**MANUSCRIPT DRAFT**

**Modality Matters: Prediction of Cognitive Outcome Using Brain Age Derived from Different Modalities**

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Objectives: Brain aging is characterized by anatomical and molecular changes. Deviations from the normal aging trajectory in the form of advanced brain aging relative to chronological age (“brain age gap”, *BAG*) is associated with cognitive decline. Such normal aging trajectories are typically estimated from magnetic resonance imaging (MRI), however, changes in neuronal glucose metabolism, visible on 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET), likely precede anatomical changes observed on MRI. Here, we compare the accuracy of brain age estimation from FDG-PET and MRI, and we associate BAG derived from both modalities with cognitive impairment, and Alzheimer’s disease biomarkers. Furthermore, we present thresholds for the prediction of cognitive decline from BAG. Analyses were conducted in individuals without (CN) and with mild cognitive impairment (MCI).

Methods: Machine learning algorithms were trained to estimate brain age from 367 matched MRI or FDG-PET scans of CN from the Alzheimer’s Disease Neuroimaging Initiative using a nested cross-validation approach. BAG was computed and correlated with measures of amyloid and tau pathology in CN and MCI (n=513). Finally, BAG was used to predict a change in individuals' cognitive diagnosis after two years using cross-validated logistic regression. Thresholds for cognitive decline were estimated from the logistic regression output.

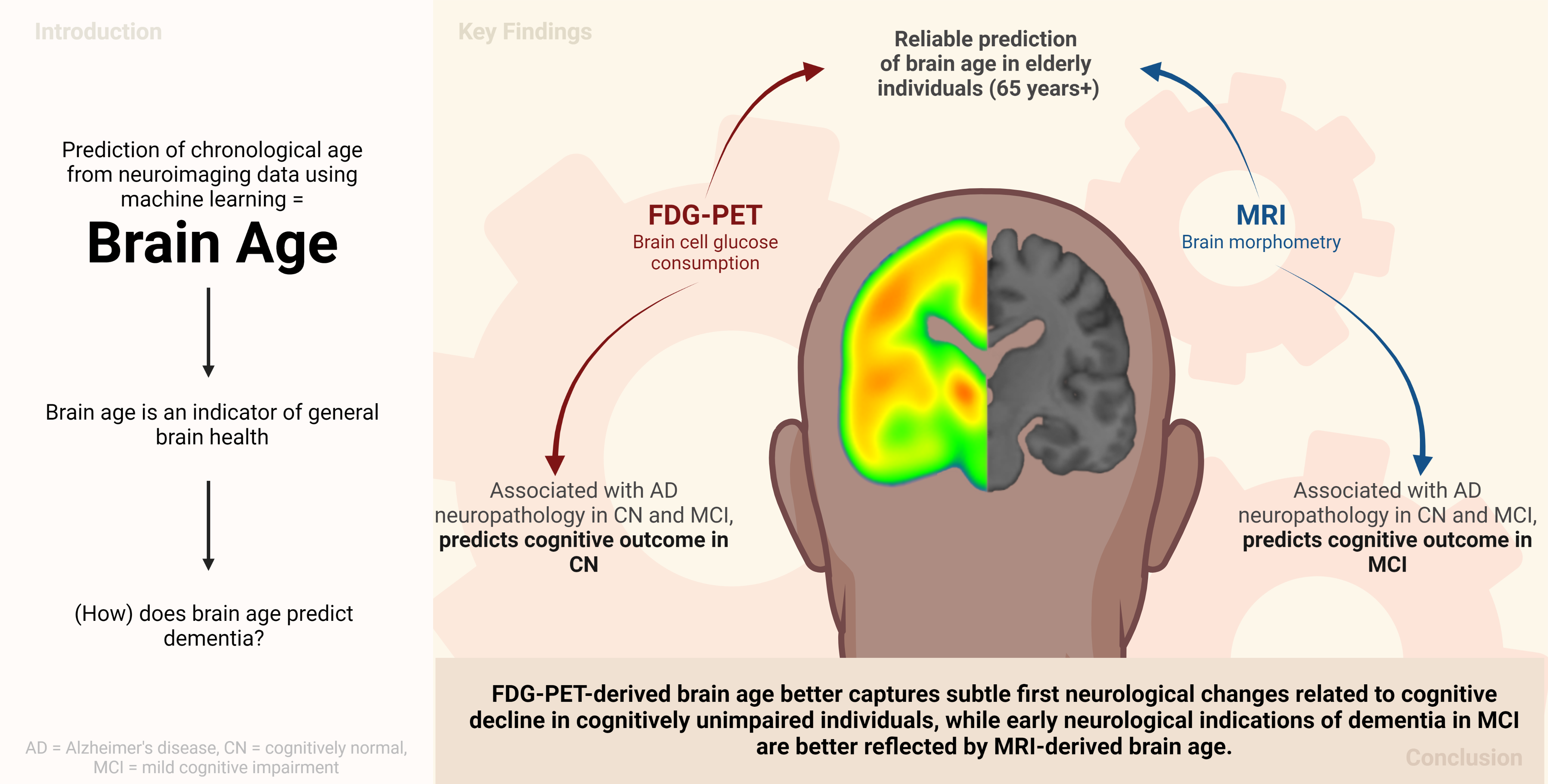
Results: FDG-PET (MAE=2.46 years) and MRI (MAE=1.96 years) both predicted chronological age well. XX

