Cognitive, Pathological and Prognostic Different Brain Ages in the Early Alzh Continuum

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Deviations of brain age from chronological age, known as the brain age gap (BAG), have been linked to intracerebral abnormalities, e.g. Alzheimer's disease (AD). MRI and FDG-PET can quantify brain atrophy and metabolism, respectively, which are useful for estimating brain age. Here, we compare the cognitive, pathological and prognostic profiles of brain age estimation from structural MRI and FDG-PET in cognitively normal individuals (CN), and individuals with subjective cognitive decline (SCD) or mild cognitive impairment (MCI).

Methods: Machine learning pipelines were trained to estimate brain age from 185 matched T1-weighted MRI or FDG-PET scans of CN from the Alzheimer's Disease Neuroimaging Initiative and validated in external test sets. BAG was correlated with measures of cognition and AD neuropathology in CN, SCD and MCI. Finally, BAG was used to predict individuals' cognitive status after two years, using logistic regression and its prognostic potential was compared with existing biomarkers of AD.

Results: MRI (mean absolute error, MAE=2.49 years) and FDG-PET (MAE=2.60 years) both estimated chronological age well. FDG-PET-derived BAG was associated with cognitive performance at the SCD and MCI stage, while MRI-derived BAG was associated with cognitive performance in MCI and with AD neuropathology in both, SCD and MCI. FDG-PET-derived BAG was not predictive of cognitive status after two years, but MRI-derived BAG showed competitive prognostic performance compared to established prognostic biomarkers of AD in MCI (AUC = .73).

Conclusion:
Brain age is reliably estimated from MRI or FDG-PET. MRI-derived BAG reflected neurological indications of AD, whereas FDG-PET-derived BAG was more sensitive to early, global cognitive dysfunction.

[+] both authors contributed equally

[*] 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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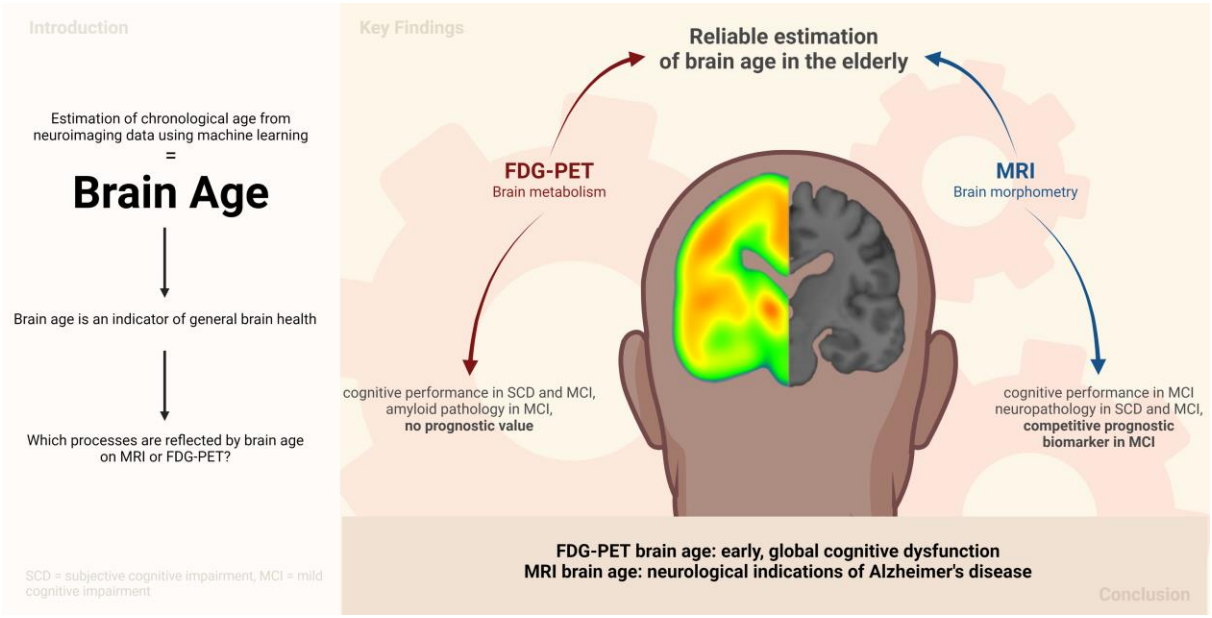

