# Amyloid-beta accumulation affects in vivo staging of tau deposition in cognitively impaired individuals

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## Background

Several recent tau PET based studies have explored the interaction between amyloid-beta (Aβ) deposition and the spread of tau pathology. Pontecorvo et al., (2017) showed higher tau-PET tracer uptake in Aβ positive mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects relative to respective Aβ negative subjects. Schwarz et al., (2016) showed Aβ positive subjects in both the MCI and AD groups had higher estimated Braak stages.

We further investigate this interaction using an approach that estimates the most likely sequence of tau spread without relying on regional abnormality cut-points. We show the benefit of fine-grained staging in identifying subjects in the earliest stages of amyloid dependent tau pathology.

## Methods

We used cross-sectional tau PET data from 344 subjects (201 cognitively normal / 109 MCI / 34 AD) within the Alzheimer's Disease Neuroimaging Initiative (ADNI), using the earliest available data-point for each subject. We downloaded the UC Berkeley flortaucipir (AV-1451) dataset (version 2018-10-15) from the ADNI website (https://ida.loni.usc.edu), containing partial volume corrected regional SUVRs (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). We normalized all SUVRs by the inferior cerebellar grey matter reference region and corrected each for sex, education level and race (white/not Hispanic versus other).
We used the latest (up to two years prior) demographic, diagnostic and amyloid burden (florbetapir, AV-45) information from the ADNIMERGE dataset, also available on the ADNI website. We used the event based model (EBM; Young et al., 2014) to find the most likely ordering of tau abnormality in the progression from normal cognition to diagnosed AD.

## Results

Our models identified the expected spread of tau pathology (Figure 1). Aβ positivity increased the fraction of MCI subjects at higher stages (Figures 2 and 3). The fine-grained model identified more CN and MCI subjects with early tau pathology, particularly among Aβ positive subjects (Figure 4).

## Conclusions

The spread of tau pathology is affected by Aβ positivity and may be better detected by fine grained staging models.

**References**

Pontecorvo, M.J., et al. 2017, Brain
Schwarz, A.J., et al. 2016, Brain

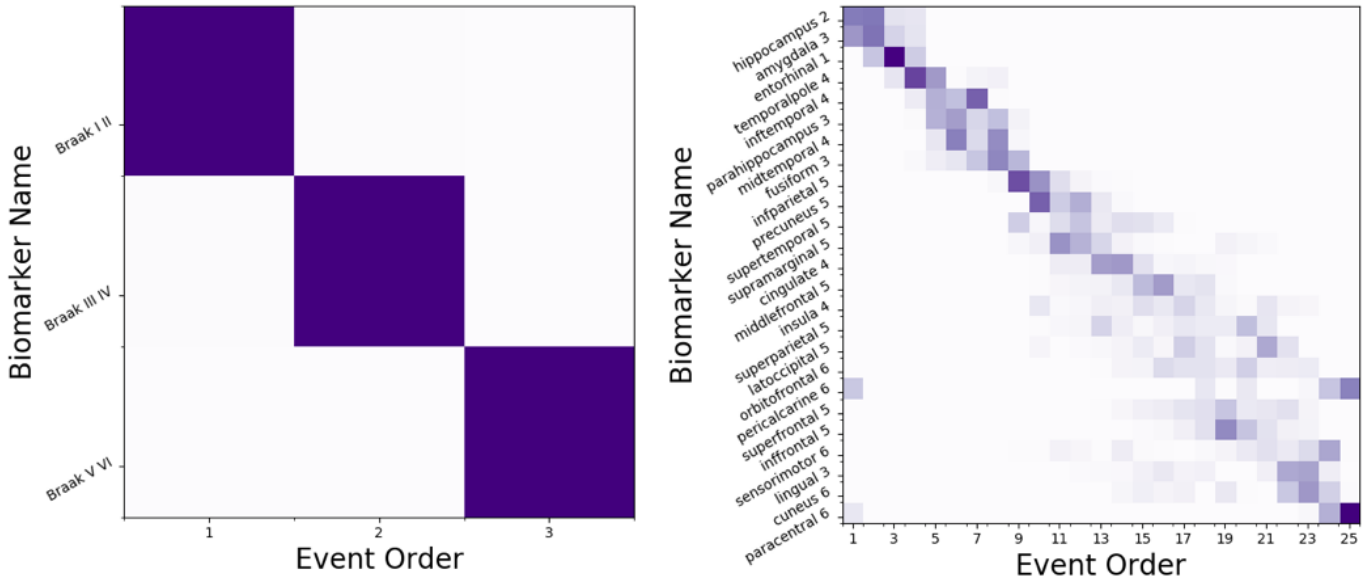


**Figure 1 Left:** positional variance diagram from event based model (EBM) showing most likely sequence of tau pathology spread in the progression from normal cognition to diagnosed AD. The distinction between normal and abnormal tau in each composite Braak region is based on a mixture of two Gaussians fit to the cognitively normal and AD subjects. **Right:** positional variance diagram for fine-grained regional staging, with expected Braak stage of each region given as a number between one and six. **Both:** the expected sequences and their uncertainty are based on 100 bootstrapped EBM sequences.