FDG-PET-derived BAG was more strongly associated with measures of amyloid in CN, whereas MRI-derived BAG correlated better with measures of cerebral amyloid and tau in MCI. In CN, FDG-PET-derived BAG significantly predicted cognitive decline, while both FDG-PET- and MRI-derived BAG were associated with an AD diagnosis after two years in MCI, however associations were stronger in MRI.

Conclusion:

Brain age is reliably estimated from FDG-PET or MRI. Amyloid-neuropathology, predisposing for Alzheimer’s disease, is related to features of advanced BAG in FDG-PET ahead of clinical onset of disease, and 18F-FDG-PET-derived BAG reliably predicts cognitive decline in CN. Onset of tau-related neurodegeneration and of pending conversion to AD is more strongly associated with increasing BAG on MRI.

**Graphical Abstract**



**1 Introduction**

Biological aging entails the change in or decline of various physiological functions. Human biological aging, as opposed to chronological aging, differs depending on the tissue under investigation – and advanced biological age of specific organs is associated with diseases of the same1. Biological age of the brain, i.e., *brain age*, is modeled via machine learning algorithms by predicting a person’s chronological age from their neuroimaging data. A positive deviation of brain age from chronological age indicates an advanced brain age (*brain age gap, “BAG”*) and it is associated with presence, or future development of cognitive impairment due to neurodegeneration2–6.

Age-related changes of the brain are most apparent from anatomical changes, such as loss of brain volume (atrophy), and molecular changes, such as a decline of neuronal metabolism (neuronal dysfunction). These two processes can be visualized by T1-weighted magnetic resonance imaging (MRI) and 18F-Fluorodeoxyglucose-PET (FDG-PET), respectively. As atrophy is preceded by neuronal dysfunction, FDG-PET is a slightly earlier indicator of neurodegeneration compared to MRI7,8. Yet, estimation of brain age is typically achieved using MRI, rather than FDG-PET. Only one recent study compared FDG-PET to the standard of MRI for brain age prediction, and the study showed slightly better performance of brain age prediction when using FDG-PET4. However, pre-processing of FDG-PET data was done using partial volume correction, thus, under consideration of information from MRI and the question arose whether this reflected combined information from both modalities, rather than unimodal FDG-PET superiority. Additionally, authors of the study showed that, in a heterogeneous sample of cognitively impaired individuals, both FDG-PET- and MRI-derived BAG are associated with cognitive performance, future cognitive decline (also in cognitively unimpaired individuals), and Alzheimer’s disease biomarkers, such as amyloid and tau pathology. Finally, regions important for the prediction of brain age differed between FDG-PET and MRI. Together, these findings argue for further exploration of FDG-PET-derived BAG, and its possibly superior performance in delineating earliest deviations from normal aging when cognitive impairment is not yet apparent. Furthermore, no threshold of BAG for elevated risk of cognitive decline has yet been published. Such a threshold might differ depending on the presence of known risk factors for cognitive decline. Eventually, a (potentially risk-factor dependent) threshold of BAG could aid clinicians in providing personalized prognoses of disease progression.

