A data-driven staging of *in-vivo* tau deposition is consistent with Braak's post mortem staging

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Introduction

The presence of aggregates of tau protein, known as neurofibrillary tangles (NFTs), is necessary to establish a definitive diagnosis of Alzheimer's disease (AD) at autopsy. Braak and Braak, (1991) defined a widely used six-stage system of staging the severity of NFT pathology based on neuropathological examination. In this autopsy scheme, pathology begins in the transentorhinal region in the earliest stages before spreading to the limbic regions and finally throughout the cortex in later stages, when clinical manifestations of AD occur.

In vivo staging of tau pathology using PET tracers shows a qualitatively similar pattern of tracer uptake evolution compared to autopsy and significant group differences in tracer uptake between healthy and AD subjects in regions related to early, mid and late Braak stages (Schöll et al., 2016). Further to this, Cho et al., (2016) used a frequentist approach based on pre-defined standardized uptake value ratio (SUVR) cut-offs to show that the spread of tau pathology using PET *in vivo* replicates the Braak autopsy staging.

Here we take a fully data-driven and automated approach to stage tau pathology using tau PET. Our approach does not rely on predefined biomarker cut-offs and, importantly, is able to quantify the uncertainty in the estimated sequence of stages. We can use the estimated sequence to stage subjects based on the pattern of tau pathology across their brain.

Methods

We analyzed cross-sectional tau PET data from 531 subjects (332 cognitively normal / 154 MCI / 45 AD) within the Alzheimer's Disease Neuroimaging Initiative (ADNI), using the earliest available data-point for each subject. We downloaded the UC Berkeley flortaucipir dataset (version 2018-10-15) from the ADNI website (https://ida.loni.usc.edu), containing partial volume corrected cortical and subcortical Freesurfer-based SUVR in regions of interest and reference regions (Baker et al., 2017; Maass et al., 2017). The dataset also contains SUVR information for composite regions as defined in (aggregated) Braak stages (I/II, III/IV and V/VI). As recommended, we normalized the composite or individual region of interest SUVRs by the inferior cerebellar grey matter reference region. We then corrected the SUVRs for sex, education level and race (white/not Hispanic versus other) and used the event based model (EBM; Young et al., 2014) to find the most likely ordering of regional tau abnormality in the progression from normal cognition to diagnosed AD. The distinction between normal and abnormal tau in a region is based on a mixture of two Gaussians fit to the cognitively normal and AD subjects. We computed the expected sequence and its uncertainty using one hundred bootstrapped EBM sequences.

Results

In Figure 1 the coarse EBM model correctly identified with high confidence the expected progression of composite Braak regions. In the fine-grained version, abnormality is seen first within the amygdala, entorhinal cortex and hippocampus, followed by the temporal and parietal lobes and finally, with increased uncertainty in ordering, within the rest of the neocortex. Insula and lingual abnormality occurs later than predicted by the Braak staging, agreeing with Cho et al., (2016).

Figure 2 shows a high fraction of cognitively normal (over 0.9 in both EBMs) and MCI subjects (over 0.6 in both cases) are assigned stage zero, meaning no abnormal regions. Only a small fraction of AD subjects (< 0.2 in both cases) are assigned stage zero in contrast.

Subjects' estimated model stage had high correlation with their MMSE score (coarse: r = -0.56, $p = 3\times10^{-45}$, fine: r = -0.57, $p = 3\times10^{-46}$) and their RAVLT immediate recall score (coarse: r = -0.48, $p = 4\times10^{-31}$, fine: r = -0.46, $p = 4\times10^{-28}$).