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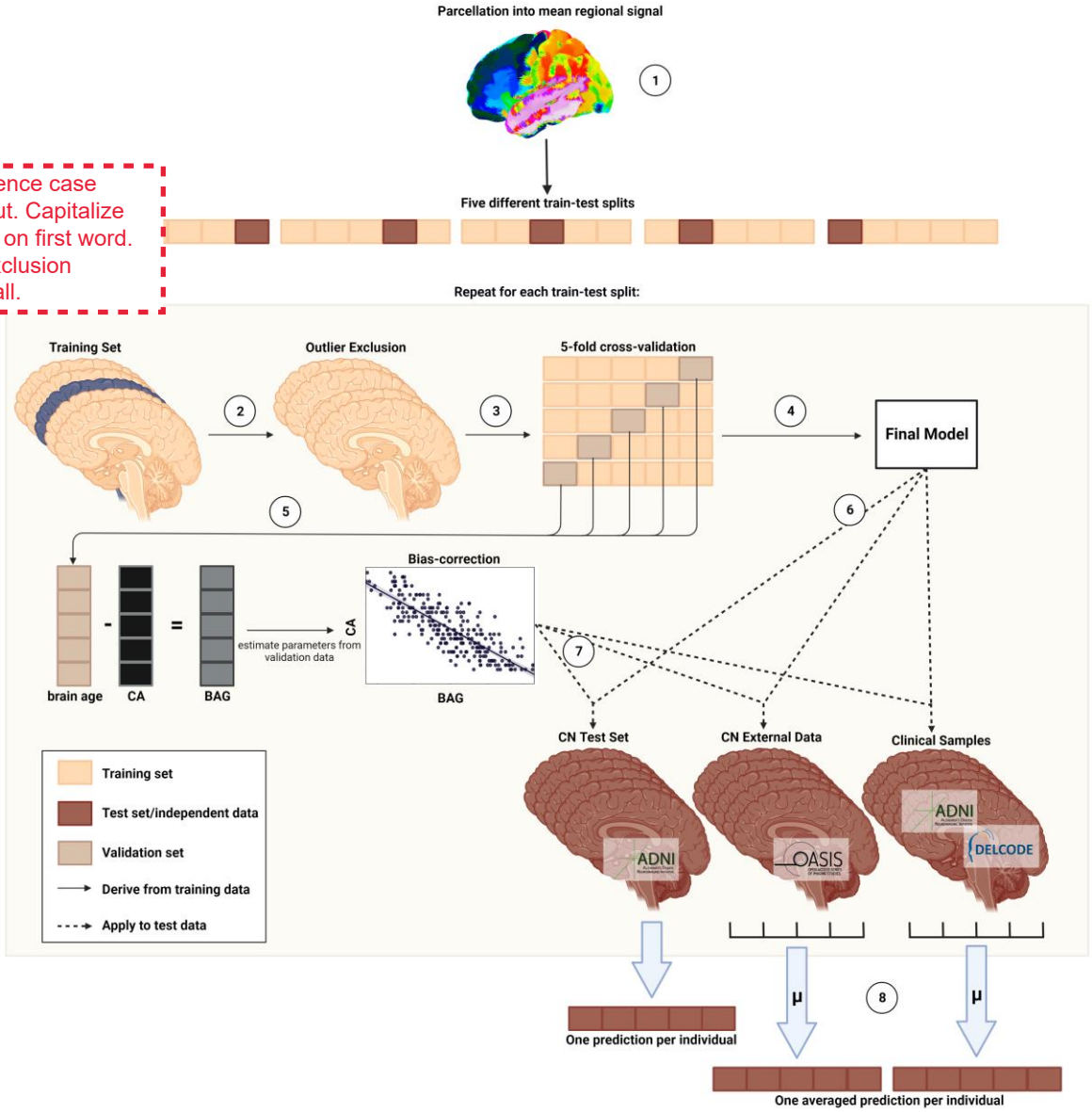
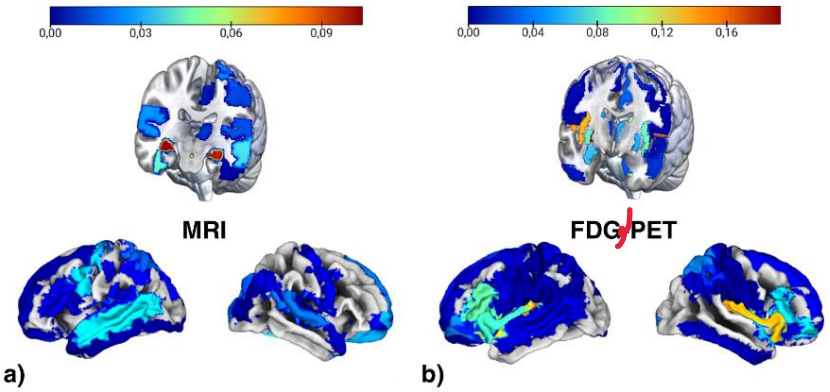


FIGURE 1. Nested cross-validation approach for brain age prediction. (1) Region-of-interest parcellation. (2) Outlier exclusion. (3) Five-fold cross-validation. (4) Selection of final model. (5) Bias correction. (6) Estimation of brain age in test sets. (7) Bias correction in test sets. (8) Ensemble averaging. BAG = brain age gap; CA = chronological age. Created with BioRender.com.



