Appendix e-1

Context for the 8 reported cases

We noticed that 7 tau-negative amnestic participants during our lab meetings to review molecular PET imaging. In order to obtain a denominator, we identified all participants who had undergone tau-PET imaging and been given a diagnosis of possible or probably Alzheimer's disease at the Mayo Clinic ADRC. A total of 74 participants were identified. Of these, 7 were tau-negative (<1.33 SUVR).

Of the participants below the age of 75, one out of the fifty was negative, and had been diagnosed with corticobasal syndrome thought to be due to AD. On visual inspection there was clearly elevated tau PET signal in the parietal and frontal regions, but not in the areas captured by the meta ROI. The presentation was non-amnestic and hence is of little relevance to the current study. The six tau-negative participants older than 75 were included in the present study. As such, of the 24 participants diagnosed with possible or probable AD-dementia above the age of 75 for which amyloid and tau pet were available, six were negative on tau imaging:

	Number of participants with possible or probably AD	Number of tau cases with tau SUVR <1.33	Percentage of tau negative cases
< 75 y/o	51	1	1.96%
≥ 75 y/o	24	6	25%

We did extend the search to amnestic MCI participants, but this is inherently challenging because of the multitude of etiologies that could underlie MCI.

	Number of participants with amnestic MCI	Number of tau cases with tau SUVR <1.33	Percentage of tau negative cases
≥ 75 y/o	13	9	69%

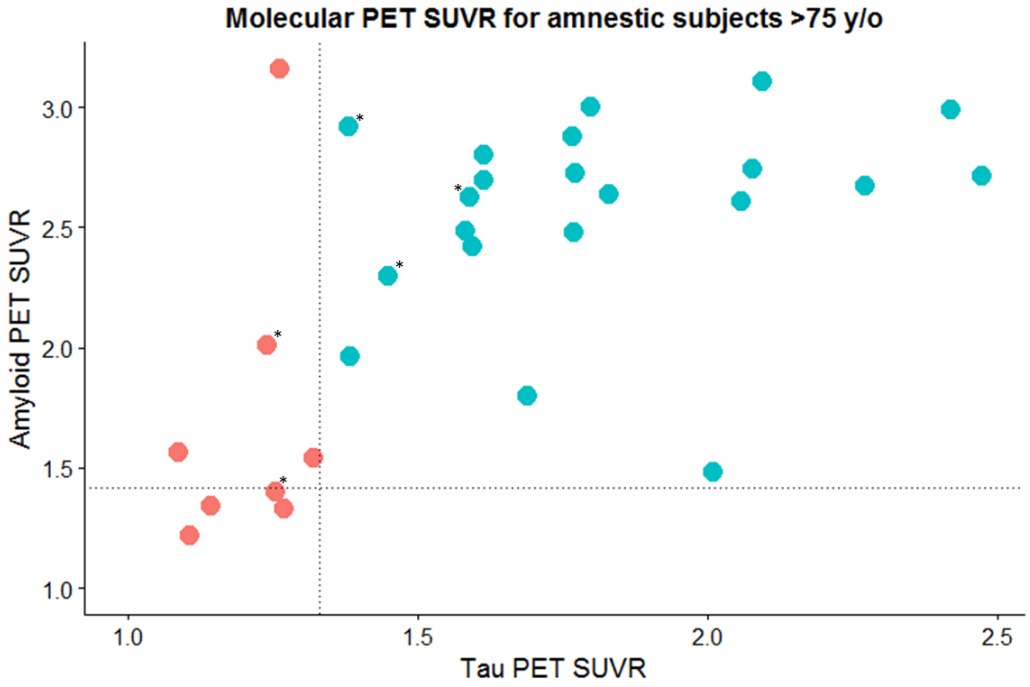
Of the aMCI cases, 4 had DLB features (3 tau-negative), two were on medications that were thought to contribute (both tau negative), one had significant depression (tau negative). After excluding these participants, a more accurate picture of the amnestic MCI cases emerges:

	Number of participants with amnestic MCI*	Number of tau cases with tau SUVR <1.33	Percentage of tau negative cases
≥ 75 y/o	6	3	50%

This includes the two cases in our study, which were specifically thought to have amnestic MCI *due to* underlying Alzheimer's disease, and one participant with amnestic MCI where no etiological prediction was made. As such, we did not include this participant. Combining all the participants identified above the age of 75, we get the following:

	Number of participants with amnestic MCI or dementia thought to be due to AD	Number of tau cases with tau SUVR <1.33	Percentage of tau negative cases
≥ 75 y/o	29	8	27.5%

These are the 8 participants are described in the current study. The relationship between amyloid and tau SUVR for these 29 subjects is given below:

