**Cognitive, Pathological and Prognostic Profiles of Different Brain Ages in the Early Alzheimer’s Disease 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, such as e.g. Alzheimer’s disease (AD). FDG-PET and MRI can quantify brain atrophy and metabolism, respectively, and are useful for estimating brain age. Here, we compare the cognitive, pathological and prognostic profiles of brain age estimation from FDG-PET and structural MRI in individuals without cognitive impairment (CN), with subjective cognitive decline (SCD) and with 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 amyloid and tau pathology in CN, SCD and MCI. Finally, BAG was used to predict cognitive outcome using logistic regression and its prognostic potential was compared with existing biomarkers of AD.

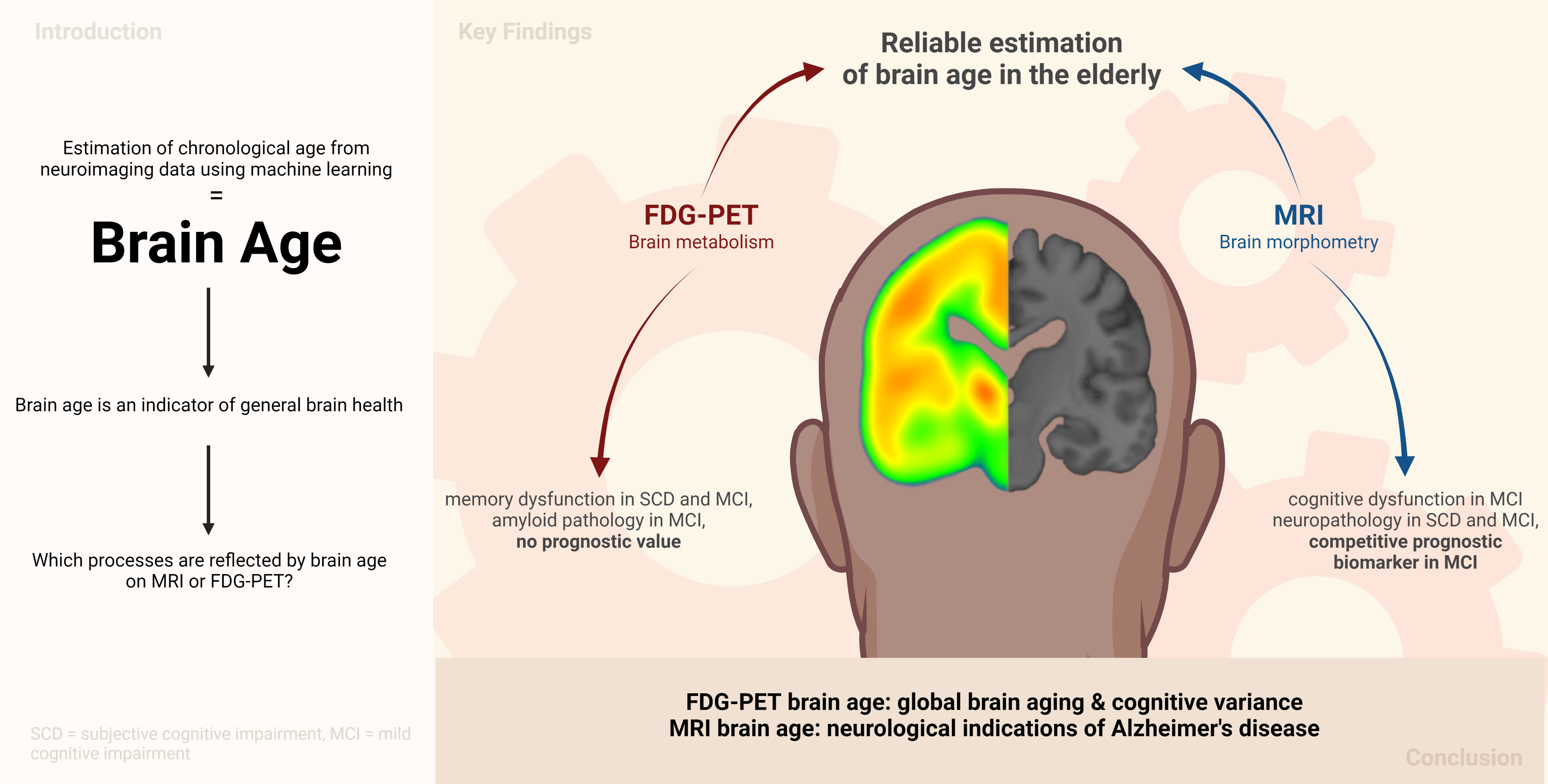
**Results**: MRI (mean absolute error, MAE=2.49 years) and FDG-PET (*MAE*=2.60 years) both estimated chronological age well. FDG-PET-derived BAG was associated with cognitive performance at the SCD stage, while both, FDG-PET- and MRI-derived BAG were dassociated with cognitive performance and AD neuropathology in MCI. FDG-PET-derived BAG was not predictive of cognitive outcome, however, MRI-derived BAG was a competitive biomarker of cognitive outcome (AUC = .73).

**Conclusion**:

Brain age is reliably estimated from FDG-PET or MRI. FDG-PET-derived BAG is more sensitive to early cognitive variance and may reflect global brain aging, whereas MRI-derived BAG reliably reflected neurological indications of AD.

RUNNING TITLE: FDG-PET or MRI for Brain Age Estimation

**Graphical Abstract**



**1 Introduction**

Brain aging entails changes in cognitive performance, as well as brain function and structural parameters of brain integrity. Brain age can be modeled using machine learning algorithms by estimating a person’s chronological age from their neuroimaging data. Deviations of brain age from chronological age (the *brain age gap, “BAG”*) are associated with a variety of neurological conditions, such as neurodegenerative diseases, including the Alzheimer’s disease (AD) continuum1–3. A recent study1 showed that BAG is associated with PET AD biomarkers in patients with mild cognitive impairment (MCI), and that BAG is significantly elevated in individuals with impending cognitive decline. These results motivate further research into the unique contribution of BAG as a marker of brain health and as a prognostic biomarker of cognitive impairment in the early stages of AD (MCI and subjective cognitive decline (SCD)).