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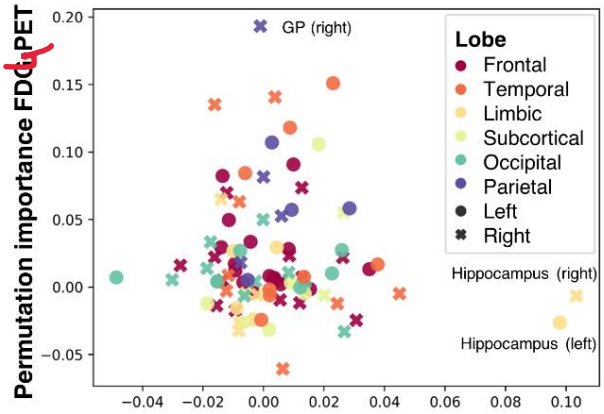

FIGURE 2 Feature importance for brain age prediction. Average regional importance for brain age prediction using MRI (a) and FDG-PET (b, thresholded at 0 for better visibility). c) Scatter plot of average feature importance across final models in FDG-PET and MRI by lobe (colors) and hemisphere (shapes).

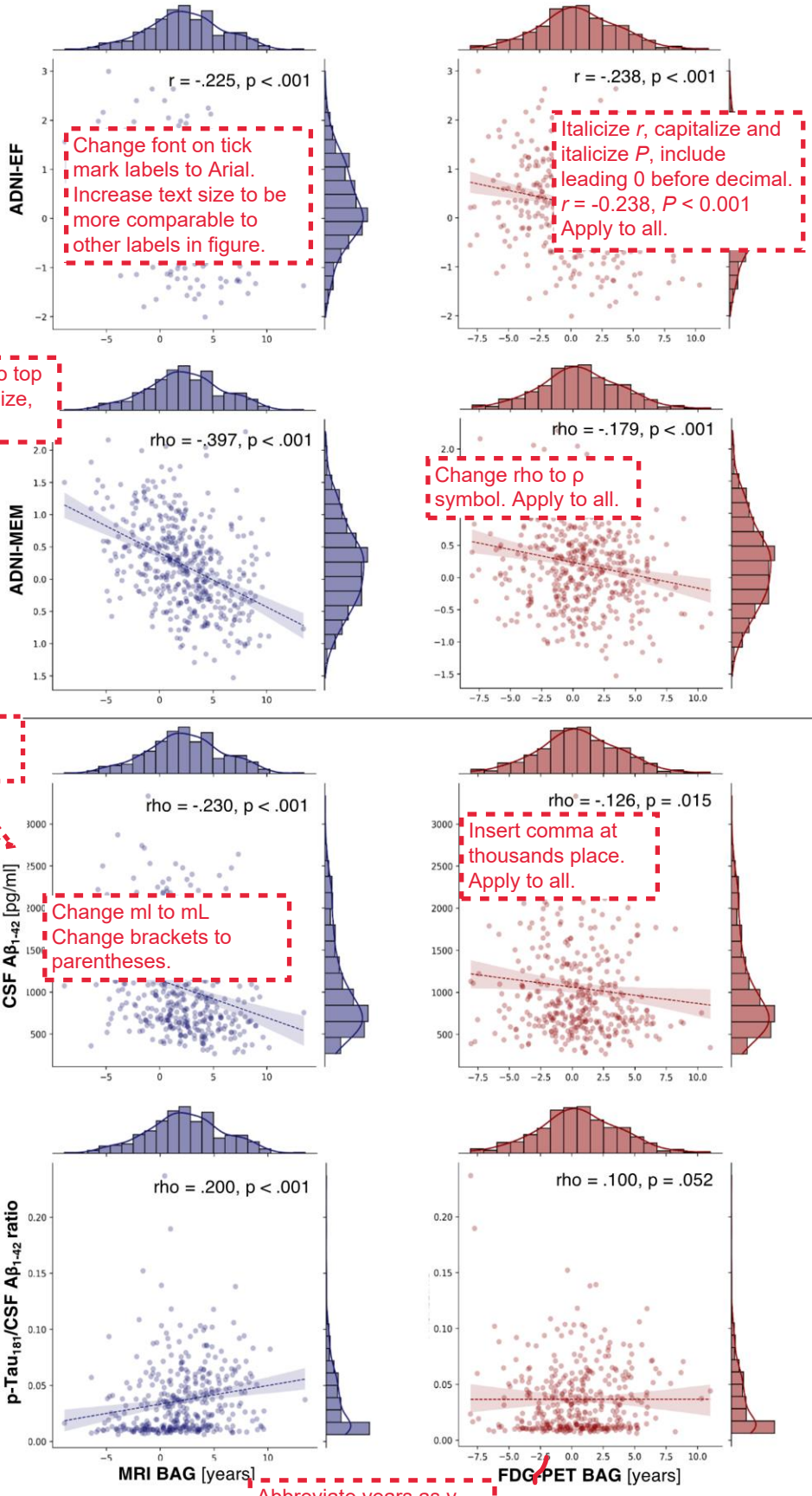

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FIGURE 3 Correlation of BA ormance (a) and AD neuropathology (b) in MCI$_{ADNI}$.