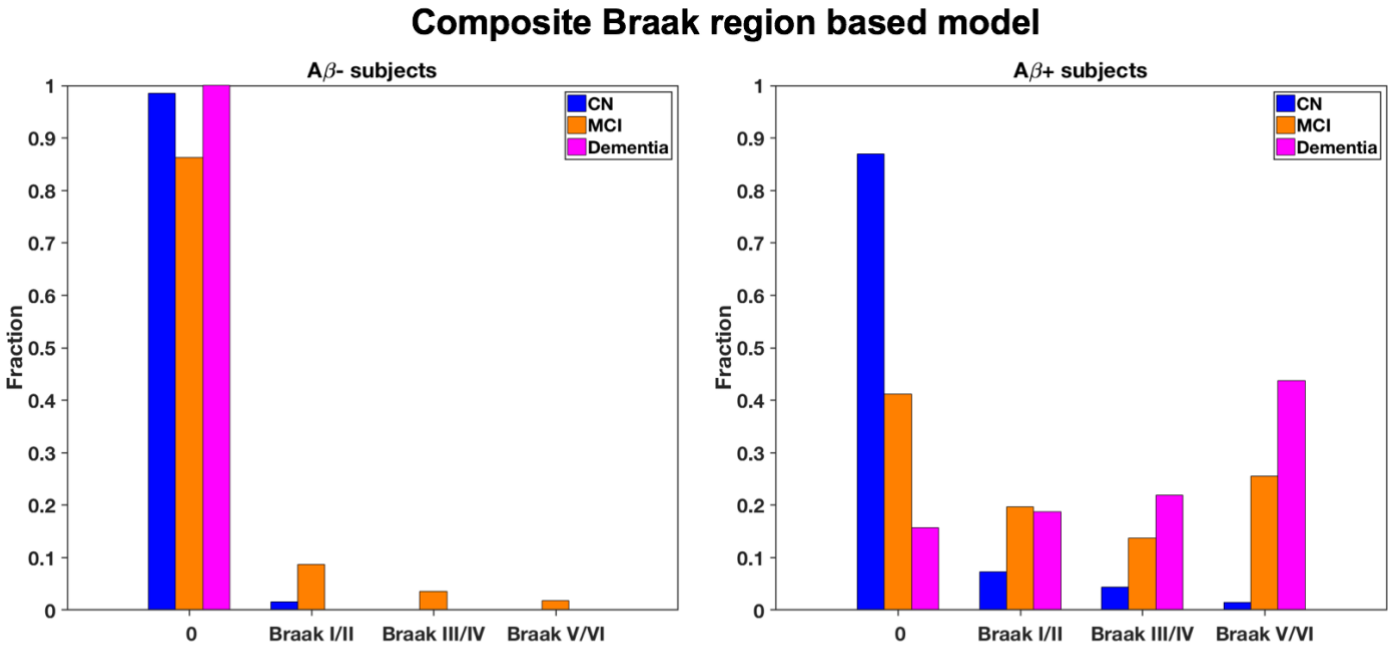


**Figure 2 Left:** fraction of Aβ negative subjects (132 CN / 58 MCI / 2 AD) within each diagnostic group at each estimated stage of tau pathology. **Right:** same Aβ positive subjects (69 CN / 51 MCI / 32 AD). Aβ positive subjects were those with florbetapir-based global SUVR > 1.11.