Age-related changes in the brain are most evident in the brain’s anatomy, such as loss of brain volume (atrophy), and metabolism (neuronal dysfunction). Brain atrophy and metabolism can be quantified by T1-weighted magnetic resonance imaging (MRI) and 18F-Fluorodeoxyglucose-PET (FDG-PET), respectively. FDG-PET is considered to be an earlier indicator of neurodegeneration compared to structural MRI, as neuronal dysfunction precedes atrophy (i.e., neuronal loss) and regional proneness to the age-related decline is different when observed with FDG-PET or MRI4. It can therefore be assumed that different age- or disease-related processes are captured by the two modalities. To date, however, brain age estimation, in the vast majority of cases, is performed using MRI rather than FDG-PET. Only one recent study compared the two modalities and showed slightly better performance when using FDG-PET1. However, in this study, FDG-PET was not investigated independently of MRI, as FDG-PET was preprocessed using partial volume correction. This argues for further exploration of FDG-PET-derived BAG, and its potentially superior performance in delineating the earliest deviations from normal aging when cognitive impairment is not yet evident.

Here, we investigated the potential of FDG-PET and MRI separately as input for brain age estimation, with a particular focus on the early stages of the AD continuum. First, we estimated brain age in cohorts of individuals who were either cognitively normal (CN), had subjective cognitive decline (SCD), or mild cognitive impairment (MCI). Second, we calculated BAG and compared associations of FDG-PET- or MRI-derived BAG with cognitive performance and AD neuropathology in these cohorts. Finally, we evaluated the prognostic capacity of BAG for the prediction of cognitive outcome by using a logistic regression classifier to predict cognitive outcome from BAG or established risk factors of cognitive decline.

**2 Methods**

**2.1 Participants**

Baseline T1-weighted MRI and FDG-PET scans of 185 CN (*CNADNI*) whose MRI and FDG-PET scans were less than a year apart (mean = 28 days, SD = 23 days) were acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](https://ida.loni.usc.edu/collaboration/access/adni.loni.usc.edu)) to train our brain age estimation frameworks. The primary goal of the ADNI study has been to test whether biological markers and clinical and neuropsychological assessments can be combined to measure the progression of MCI and dementia. An additional 49 MRI and FDG-PET scans of CN were acquired from the Open Access of Imaging Studies-3 database5 (OASIS-3, https://www.oasis-brains.org/, *CNOASIS*) to validate the models in an external dataset. Finally, we assessed brain age in SCD and MCI patient groups from the ADNI and DZNE-Longitudinal Cognitive Impairment and Dementia Study6 (DELCODE) studies (for an overview, see **Table 1**). To be included, participants in all samples had to be older than 60 years at the time of their scan. CN, SCD and MCI diagnoses from ADNI, OASIS, and DELCODE followed the current recommendations for the respective groups7,8 (details provided in the Supplementary Materials (SM) section 1a).

**2.2 Acquisition & Preprocessing of MRI and FDG-PET Scans**

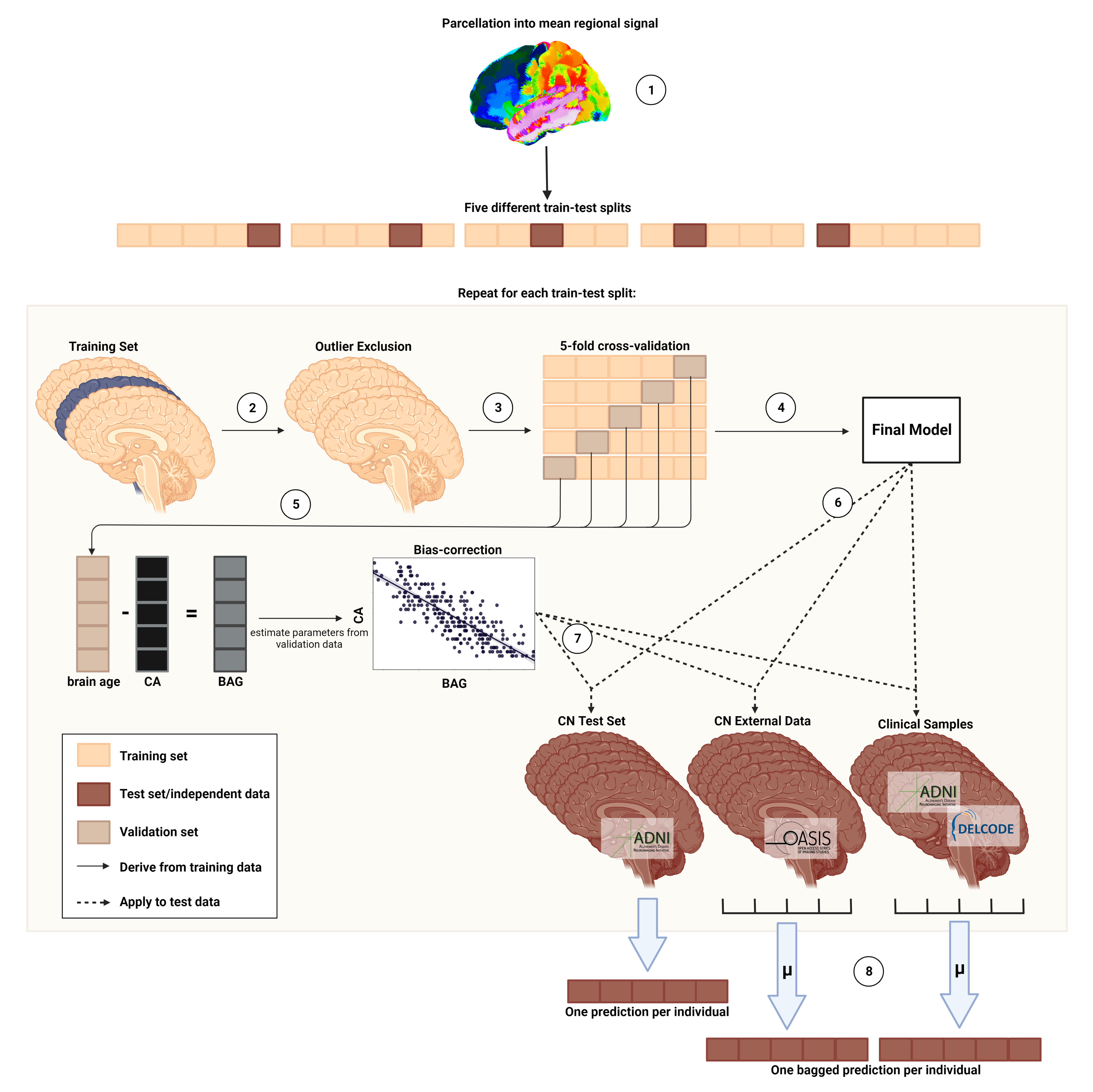
FDG-PET scans in ADNI and OASIS were acquired dynamically 30-60 minutes (6x5 min frames) after injection with an average dose of 185 MBq (5 mCi). The DELCODE FDG-PET data were acquired 40-60 minutes (4x5 min frames) after injection with an average dose of 170-180 MBq. All FDG-PET data was preprocessed and intensity-standardized9 using SPM12 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK) based on MATLAB. T1-weighted MRI scans were acquired according to previously published MRI acquisition protocols5,6,10 and were preprocessed with the CAT toolbox (version 12.5) in SPM1211. After preprocessing, both FDG-PET and MRI images were in the standard MNI152 space (see details in the SM section 1b).