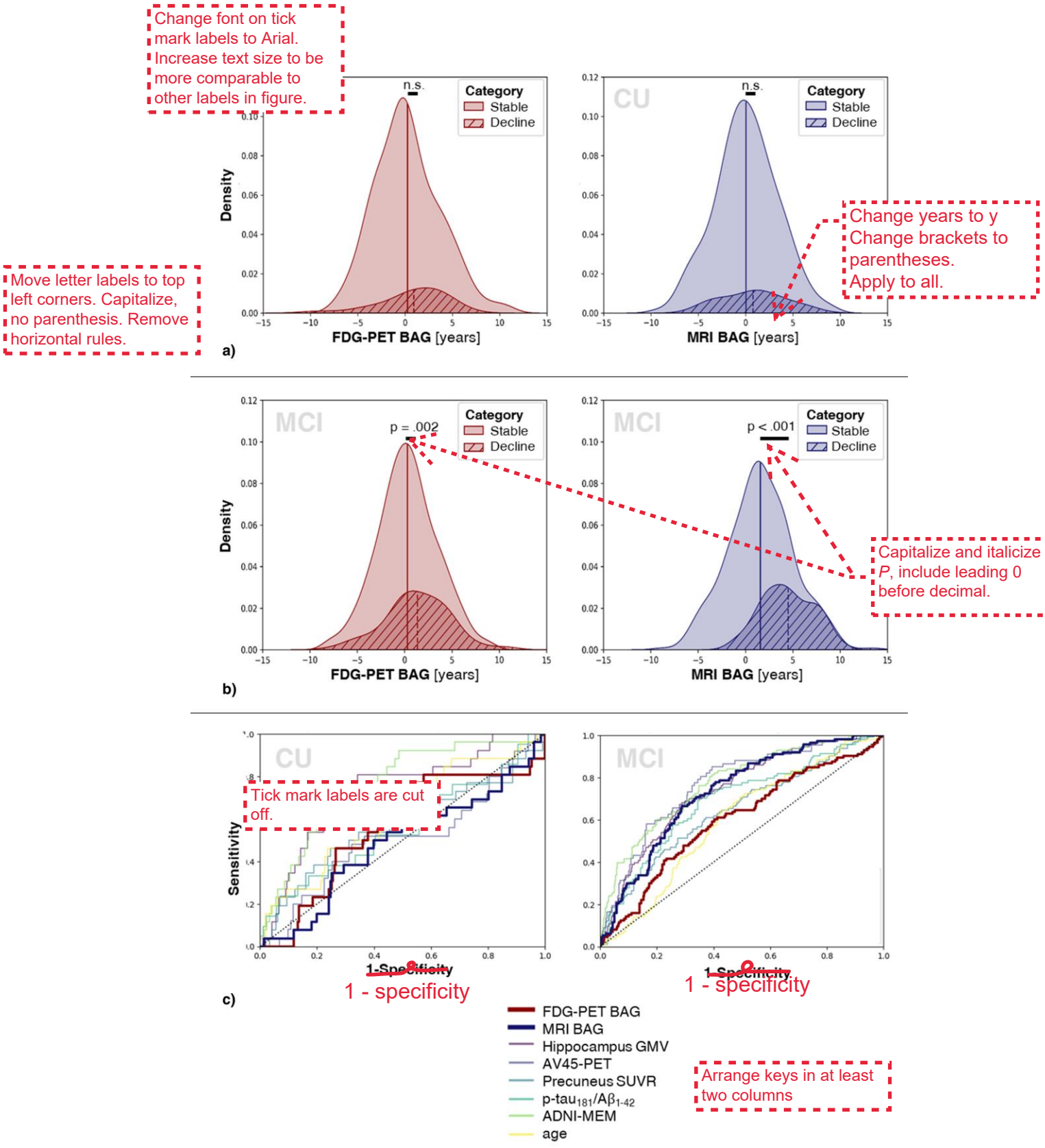

FIGURE 4 BAG for the Prediction of Cognitive Status. Density plots showing MRI and BAG distribution by cognitive status at follow-up in CU_{ADNI} (a)) and MCI_{ADNI} (b)). c) Results from ten-fold stratified cross-validation to predict cognitive status.

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