, Scholl M, Strandberg O, et al. Earliest accumulation of beta-amyloid occurs within the default-mode network and concurrently affects brain connectivity. Nature communications 2017;8:1214.
11. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924-1938.