**2.3 Estimation of brain age**

To estimate brain age, we implemented a pipeline (**FIGURE 1)** in Python 3.8.5 using the Julearn library (<https://juaml.github.io/julearn/main/index.html>), which is based on scikit-learn12. The same pipeline was run independently for MRI and FDG-PET and was evaluated by means of the mean absolute error (MAE) between chronological and brain age. First, signal of 90 cortical and subcortical regions of interest was extracted for the respective modality (MRI: gray matter volume, FDG-PET: SUVR) using the automated anatomical labeling (AAL) atlas13. To assess atlas-dependence of our results, we also conducted our analyses with a composite atlas containing 216 regions. Next, we applied a five-fold nested cross-validation (CV) approach, wherein the CNADNI sample was split into five different training and test sets, stratified by age bin (<74, 75-84 and >85 years) for the outer CV, and each training set was again split into five different training and validation folds for the inner CV.

Support vector regression (SVR) and relevance vector regression (RVR) with were used to estimate brain age as they are recommended for brain age estimation with small sample sizes14. Prior to the inner CV loop, outlier exclusion was performed in the outer CV loop (SM section 1c). The inner CV loop was used to select optimal hyperparameters (SM section 1d) and the final model was selected across SVR and RVR based on the MAE on the validation folds. Bias correction parameters were then estimated based on predictions yielded from the validation folds15 (SM section 1e). Subsequently, the final model was used to estimate brain age in the test and clinical samples and bias correction was applied.

**FIGURE 1. Nested cross-validation approach for brain age prediction.** Five different train-test splits were used to train and test the models. (1) Region-of-interest parcellation. (2) Outlier exclusion. (3) Five-fold CV. (4) Selection of final model. (5) Bias correction. (6) Estimation of brain age in test sets. (7) Bias correction in test sets. (8) Bagging. BAG = brain age gap; CA = chronological age; CV = cross-validation. Created with BioRender.



As a result of the nested CV approach, we obtained five final models per modality. Thus, per modality, we obtained one brain age estimate per (non-outlier) subject in the CNADNI sample, and five estimates per subject in the OASIS and patient samples. In the OASIS and patient samples, the average of the five estimates was treated as the final brain age estimate (*bagging*).

**2.4 Statistical analyses**

BAG was calculated for each individual as the difference between brain age and chronological age, such that higher bag reflected more advanced brain age. The accuracy of brain age estimation from MRI or FDG-PET was assessed by comparing the MAE of brain age estimations from the two modalities using a paired t-test in the CNADNI sample. To assess generalizability of our brain age frameworks, we compared the MAE of MRI- or FDG-PET-based brain age between CNADNI and CNOASIS by means of a standard t-test. To assess advancement of brain age in the clinical samples, we compared the average BAG (*mean error*, ME) between CNADNI and each clinical cohort using standard t-tests.

To understand the differences of brain age estimation from MRI or FDG-PET, we assessed the Pearson correlation of BAG and feature importance (δ) across modalities. Feature importance was assessed using permutation importance, which measures the impact of shuffling a feature's values on a model's performance, indicating the feature's importance to the model. For simplicity, we computed correlations using the average feature importance over all final models per modality. We further summarized brain regions’ feature importance per modality into median signal in lobes (frontal, temporal, limbic, subcortical, occipital, parietal, see SM section 1f), hemispheres (left, right) and lobes-by-hemisphere to assess whether brain regions of a particular category were preferential for brain age estimation in a given modality.

To assess whether BAG is associated with cognitive performance, we calculated partial correlations between BAG and composite scores of memory (ADNI-MEM)16 and executive function (ADNI-EF)17. In addition, partial correlations of BAG with PET amyloid load (AV45-PET)18, cerebrospinal fluid (CSF) markers19 of beta-amyloid1-42 (CSF Aβ1-42) and p-Tau181-to-Aβ1-42 ratio (p-Tau181/Aβ1-42)20 were calculated to assess whether BAG is associated with AD neuropathology. Correlations were computed for CNADNI, SCDADNI and MCIADNI. Pearson or Spearman correlations were assessed, depending on normality (Shapiro-Wilk test) and all partial correlations were corrected for age, sex, years of education and APOE-ε4 carriership. Significance levels were as follows: p < .1 = “trend significant”, p < .05 = “significant”, p < Bonferroni correction = “significant after Bonferroni correction” (cognitive performance: α = .05/2, AD neuropathology: α = .05/3). Descriptions of the variables assessed are provided in SM sections 1g and 1h.

Finally, we aimed to assess the prognostic value of the brain age gap for cognitive outcome in comparison to existing biomarkers. All BAG assessments took place at baseline. We differentiated between cognitively “stable” individuals, who maintained their baseline diagnosis until the two-year follow-up screening, and “decliners”, who received a diagnosis of (more severe) cognitive impairment within two years after baseline. Due to the small number of decliners in the CNADNI (n=16≙10%) and SCDADNI samples (n=10≙12%), we combined the two groups to a cognitively unimpaired (CUADNI) cohort. First, we computed an analysis of covariance of BAG between individuals with and without impending cognitive impairment, while correcting for sex, years of education and APOE-ε4 carriership in CNADNI, SCDADNI, and CUADNI and age, sex, years of education and APOE-ε4 carriership in MCIADNI (where a bias remained when BAG was estimated from MRI). Subsequently, we trained multiple single-feature logistic regression classifiers in a stratified ten-fold cross-validated manner to predict cognitive outcome in different cognitive groups from FDG-PET BAG, MRI BAG, hippocampal volume, global AV45-PET SUVr, FDG-PET SUVr in the precuneus, p-tau181/Aβ1-42 ratio, mini mental state exam score or chronological age. To correct for the effects of age, sex, years of education, and APOE status in our prediction models, standardized residuals were calculated for each predictor variable using a linear model trained on the stable individuals in each training fold, which was subsequently applied to all training and validation data of the current fold21. Age was not corrected for when age or BAG (in CUADNI) were the predictor of cognitive outcome. We compared the mean area under the curve (AUC) obtained from the validation folds across all predictors. If BAG of one modality showed high performance, we derived a cut-off given the a priori probability of cognitive decline in each training fold, and we validated this cut-off in the corresponding DELCODE cohort.