Here, we aimed to further investigate the unimodal potential of FDG-PET and MRI to serve as predictors of chronological age, using a cohort of cognitively normal individuals (CN), and patients with mild cognitive impairment (MCI). First, we compared the accuracy of BPA using FDG-PET or MRI in CN, with chronological age serving as ground truth. Then, we compared associations of FDG-PET- and MRI-derived BAG and cognitive performance/Alzheimer’s disease pathology in CN and MCI. Finally, we applied machine learning classification to predict cognitive decline (CD) from BAG and known risk factors in CN and MCI, and subsequently calculated a threshold for BAG for elevated risk of cognitive decline.

**2 Method**

**2.1 Participants**

Baseline T1-weighted MRI and FDG-PET scans of 376 CN and 596 individuals with MCI used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](https://ida.loni.usc.edu/collaboration/access/adni.loni.usc.edu)). The primary goal of ADNI has been to test whether biological markers and clinical and neuropsychological assessment can be combined to measure the progression of MCI and dementia. Scans from the ADNI database were selected such that MRI and FDG-PET scans from the same individual were not more than one year apart (CN: mean = 31 days, SD = 28 days[[2]](#footnote-2), 337 of 376 FDG-PET scans acquired after day of MRI scan; MCI: mean = 29 days, SD = 25 days, 531 of 596 FDG-PET scans acquired after day of MRI scan). CN and MCI diagnoses were based on the ADNI standard: A diagnosis of CN entailed individuals had no significant impairment in memory or cognitive functions or activities of daily living. Individuals with subjective, but no objective cognitive impairment (“subjective cognitive impairment”, *SCI,* n = 106) were also included in this cohort. An MCI diagnosis was provided to individuals with measurable impairment in cognitive function in the absence of dementia or significant impairments of daily living (https://adni.loni.usc.edu/methods/documents/).

MRI and FDG-PET scans from 59 CN individuals from the Open Access of Imaging Studies-3 (OASIS-3, https://www.oasis-brains.org/20) database was used to validate the accuracy of brain age estimation in CN per modality in an external dataset. All individuals were older than 65 years of age; however, given the limited availability of participants who received both an MRI and FDG-PET scan within 12 months, we eliminated this time constraint for the OASIS test set.

To validate modality-specific BAG thresholds for cognitive decline for clinical purposes, we used 88 FDG-PET scans from SCI, and 80 MRI scans from MCI patients from the DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE).

**2.2 Acquisition & Preprocessing of Biomarkers of Neurodegeneration**

FDG-PET scans in all samples were acquired dynamically 30-60 minutes (6x5min frames) after injection with an average dose of 185 MBq (5mCi) and downloaded with minimal pre-processing (“Co-registered, averaged”-format). Pre-processing was performed using the Statistical Parametric Mapping 12 toolbox (SPM12; [www.fil.ion.ucl.ac.uk](http://www.fil.ion.ucl.ac.uk)): All 18F-FDG-PET scans were aligned to the anterior commissure/posterior commissure, and subsequently co-registered and normalized to a template in standard space. Lastly, standardized uptake value ratios (SUVr) were calculated (reference: pons10).

T1-weighted MRI scans were acquired on XX-T scanners according to the ADNI MRI acquisition protocol11. First, scans were pre-processed using denoising (spatial-adaptive Non-Local Means), spatial registration, bias-correction, and skull-striping. Then the images are segmented by an adaptive maximum a posteriori approach (Rajapakse et al. 1997) with partial volume model (Tohka et al. 2004). For non-linear transformation, the Geodesic Shooting Algorithm (Ashburner & Friston 2011) was used based on SPM12.