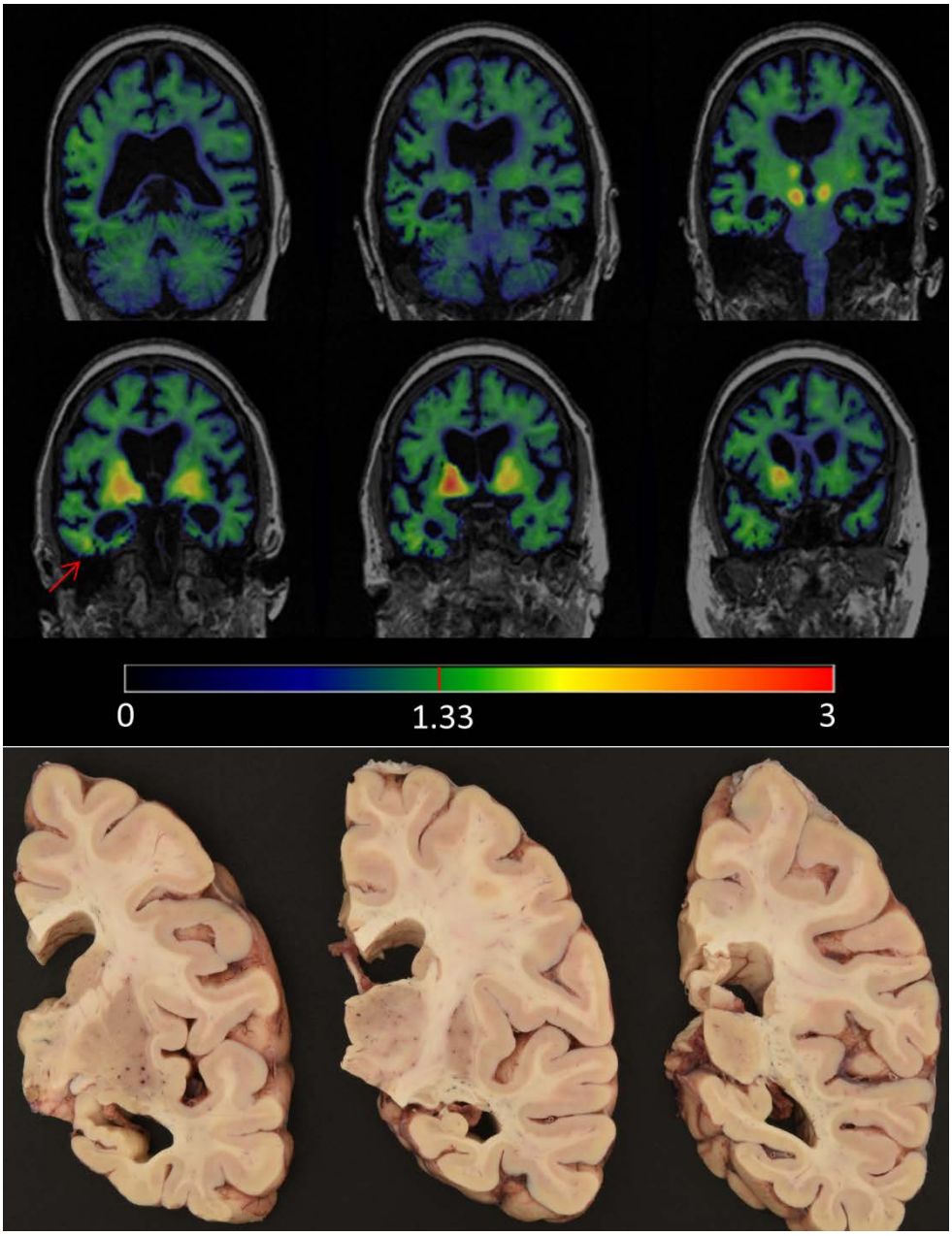


Supplemental Figure 1: Amyloid and tau PET SUVR for amnestic subjects ≥ 75.

Cut-points are indicated by dotted lines. Red = tau-negative subjects. * = aMCI participant

Details of Participant 2

This participant was near the tau SUVR cut point, and had a higher SUVR in the entorhinal versus the meta-ROI. Despite the low levels of tau PET signal seen in the inferior temporal and some other meta-ROI regions, highlighted in Supplemental Figure 2, she did not have significant AD pathology (A1B1C0, Thal 1, Braak I-II). Instead, she harbored evidence of TDP-43 positive inclusions and pathologic evidence of hippocampal sclerosis, along with PART and argyllophillic grain disease.



Supplemental Figure 2: Representative tau PET images and gross pathological images for participant 2.

Note the low level elevation in flortaucipir (arrow) in the setting of marked hippocampal atrophy (top panels), which is evident on post mortem examination too (bottom panel).