**3 Results**

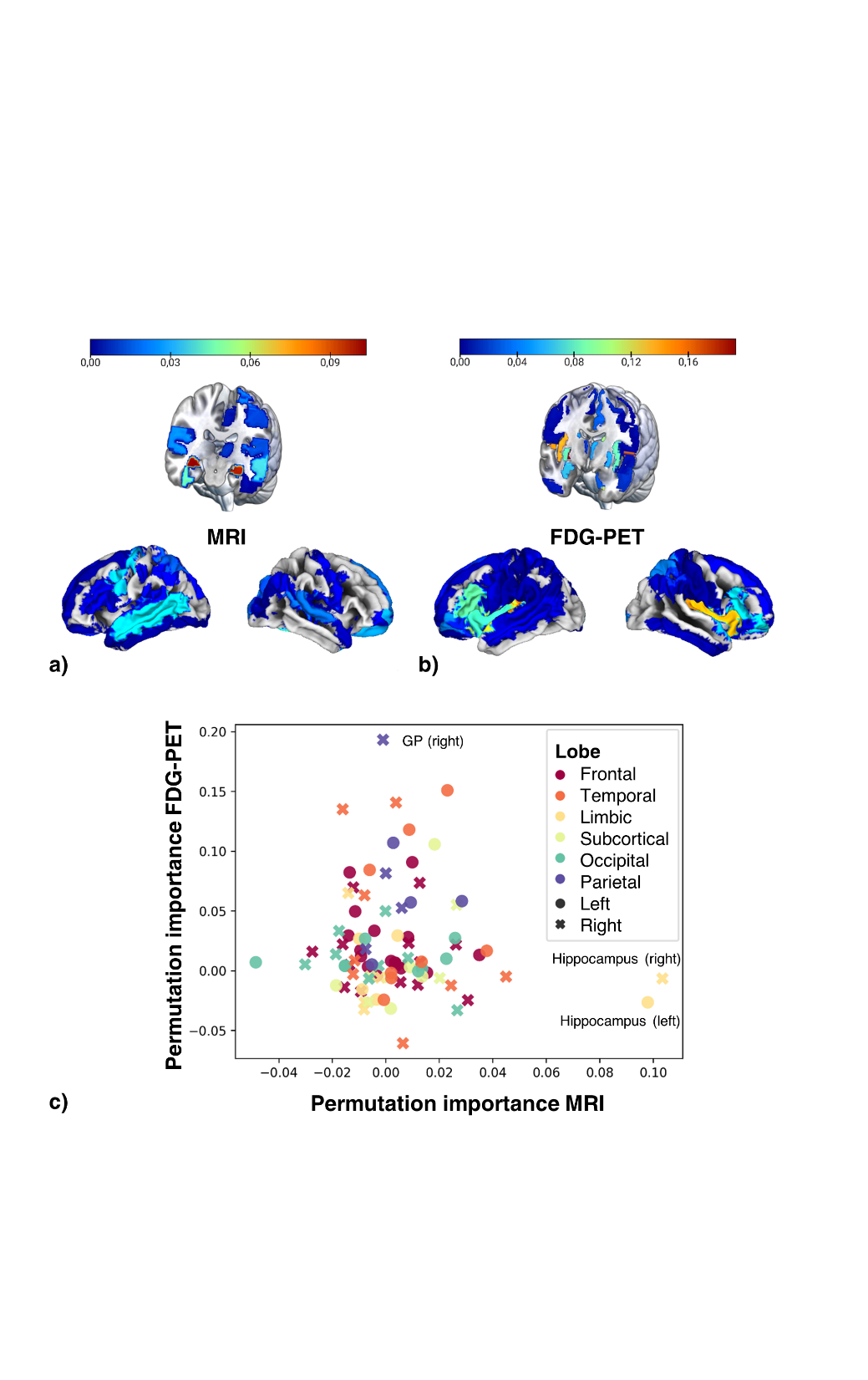
**3.1 Participants**

An overview of participant characteristics is shown in **Table 1**. CNOASIS, SCDADNI and SCDDELCODE subjects were significantly younger compared to the main CNADNI cohort. The SCD and MCI cohorts further differed from CNADNI in terms of cognitive performance (MCIADNI and MCIDELCODE), years of education (SCDADNI and MCIDELCODE), amyloid status (SCDDELCODE and MCIADNI) and APOE-ε4 carriership (MCIADNI and MCIDELCODE).

**3.2 Accuracy and demographic profile of estimated brain age**

MRI- and FDG-PET estimated chronological age comparably well in CNADNI (MAEMRI = 2.49, MAEFDG-PET = 2.60), CNOASIS (MAEMRI = 2.92, MAEFDG-PET = 2.54) and SCDADNI (MAEMRI  = 2.50, MAEFDG-PET = 2.56), while the MAE of MRI-derived brain age (MAEMRI = 3.30) was significantly higher compared to FDG-PET (MAEFDG-PET = 2.59; **Table 2**). Within-modality comparison of MAE in CNOASIS and CNADNI yielded no significant differences, thus suggesting high generalization performance of our frameworks to external datasets comprising CN populations. FDG-PET-, but not MRI-derived brain age was trend significantly advanced in SCDADNI. In all other clinical cohorts brain age was significantly advanced compared to CNADNI in all available modalities. Bias correction successfully eliminated the correlation of BAG and age with the exception of MRI-derived BAG in MCI (Table SM1). Results using the composite atlas were largely comparable to those obtained with AAL (SM section 2b).

BAG was trend significantly correlated between MRI- and FDG-PET-based models (r = .128, *p* = .09, 95% CI [-0.02, 0.27]). Model selection returned different model types with mostly linear kernels (see Table SM3). Bilateral hippocampi were most relevant for brain age estimation from MRI (δleft\_hippocampus = .098, δright\_hippocampus = .103), while median permutation importance in the lobes, hemispheres or lobes-by-hemisphere showed no obvious trends (**FIGURE 2**). Especially subcortical regions (δsubcortical = .058, δleft\_subcortical = .058, δright\_subcortical = .067), and, to a lesser extent, also left-hemispheric frontal (δleft\_frontal = .013) and temporal regions (δleft\_temporal = .012) were most relevant for brain age estimation from FDG-PET. No overall hemispheric preference was observed for FDG-PET models. Average regional importance was not correlated between MRI- and FDG-PET-based models (r = -.069, *p* = .52, 95% CI [-.27, .14]).