**2.3 Calculation of brain-predicted age**

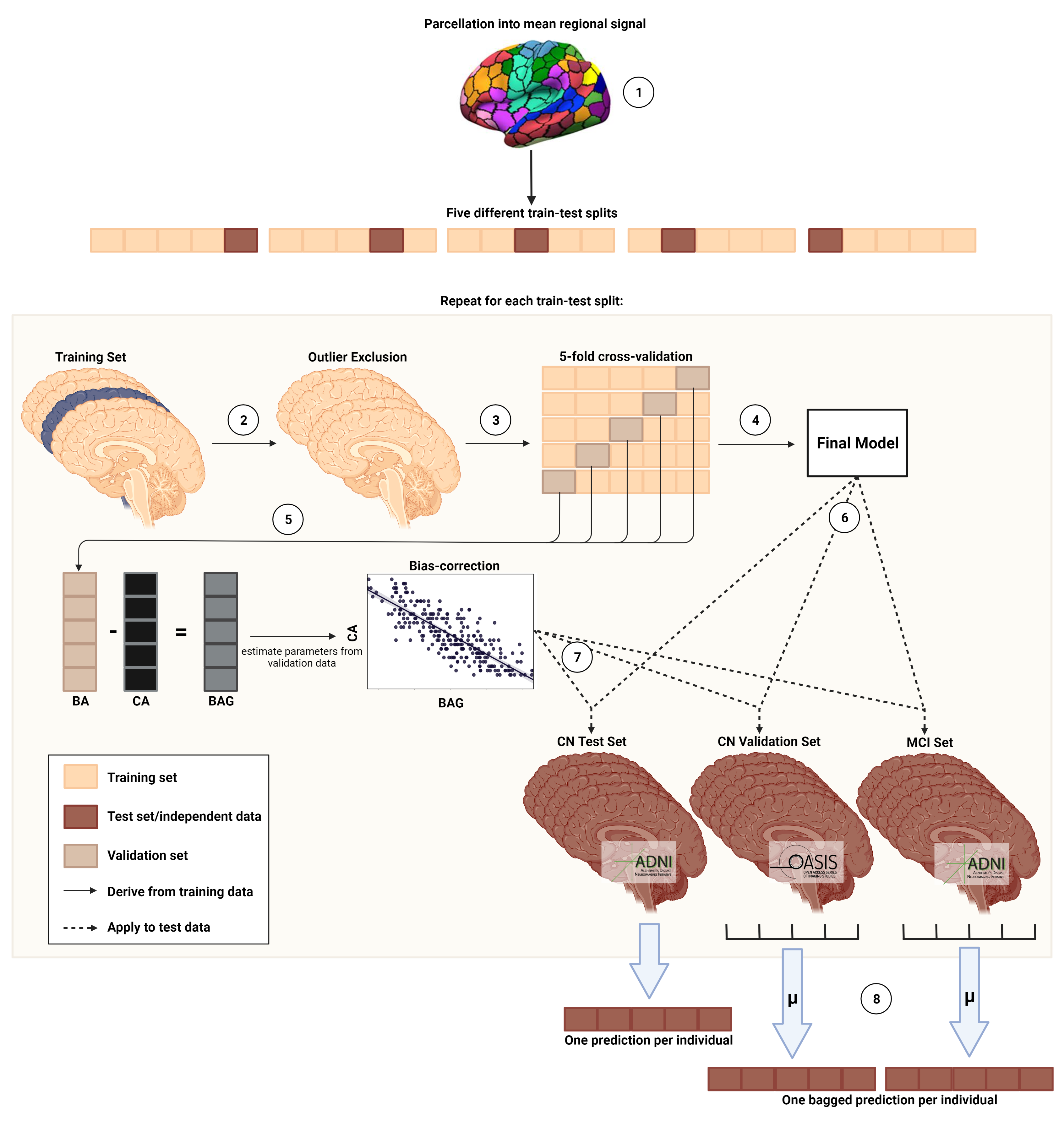
Using the Julearn library (<https://juaml.github.io/julearn/main/index.html>, based on scikit-learn14) in Python 3.8.5, we implemented a pipeline for brain age estimation, which is depicted in **Fig 1**. These pipelines were run independently for FDG-PET and MRI. First, regional averages of the signal of interest was extracted for the respective modality (FDG-PET: SUVR, MRI: gray matter volume) using a composite atlas containing 200 cortical12 and 16 sub-cortical regions13. Next, we applied a nested cross-validation approach: We repeatedly (five times) split the CN sample into different train (70%) and test sets (30%), such that each individual occurred in a test set exactly once. Through stratification, the original proportions of young-old (65 - 74 years, ~50% of our sample), middle-old (75 - 84 years, ~42% of our sample) and oldest-old individuals (85 years+, ~8% of our sample)15 in the CN sample were maintained in each train and test set. Each outer cross-validation loop consisted of outlier exclusion, an inner cross-validation yielding of a final model, estimation of parameters for bias correction, estimation of brain age in the test sets, and application of bias correction to the respective CN test set, as well as the CN\_validation and MCI sample.