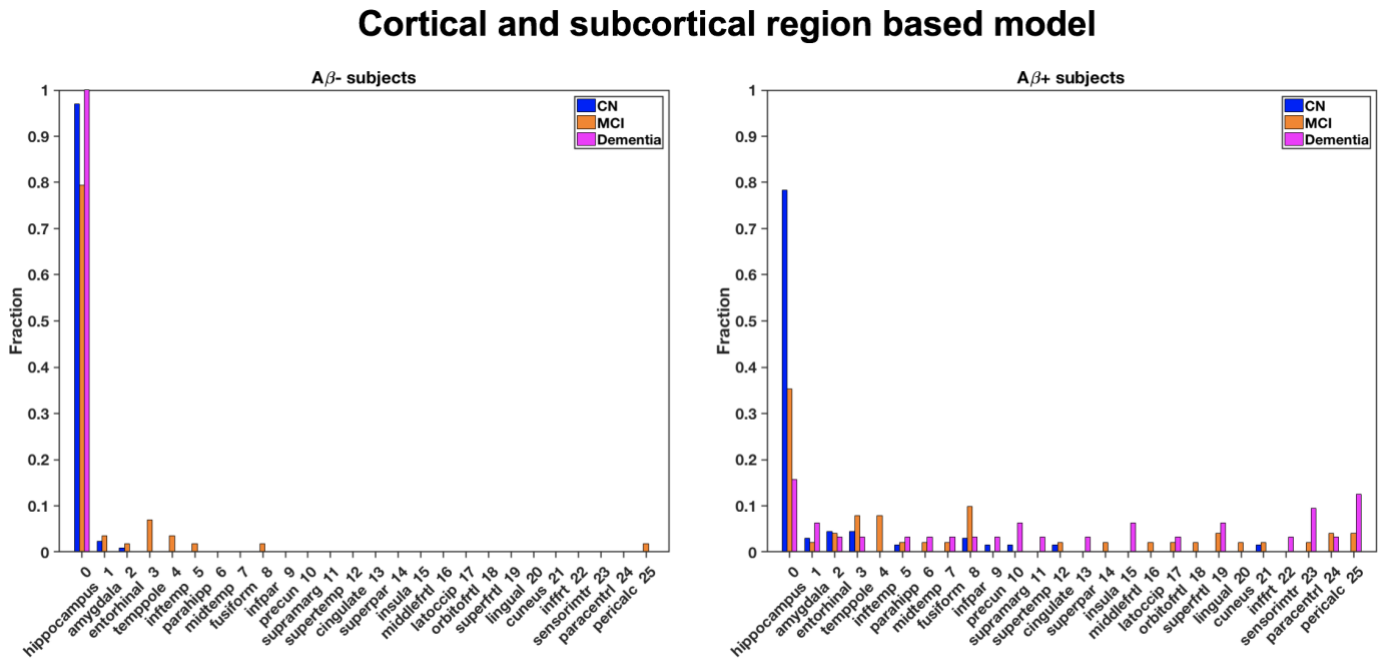


**Figure 3 Left:** fraction of Aβ negative subjects (132 CN / 58 MCI / 2 AD) within each diagnostic group at each estimated stage of tau pathology. **Right:** same Aβ positive subjects (69 CN / 51 MCI / 32 AD). Aβ positive subjects were those with florbetapir-based global SUVR > 1.11.

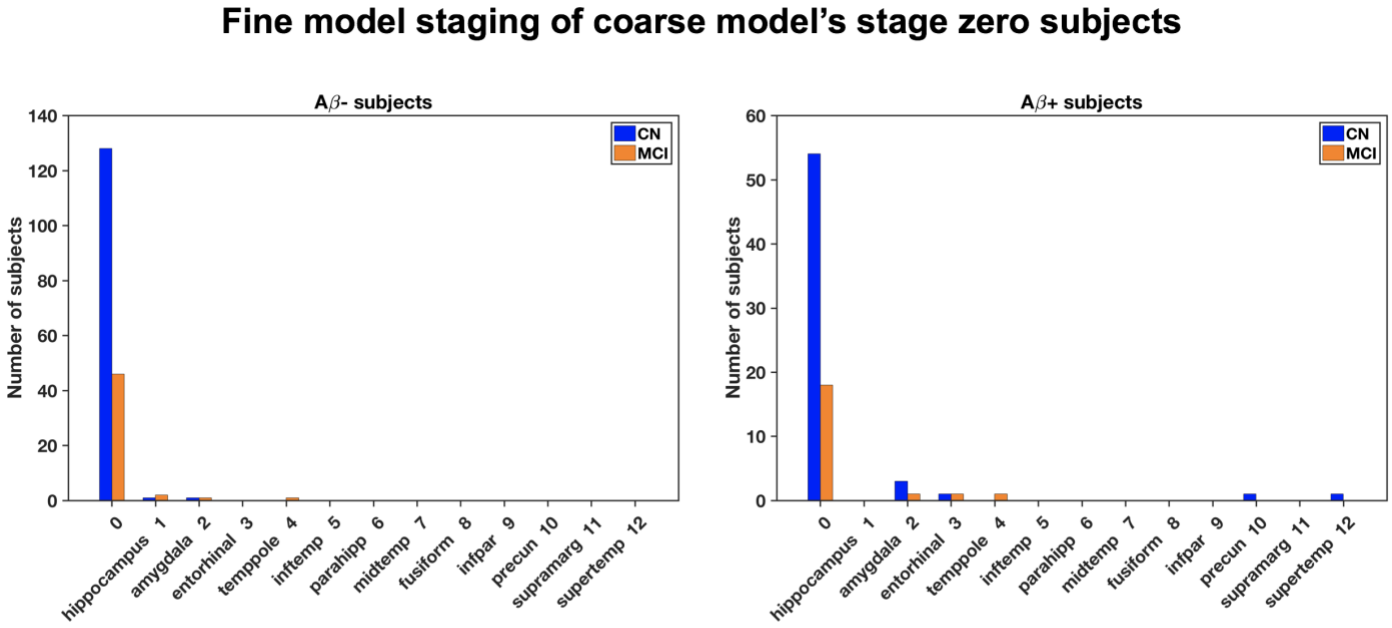


**Figure 4 Left:** fine-grained stages of Aβ negative subjects at coarse stage zero: 2% of CN subjects (2/130) and 8% of MCI subjects (4/50) have fine stage greater than zero. **Right:** same for Aβ positive subjects: 10% of CN subjects (6/60) and 14% of MCI subjects (3/21) at coarse stage zero have fine stage greater than zero. **Both:** no fine stage zero subjects had greater than zero coarse stage.