**** **3.3 BAG and cognitive performance**

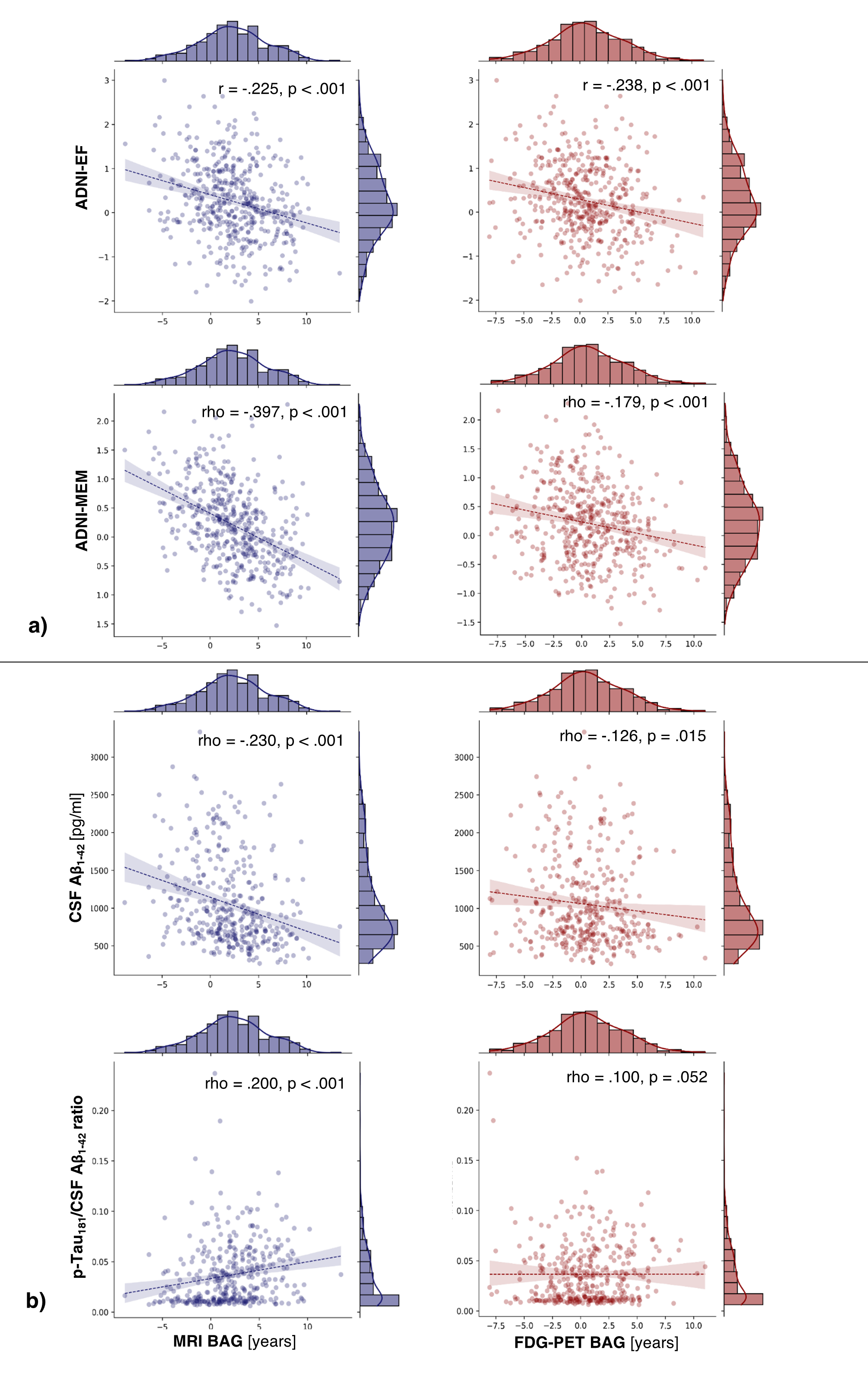
**FIGURE 2** **Feature importance for brain age prediction.** Average regional importance for brain age prediction using MRI (a) and FDG-PET (b, thresholded at 0 for visibility). c) Scatter plot of average feature importance across final models in FDG-PET and MRI by lobe (colors) and hemisphere (shapes).

In CNADNI, neither MRI-, nor FDG-PET BAG were associated with executive function or memory performance (n = 154, *ADNI-EF*: rMRI = .016, *p* = .84, 95% CI [-.14, .18]; rFDG-PET = .100, *p* = .22, 95% CI [-.06, .26]; *ADNI-MEM*: rMRI = -.001, *p* = .99, 95% CI [-.16, .16]; rFDG-PET = .095, *p* = .25, 95% CI [-.07, .25]). In SCDADNI, FDG-PET BAG was significantly negatively associated with memory performance after Bonferroni correction, and trend significantly with executive function. MRI BAG was not correlated with these measures (n=83, *ADNI-EF*: rMRI = .048, *p* = .68, 95% CI [-.18, .27]; rFDG-PET = -.190, *p* = .09, 95% CI [-.39, .03]; *ADNI-MEM*: rMRI = -.132, *p* = .25, 95% CI [-.34, .09]; rFDG-PET = -.259, *p* = .02, 95% CI [-.45, -.04]). In MCIADNI, both, MRI- and FDG-PET-derived BAG were significantly negatively correlated with executive function and memory performance after Bonferroni correction (n=460, *ADNI-EF*: rMRI = -.225, p < .001, 95% CI [-.31, -.14]; rFDG-PET = -.238, p < .001, 95% CI [-.32, -.15]; *ADNI-MEM*: rhoMRI = -.397, *p* < .001, 95% CI [-.47, -.32]; rhoFDG-PET = -.179, *p* < .001, 95% CI [-.27, -.09], **FIGURE 3**).