**2.3.1 Outlier exclusion**

Outlier exclusion was performed to ensure data quality in an automated manner as part of the outer cross-validation loop. The interquartile range (IQR) was inferred from the training set. Subjects outside 6xIQR were removed from the train and respective tests sets. In the CN test sets, between two and six individuals were excluded in each outer cross-validation loop (ntotal = 22), while in the OASIS validation, between five and seven individuals were excluded. XX DELCODE XX Importantly, as previous works have shown, MCI subjects show an advanced brain age, which translates to a reduced signal in age-relevant brain regions6. Thus, outlier exclusion was not applied to the MCI samples of either ADNI or DELCODE.

**2.3.2 Inner cross-validation**

The inner cross-validation procedure was performed for hyperparameter tuning and yielded five ‘final models’, i.e., one that was optimized for each train set. Two types of algorithms previously recommended for small sample sizes16 were implemented for brain age prediction: support vector regression (SVR) and relevance vector regression (RVR). Hyperparameter tuning was performed using five-fold stratified cross-validation (for a list of hyperparameters, see Supplementary Materials Table 1). During each iteration of the inner cross-validation, four parts of the training data were first scaled (by removing the median and scaling the data according to the IQR, “robust scaler” from the scikit-learn library) and then used to fit the models. The respective scaling parameters and fitted models were subsequently applied to the fifth part of training data, i.e., the validation set. As a result of the inner cross-validation, one optimal RVR and one optimal SVR was yielded, where “optimal” refers to the respective hyperparameter configuration that allowed for the smallest average MAE between CA and BPA across the validation set. The final model was the model with the smallest average MAE across the remaining two optimal models.



**Fig 1. Nested cross-validation approach for brain age prediction.** Five different train-test splits were used to train and test the models. (1) Mean regional gray matter volume or SUVr were inferred from a composite atlas. (2) Outlier exclusion ranges were inferred from the training data, and applied to both the training and test data. (3) Models were trained using five-fold cross-validation. (4) The model with the smallest MAE on the validation folds was chosen as the final model. (5) BA and CA from the validation folds was used to derive bias correction parameters. (6) The final model was subsequently applied to the test sets. (7) Bias correction parameters were applied to predictions in the test set. (8) Mean of predictions across five models is considered as final prediction for CN Validation and MCI set. BA = brain age; CA = chronological age; BAG = brain age gap

**2.3.3 Bias correction**

BPA is subject to a frequently reported bias, in which BPA of older individuals is under- and BPA of younger individuals is overestimated17, regardless of the data or method under consideration18. Several approaches have been suggested for the correction of this bias, which can be broadly summarized into methods including chronological age in the correction and methods not including chronological age in the correction19. Here, bias correction parameters were estimated from BPA in the validation set, and subsequently applied to all test sets. To obtain an in-depth understanding of the effect of the different methods of bias correction on the prediction of CA from MRI and FDG-PET in our data, we implemented bias correction with and without including chronological age17,20. We found that only bias correction with chronological age successfully eliminated the correlation between BPA and chronological age in both MRI and FDG-PET across all five test sets (see Supplementary Materials for a description of bias-correction without CA and Supplementary Table S4 for results of the methodological comparison). The final BPA was therefore calculated under consideration of chronological age, using slope (ɑ) and an intercept (β) as follows:

**2.3.4 Precision of brain-predicted age and brain age gap**

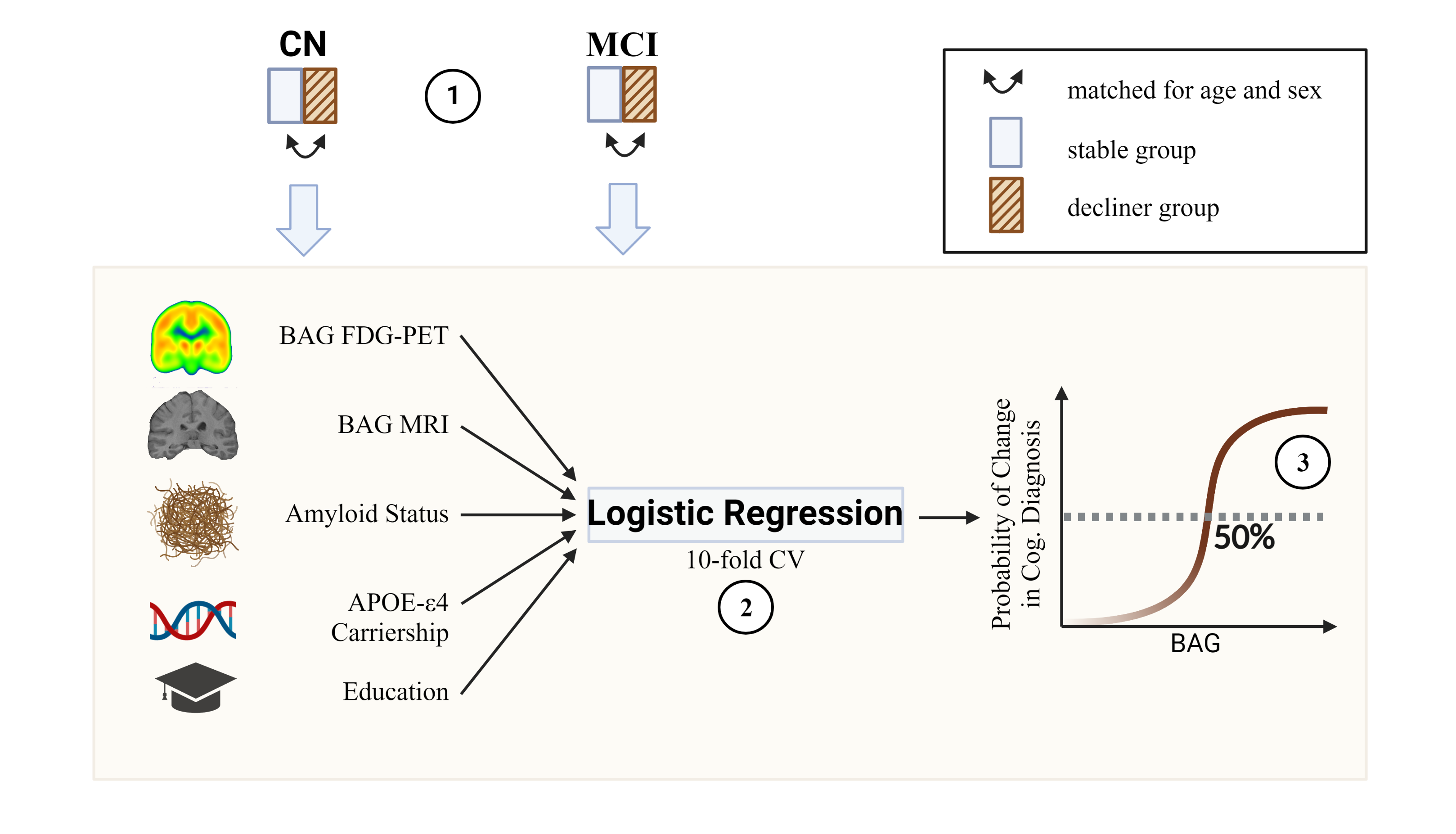
As a result of the above described nested cross-validation approach, we obtained five final models per modality. Thus, per modality, we obtained one prediction per (non-outlier) subject in the CN sample (n = 345), and five predictions per (non-outlier) subject in the CN\_validation (rangen = [52, 54]) and MCI sample (n = 513). For each individual, BAG was calculated as BPA – CA. MAE and average BAG of all samples was compared between modalities using a paired t-test.

**2.4 Associations of brain age gap with cognitive performance, Alzheimer’s disease neuropathology, and cognitive decline**

To assess whether BAG is associated with cognitive performance, we calculated partial correlations between BAG and composite scores of memory (ADNI-MEM21), and executive function (ADNI-EF22), while correcting for age, sex, years of education and APOE-ε4 carriership status. The correlations were tested against a Bonferroni-corrected alpha level of .025 (0.05/2). ADNI-MEM combines several scores used to evaluate individuals’ memory performance from the Rey Auditory Verbal Learning Test, Alzheimer’s Disease Assessment Scale and Mini Mental State Exam. ADNI-EF is a summary score of several executive function tasks, including: Category Fluency, Trails, Digit span backwards, Wechsler Adult Intelligence Scale-R Digit Symbol Substitution, Number Cancellation, and Clock Drawing items.