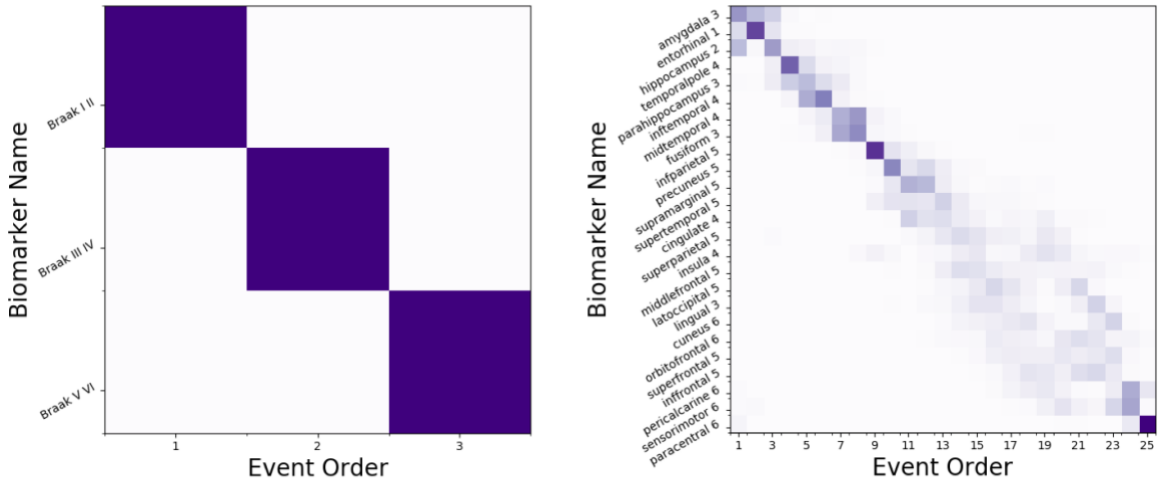

Figure 1 Left: Positional variance diagram showing most likely sequence of events in the progression from normal cognition to diagnosed AD. In this case an event is a transition from normal to abnormal levels of SUVR within a composite Braak region. Within each region, a mixture of two normal distributions was fitted to describe the likelihood of a measurement given a subject is either cognitively normal or diagnosed AD. **Right:** same for individual cortical and subcortical ROIs, with expected Braak stage given as a number between one and six. **Both:** the ordering shown is the expectation across 100 bootstrapped orderings.

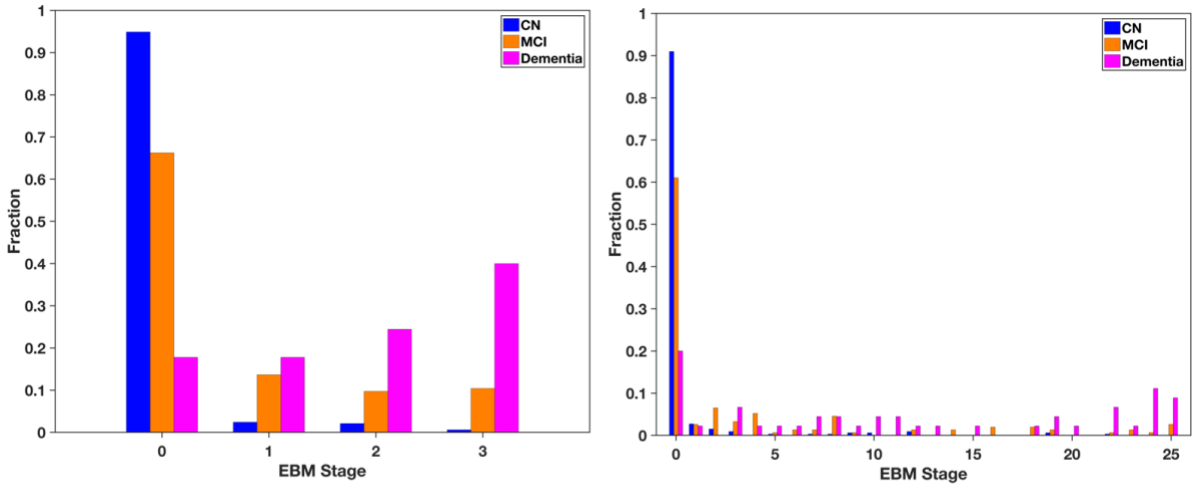

Figure 1 Left: Fraction of subjects from each diagnostic group at each EBM stage for composite Braak region based staging. **Right:** Same for fine individual cortical and subcortical ROI based staging.

Conclusions

The EBM recovers a fine-grained evolution of in-vivo tau pathology stages and is consistent with Braak's post mortem staging. The EBM approach avoids predefined cut-points and easily allows a priori defined regions.

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