**3.4 BAG and AD neuropathology**

In CNADNI, BAG and AD neuropathology were not significantly correlated although PET BAG tended to be elevated in the presence of pathology in CSF(*AV45-PET* (n=148): rhoMRI = -.002, *p* = .97, 95% CI [-.17, .16]; rhoFDG-PET = .011, *p* = .90, 95% CI [-.15, .17]; *CSF Aβ1-42* (n=133): rhoMRI = .003, *p* = .97, 95% CI [-.17, .18]; rhoFDG-PET = -.110, *p* = .21, 95% CI [-.28, .06]; *p-Tau181/Aβ1-42* (n=132): rhoMRI = .029, *p* = .75, 95% CI [-.15, .20]; rhoFDG-PET = .141, *p* = .11, 95% CI [-.03, .31]). In SCDADNI, lower levels of amyloid in CSF were significantly correlated with increased MRI BAG, while higher amyloid load in PET was trend significantly associated with elevated FDG-PET BAG (*AV45-PET* (n=82): rhoMRI = .014, *p* = .91, 95% CI [-.21, .24]; rhoFDG-PET = .191, *p* = .09, 95% CI [-.03, .40]; *CSF Aβ1-42* (n=77): rMRI = -.238, *p* = .04, 95% CI [-.44, -.01]; rFDG-PET = -.161, *p* = .17, 95% CI [-.38, .07]; *p-Tau181/Aβ1-42* (n=77): rhoMRI = .017, *p* = .89, 95% CI [-.21, .25]; rhoFDG-PET = .087, *p* = .46, 95% CI [-.15, .31]). In MCIADNI, MRI BAG was at least trend significantly correlated with all three markers of AD neuropathology. FDG-PET BAG was also associated with pathology markers, but only those obtained from CSF (*AV45-PET* (n=326): rhoMRI = .095, *p* = .09, 95% CI [-.01, .02]; rhoFDG-PET = .056, *p* = .32, 95% CI [-.05, .16]; *CSF Aβ1-42* (n=376): rhoMRI = -.230, *p* < .001, 95% CI [-.32, -.13]; rhoFDG-PET = -.126, *p* = .02, 95% CI [-.22, -.02]; *p-Tau181/Aβ1-42* (n=376): rhoMRI = .200, *p* < .001, 95% CI [.10, .30]; rhoFDG-PET = .101, *p* = .052, 95% CI [-.00, .20], **FIGURE 3**).

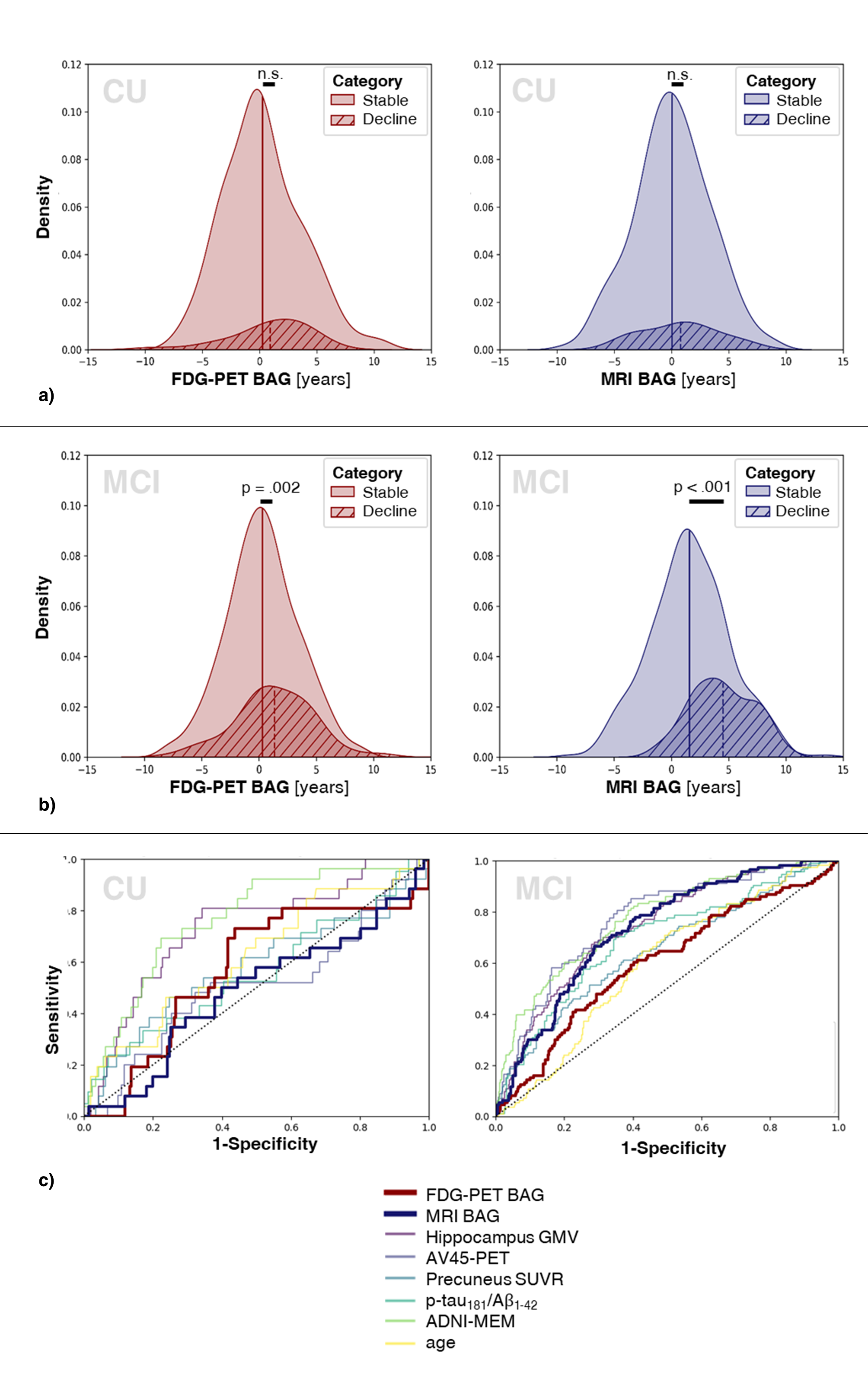
**FIGURE 3 Correlation of BAG with cognitive performance (a) and AD neuropathology (b) in MCI.**