To assess whether BAG is associated with AD neuropathology, we calculated partial correlations between BAG and PET amyloid load (AV45-PET), as well as amyloid, tau and phosphor-tau accumulation in cerebrospinal fluid (CSF), while correcting for age, sex, years of education and APOE- ε4 carriership. The Bonferroni-corrected alpha level was set to 0.0125 (0.05/4). For AV45-PET, mean SUVr are publicly available from previous analyses23–26. CSF measures of amyloid, tau and phospho-tau were acquired via lumbar puncture and analyzed using the Roche Elecsys® beta-Amyloid1-42, Total Tau and Phospho Tau181p immunoassays27. The number of tau PET scans already evaluated for SUVr in the current cohorts was too small to include this biomarker into the current analyses.

Finally, we trained a logistic regression classifier to predict cognitive outcome within two years. Cognitive outcome was a binary variable (“stables” vs. “decliners”), based on the final diagnosis after two years. Thus, CN who received a diagnosis of MCI or AD within two years were cognitive *decliners*, while CN who maintained the CN diagnosis until 24 months after BAG assessment yielded the group of *stables*. For MCI, decliners were those individuals who progressed to ‘probable AD’ within two years. Probable AD at follow-up entailed presence of dementia symptoms, abnormal memory and cognitive function and fulfillment of NINCDS/ADRDA criteria for probable AD. MCI patients who were diagnosed as CN after two years were disregarded in the current analyses (n=29). Both in CN and MCI, we extracted a semi-random sample of stables, matched in number, age and sex to the complete cohort of decliners. MRI- and FDG-derived BAG in these samples, together with amyloid status (CSF amyloid1-42 <= 1100 pg/ ml28), APOE-ε4 carriership and years of education, were used as input to predict cognitive outcome using a 10-fold cross-validated logistic regression classifier, as depicted in **Fig 2**. Significant predictors of cognitive outcome were recorded. For each validation fold, the logistic regression classifier yielded an estimated probability of diagnosis change within two years. To derive a BAG threshold for elevated risk of a change in cognitive diagnosis, a logistic curve was fitted to model the relationship between BAG estimated from the significant BAG, and estimated probability of diagnosis change. The intercept of this curve at 50% probability was set as a threshold and validated in the current (ADNI), as well as the DELCODE sample.



**Fig 2. Estimation of a BAG threshold for cognitive decline.** (1) A stable group was created matched in age and sex to the group of all decliners in CN or MCI. (2) 10-fold cross-validated prediction of cognitive decline within two years was conducted with FDG-PET and MRI BAG, as well as amyloid status, APOE-ε4 carriership and education as predictors. (3) The BAG threshold for increased risk of cognitive decline was inferred from 50% probability of a change in cognitive diagnosis in the cross-validated classification output.

**3 Results**

**3.1 Participants**

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| **Table 1.** Overview of samples | | | | | |
|  | CN+SCIADNI | CNOASIS | SCIDELCODE | MCIADNI | MCIDELCODE | |
| *n* total | 376 | 59 | 88 | 596 | 80 | |
| Age at PET scan [avg. years (SD)] | 73.9 (5.94) | 71.7**-** (4.22) | 70.9**-** (5.57) | 73.2 (6.93) | NA | |
| Age at MRI scan [avg. years (SD)] | 73.8 (5.92) | 70.36**-** (4.17) | NA | 73.2 (6.92) | 73.4 (5.87) | |
| Sex [%female (nNA)] | 51 (0) | 59 (0) | 41 (0) | 42 (2) | 45 (0) | |
| CSFAβ1-42 Status [%positive (nNA)] | 39 (85) | NA | 43 (28) | 65 (139) | 52 (38) | |
| MMSE [avg. score] | 29 (1.23) | 29 (1.01) | 29**+** (1.03) | 28 (1.75) | 28 (1.67) | |
| Education [avg. years (SD)] | 16 (2.71) | 16 (2.70) | 16**-** (3.00) | 16 (2.67) | 14**-** (3.06) | |
| Notes. Percentage of CSFAβ1-42 Status indicates percentage of amyloid positive individuals among all who received lumbar puncture (excluding NA). Number of individuals who did not receive lumbar puncture for Aβ1-42 is in parentheses. +significantly higher than CN+SCIADNI, -significantly lower than CN+SCIADNI. Comparisons done within modality and group, via t-test for numeric, and χ² for categorical variables, with α = 0.05. | | | | | | |

