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Topographic staging of tau positron emission tomography images

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Abstract

Introduction: It has been proposed that the signal distribution on tau positron emission tomography (PET) images could be used to define pathologic stages similar to those seen in neuropathology.
Methods: Three topographic staging schemes for tau PET, two sampling the temporal and occipital subregions only and one sampling cortical gray matter across the major brain lobes, were evaluated on flortaucipir F 18 PET images in a test-retest scenario and from Alzheimer's Disease Neuroimaging Initiative 2.
Results: All three schemes estimated stages that were significantly associated with amyloid status and when dichotomized to tau positive or negative were 90% to 94% concordant in the populations identified. However, the schemes with fewer regions and simpler decision rules yielded more robust performance in terms of fewer unclassified scans and increased test-retest reproducibility of assigned stage.
Discussion: Tau PET staging schemes could be useful tools to concisely index the regional involvement of tau pathology in living subjects. Simpler schemes may be more robust.

Keywords: Tau; PET; Flortaucipir; Alzheimer; Staging; Stage; Classification; Image; Braak; AV-1451; T807

1. Introduction

Alzheimer's disease (AD) is defined neuropathologically by the presence of amyloid β plaques and neurofibrillary tangles (NFTs) of misfolded phosphorylated tau protein [1–3]. Whereas amyloid plaques are widespread in the neocortex [2], in sporadic AD, NFTs present in characteristic patterns that suggest tau pathology begins in the entorhinal cortex and then spreads in a largely stereotypical fashion first into the inferior and lateral temporal cortices, followed by regions in the parietal and frontal lobes, and finally the primary sensory cortices in end-stage disease [1]. This has been codified topographically in neuropathologic tau staging schemes [4,5].

The recent development of radiolabeled positron emission tomography (PET) ligands for tau tangles [6–8] has enabled NFTs to be imaged in the brains of living humans. Initial studies have demonstrated that in vivo tau PET

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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images show diverse patterns of tracer binding consistent with those observed in neuropathologic studies, providing strong prima facie evidence that these ligands reflect the distribution of tau pathology in the living brain [9–13].

The availability of these PET tracers and other biomarkers has stimulated the formulation of classification frameworks for clinical AD research based on sequential biological changes in the brain [14–20]. These criteria enable the severity of cognitive and functional impairment to be complemented by objective measures of disease pathology and are refining the concepts of both diagnosis and stage in the study of AD. To date, much of the emphasis has been on dichotomized biomarker measurements, indicating the presence or absence of different pathological changes [21], exemplified most recently by the A/T/N system based on abnormal amyloid, tau, and/or neurodegeneration [16]. However, the stereotypical patterns of NFT localization also allow for a more granular regional staging of tau pathology per se, and neuropathologic observations can inform image-based classification or staging schemes that can be applied to tau PET images in vivo [10,11]. These topographic image classification schemes provide a concise summary of the anatomical distribution of tracer binding that conveys the extent of regional involvement. Interpretation of these profiles within a staging framework rests on the assumption that certain profiles succeed others as the disease progresses. Findings in both neuropathology studies and emerging data with tau PET tracers support this view, with the degree of regional involvement associated with amyloid status, cognitive performance, and clinical disease stage [10,13,22,23].

One of these recently described staging algorithms [10] is based on small regions of interest (ROIs) in the anterior temporal and occipital lobes and classification rules that match as accurately as possible the 6-stage operationalized neuropathologic staging scheme proposed by Braak *et al.* [4]. This approach confirmed the predominance of stereotypical tau PET patterns in individuals across the AD spectrum, but 7% of the scans in that study were not able to be matched to one of the a priori–defined patterns, which could be a limitation for prospective use of that method in clinical research. Moreover, the very small ROIs in that scheme are potentially sensitive to variations in image preprocessing, atrophy, and experimental noise. In addition, the medial temporal lobe (MTL) regions distinguishing stages 1–3 are potentially prone to contamination from adjacent extraparenchymal signals (e.g., optic nerve) and to tracer binding in the choroid plexus. As a result, it may be difficult to reliably distinguish between stages 1, 2, and 3 using that method. Finally, the more advanced stages 5–6 do not capture the variability across subjects in the broader neocortical involvement of tau in the later stages of AD.

Motivated by these limitations, we propose two simpler tau PET staging schemes that use fewer, larger ROIs and simplified decision rules. The first of these also targets regions restricted to the anterior temporal and occipital lobes but uses larger atlas-based masks and consolidates regions in the MTL. The second is based on the average signal in each of the temporal, parietal, and frontal lobes, thus sampling more of the cortex overall. The rationale for these alternative schemes is to improve robustness to image noise (e.g., test-retest), simplify implementation, and minimize unclassifiable scans. In the case of the second scheme, the rationale was also to provide more dynamic range in the assigned stages for cases with more widespread tau load. Here, we evaluate these two schemes, in comparison to that previously described [10], applied to flortaucipir F 18 scans acquired in a test-retest scenario and in the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI-2) study. In addition to profiling each scheme as a staging tool, we also assess the three staging schemes when dichotomized to define each scan as tau positive or tau negative.

2. Methods

2.1. Data sets

Data from four tau imaging studies were used to form three data sets for the present analysis. The first data set was a set of flortaucipir F 18 scans from N = 14 young healthy individuals visually and quantitatively (bilateral entorhinal cortex standardized uptake value ratio [SUVr] < 1.2) determined to be tau negative and used as a reference sample [10]. These scans were drawn from an exploratory phase 1 study and from a larger phase 2 study (NCT02016560) undertaken as part of Avid Radiopharmaceuticals' clinical development program for the flortaucipir F 18 PET radiotracer. The second data set was a test-retest study (N = 21, retest interval 4–28 days) in participants assessed as cognitively normal (CN) or diagnosed with either mild cognitive impairment (MCI) or symptomatic AD [24]. This data set was used to assess within-subject reproducibility of the staging algorithms. The third data set comprised N = 98 participants in the ADNI-2 that received a flortaucipir F 18 PET scan. Further details of the ADNI consortium are provided in the Supplementary Material. Amyloid positivity (A+) in ADNI-2 was determined from a Florbetapir F 18 PET scan, processed by the ADNI PET core (University of California, Berkeley) and with a cortical SUVr > 1.11. All subjects gave informed consent.

2.2. PET image acquisition and processing

Participants received an intravenous injection of approximately 10 mCi flortaucipir F 18, and PET images from four 5-minute frames between 80 and 100 minutes following the radiotracer injection were analyzed.

The four 5-minute flortaucipir F 18 PET scans were corrected for motion, averaged, and coregistered to the individual participant's accompanying T1-weighted magnetic resonance imaging (MRI) scan. For the ADNI-2 study, preprocessed flortaucipir F 18 PET scans were downloaded from the ADNI Laboratory of Neuro Imaging (http://adni.loni.usc.edu) site. The MRI scan was spatially normalized to the MNI152 T1 MRI template, and this transformation