**3.5 BAG and Cognitive Outcome**

In SCDADNI and CUADNI, brain age was higher in decliners compared to stables, although this effect was not significant and not observed in CNADNI (**CNADNI**: MRI BAG: F(1, 149) = 0.617, *p* = .43; FDG-PET BAG: F(1, 149) = 0.023, *p* = .88; **SCDADNI**: MRI BAG: F(1, 78) = 0.247, *p* = .62; FDG-PET BAG: F(1, 78) = 1.66, *p* = .20; **CUADNI**: MRI BAG: F(1, 232) = 0.870, *p* = .35; FDG-PET BAG: F(1, 232) = 0.619, *p* = .43, **FIGURE 4a** and SM FIGURE 1 for CNADNI and SCDADNI). However, there was a significant covariate effect of sex on baseline MRI BAG (F(1, 232) = 18.92, *p* < .001). In MCIADNI, we found a significant main effect of group for both, MRI and FDG-PET BAG (MRI BAG: F(1, 454) = 59.64, *p* < .001; FDG-PET BAG: F(1, 454) = 10.18, *p* = .002), with decliners showing advanced baseline BAG (MMRI = 4.51, SDMRI = 2.79; MFDG-PET = 1.35, SDFDG-PET = 3.38) compared to stable individuals (MMRI = 1.58, SDMRI = 3.40; MFDG-PET = 0.31, SDFDG-PET = 3.14; **FIGURE 4b**). Moreover, we found significant covariate effects of age (F(1, 454) = 6.06, *p* = .01) and sex (F(1, 454) = 29.57, *p* < .001) on baseline MRI BAG.

Next, we trained a logistic regression classifier to predict cognitive outcome within two years from baseline BAG using (age), sex, education and APOE-residualized biomarkers as predictors. We found that only ADNI-MEM (AUC = .77) and hippocampal volume (AUC = .74), but not MRI (AUC = .56) or FDG-PET BAG (AUC = .63) predicted cognitive outcome in CUADNI. In MCIADNI, MRI BAG predicted cognitive outcome (AUC = .73), as did ADNI-MEM (AUC = .78), AV45-PET (AUC = .77), hippocampal volume (AUC = .75) and p-Tau181/Aβ ratio (AUC = .70). FDG-PET BAG (AUC = .60). From a priori probabilities of cognitive decline in each training fold, we derived a mean probability cut-off for MRI-BAG prediction of cognitive outcome of .25 (range: .24 – .25), yielding sensitivities and specificities of .69 and .69 in MCIADNI and, comparably, .69 and .62 in MCIDELCODE (AUC of MRI BAG-derived cognitive outcome in DELCODE = .75). All AUCs for the ADNI samples are shown in **FIGURE 4c**).



**FIGURE 4 BAG for the Prediction of Cognitive Outcome.** Density plots showing MRI and BAG distribution by cognitive outcome in CUADNI (a)) and MCIADNI (b)). c) Results from ten-fold stratified cross-validation to predict cognitive outcome from residualized features.

**4 Discussion**

Previous studies have mainly used MRI to estimate brain age. Here, we compared the accuracy of FDG-PET and MRI-estimated brain age and provided a comprehensive overview of the cognitive and neuropathological profile of FDG-PET and MRI-derived BAG in different cognitive groups. We showed that 1) MRI and FDG-PET both estimated brain age with high accuracy; 2) FDG-PET-derived BAG better reflected cognitive variance in SCD, while both, MRI and FDG-PET BAG reflected cognitive scores in MCI; 3) MRI and FDG-PET BAG are, to some extent, associated with markers of amyloid in SCD and MCI. Finally, we showed that MRI-derived BAG holds prognostic value that generalizes across datasets and is competitive to state-of-the-art biomarkers of cognitive decline in MCI.

Our findings suggest that advanced brain age captures brain health, in the form of cognitive and neuropathological variance in the early AD continuum as early as the SCD stage. The observed negative association between FDG-PET BAG and memory performance in the lack of clinically manifest cognitive dysfunction may suggest that FDG-PET BAG has the capacity to detect subtle cognitive decline at its nascent stages. Notably, there was a discernible trend towards higher ME in SCDADNI compared to CNADNI, as well as between declining SCDADNI and stableADNI, although these results did not reach statistical significance. These observations provide preliminary evidence for the utility of FDG-PET BAG as a potential early biomarker for cognitive impairment.

While previous work has outlined the association of brain age advancement and cognitive outcome in CU and MCI1, we have shown that MRI-derived BAG is truly predictive of progression to dementia in MCI even after correction for confounding factors. Notably, performance of MRI BAG was *en pars* with established AD biomarkers, such as amyloid PET, composite memory performance and hippocampal volume. MRI BAG estimation was strongly, but not exclusively based on hippocampal volume, thus, in comparison, MRI BAG provides the opportunity to quantify neurodegeneration beyond this brain structure into a single number. It is worth mentioning that none of the individual biomarkers achieved high predictive performance, when confounding factors were controlled for. Thus, more research into prognostic biomarkers for AD is required and our findings show that MRI BAG could possibly complement such measures.

Similar to previous studies1,4, we found differences in brain regions displaying aging as observed on FDG-PET and MRI, suggesting that brain age estimated from MRI and FDG-PET capture different cumulative effects of various biological processes that contribute to brain aging. Consistently, we have shown that BAG between the two modalities was only marginally correlated. Since MRI BAG was mostly estimated from hippocampal volume and predictive of conversion from MCI to dementia, biological processes underlying MRI BAG may be more closely related to AD etiology than those captured by FDG-PET BAG, as it has repeatedly been shown that hippocampal volume plays a pivotal role in memory, and AD-related decline thereof22. Therefore, AD-related neurodegeneration can likely be well described as accelerated brain aging on MRI. FDG-PET brain age estimation was mostly driven by a combination of subcortical, left-hemispheric temporal and frontal regions. Together with the observation that FDG-PET BAG reflected cognitive variance in SCD and MCI, these results suggests that FDG-PET may capture a more global, disease-unspecific, aspect of cognitive brain aging.

Some limitations should be acknowledged. First, although generalizability to OASIS data proved to be accurate and although we trained our models on ADNI data, which was acquired on different scanners, we observed strong cohort effects for brain age assessment in the external clinical cohorts. These results suggest that methodological differences, such as variation in the diagnostic or scan procedure (e.g., the different acquisition time in DELCODE (40 – 60 min post injection) and ADNI or OASIS (30 – 60 min post injection)), can significantly influence the applicability of brain age frameworks. Lee and colleagues has shown that brain age estimation frameworks profit from multi-dataset training1. Therefore, we recommend for future brain age frameworks to be trained on multi-centric datasets and bigger sample sizes before deployment into clinical practice. Second, due to data availability and increased risk of cognitive deficits due to neurodegenerative processes23, we only included participants over the age of 60. Thus, accelerated aging starting before this age remained uninvestigated in our study

In summary, we have shown that MRI and FDG-PET can both be used to estimate brain age but they reflect different aspects of brain aging: While both, MRI- and FDG-PET-derived BAG were elevated in the presence of AD neuropathology in MCI, MRI BAG showed greater sensitivity for AD-related changes and pending cognitive decline, whereas FDG-PET displayed more global aspects of brain aging and cognitive variance in SCD. Overall, this study highlights the potential of neuroimaging as a powerful tool for investigating brain aging and cognitive outcome, and it underscores the need for further research in this area to improve our understanding of brain health in aging populations.

**Code Availability**

The code used for this project will be made publicly available on the GitHub page of the first author upon publication.

**Author Contributions**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ElD and GA, with support from KRP and MCH. KRP, TvE, SBE and AD jointly supervised this work. DELCODE data preparation was supervised by MD and HB (PET), EmD (MRI) and FJ (clinical data). The first draft of the manuscript was written by ED and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Disclosure**

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**Key Points**

**QUESTION:** What is the neuropathological and predictive profile of brain age gaps (BAGs) derived from structural MRI or FDG-PET?

**PERTINENT FINDINGS**: BAG was computed from structural MRI and FDG-PET and subsequently associated with neuropathological markers of Alzheimer’s disease, as well as risk of cognitive deterioration. While both, MRI- and FDG-PET-derived BAG were indicative of existing amyloid pathology already in individuals without cognitive impairment, the predictive capacity of BAG for cognitive outcome was group-dependent: FDG-PET-derived BAG predicted cognitive deterioration in cognitively unimpaired individuals and MRI-derived BAG predicted cognitive deterioration in patients with mild cognitive impairment.

**IMPLICATIONS FOR PATIENT CARE:** A group-dependent choice of modality for BAG assessment can complement care management plans of cognitively unimpaired and impaired individuals by providing estimates of cognitive outcomes.

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| --- | --- | --- | --- | --- | --- | --- |
| **Table 1.** Overview of samples | | | | | | |
|  | CNADNI | CNOASIS | SCDADNI | MCIADNI | SCDDELCODE | MCIDELCODE | |
| *n* total | 186 | 49 | 102 | 595 | 88 | 80 | |
| Age at PET scan [avg. years (SD)] | 73.8 (6.46) | 70.6 (5.07)+ | 72.3 (5.60)+ | 73.2 (6.93) | 70.9 (5.57)+ | NA | |
| Age at MRI scan [avg. years (SD)] | 73.8 (6.44) | 69.2 (4.98)+ | 72.3 (5.60)+ | 73.2 (6.92) | NA | 73.4 (5.87) | |
| Sex [%female (nNA)] | 53 (0) | 53 (0) | 59 (0) | 42 (2)+ | 36 (0)+ | 36 (0)+ | |
| MMSE [avg. score] | 29 (1.26) | 29 (0.78) | 29 (1.20) | 28 (1.75)+ | 29 (1.03) | 28 (1.67)+ | |
| Education [avg. years (SD)] | 16 (2.54) | 16 (2.51) | 17 (2.50)+ | 16 (2.67) | 16 (3.00) | 14 (3.06)+ | |
| CSFAβ1-42 Status [%positive (nNA)] | 41 (27) | NA | 35 (9) | 64 (126)+ | 22 (28)+ | 38 (38) | |
| APOE [% ε4-carriers (nNA)] | 29 (1) | NA | 31 (0) | 49 (4)+ | 38 (3) | 49 (0)+ | |
| Notes. Percentage of CSFAβ1-42 status indicates percentage of amyloid positive individuals among all who received lumbar puncture (excluding NA). Thresholds for amyloid positivity was 1100 pg/ml in ADNI and 496 pg/ml in DELCODE. +significantly different from CNADNI as assessed per t-test (age, MMSE, education) or χ² (sex, amyloid status, APOE status). | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2.** Accuracy of estimating chronological age from FDG-PET and MRI scans using AAL atlas. | | | | | | | | | |
|  | Modality | *n* | MAE | Range | ME | R² | **Accuracy**  MAE MRI vs FDG-PET | **Generalizability**  MAE current vs CNADNI | **Brain age advancement**  MEcurrent vs CNADNI |
| **CNADNI** | MRI | 175+ | 2.49 | [-9.4, 8.7] | 0.06 | .74 | t = 0.48  95% CI [-0.33, 0.55] | NA | NA |
| FDG-PET | 175+ | 2.60 | [-10.1, 9.6] | -0.10 | .70 | NA |
| **CNOASIS** | MRI | 49+ | 2.92 | [-7.1, 8.4] | 0.13 | .42 | t = - 0.94  95% CI [-1.20, 0.43] | t = 1.16  95% CI [-0.31, 1.18] | t = 0.12  95% CI [-1.12, 1.26] |
| FDG-PET | 49+ | 2.54 | [-5.0, 6.8] | 0.89 | .63 | t = -0.18  95% CI [-0.64, 0.53] | t = 2.00\*  95% CI [0.01, 1.97] |
| **SCDADNI** | MRI | 102 | 2.50 | [-6.6, 7.0] | 0.11 | .69 | t = 0.26 95% CI [-0.42, 0.54] | NA | t = 0.11  95% CI [-0.73, 0.82] |
| FDG-PET | 102 | 2.56 | [-5.6, 9.8] | 0.64 | .69 | NA | t = 1.86+  95% CI [-0.05, 1.53] |
| **MCIADNI** | MRI | 595 | 3.30 | [-10.5, 13.5] | 2.16 | .65 | t = -5.72\*\*  95% CI [-0.95, 0.46] | NA | t = 7.47\*\*  95% CI [1.55, 2.65] |
| FDG-PET | 595 | 2.59 | [-10.0, 11.0] | 0.55 | .78 | NA | t=2.23\*  95% CI [0.08, 1.22] |
| **SCDDELCODE** | FDG-PET | 88 | 3.16 | [-2.7, 9.3] | 2.77 | .52 | NA | NA | t = 7.45\*\*  95% CI [2.11, 3.63] |
| **MCIDELCODE** | MRI | 80 | 3.69 | [-5.1, 11.6] | 2.89 | .38 | NA | NA | t = 6.04\*\*  95% CI [1.90, 3.75] |
| *Notes.* +After outlier exclusion using CN train set (IQR > 6). Accuracy differences were assessed with paired t-tests, while generalizability and brain age advancement were tested with standard t-tests. +trend significant with α = .1, \* significant with α = .05, \*\* significant with α = .01 | | | | | | | | | |

1. + both authors contributed equally

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