This study included 972 MRI and FDG-PET scans (respectively) from the ADNI database (CN+SCIADNI: n = 376; MCIADNI: n = 596), as well as data from two validation cohorts. To validate brain age estimation, we used 59 MRI and FDG-PET scans (respectively) of CN from the OASIS-3. To validate BAG thresholds for the prediction of cognitive outcome, we used 88 FDG-PET scans of SCI and 80 MRI scans of MCI patients from DELCODE. An overview of participant characteristics is presented in **Table 1**. In the cognitively unimpaired cohorts, CNOASIS and SCIDELCODE were significantly younger than CN+SCIADNI (t = 3.44, *p* < .001), especially in the MRI cohort, and the MMSE of SCIDELCODE was higher compared to CN+SCIADNI (t = -2.30, *p* = .03). Among MCI samples, MCIDELCODE had significantly less years of education (t = 6.01, *p* < .001)

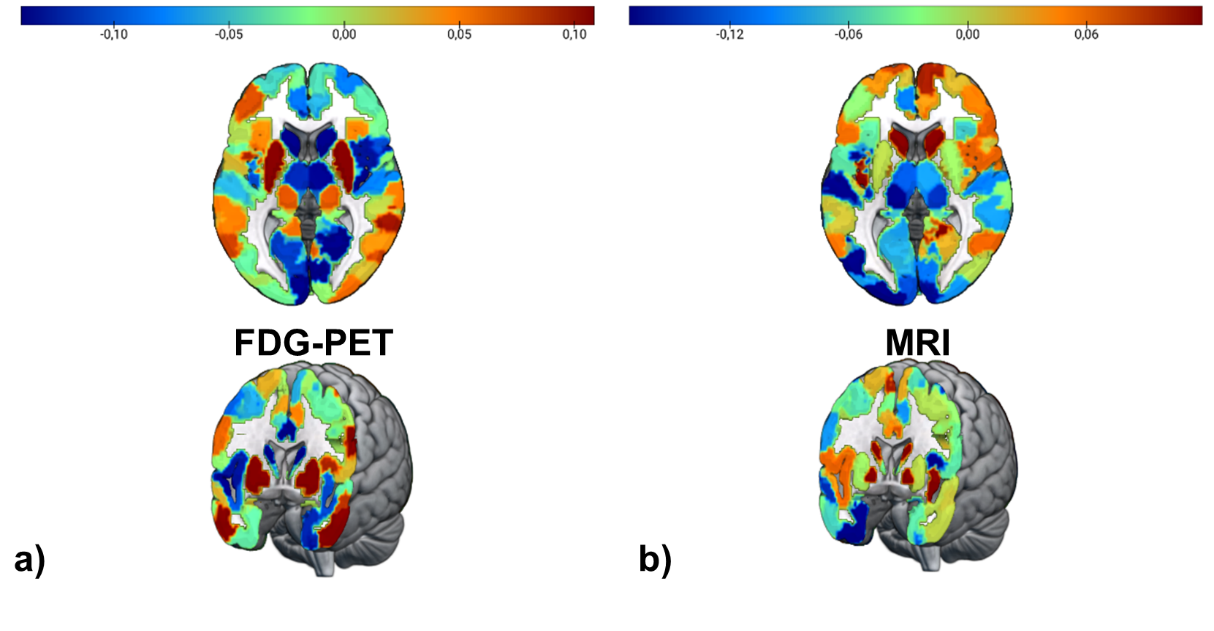
**3.2 Precision and demographic profile of brain-predicted age**

To compare the potential of FDG-PET and MRI to predict chronological age, we used a nested five-fold cross-validation approach including bias correction (see **Fig 1**), yielding one test prediction for (almost[[3]](#footnote-3)) every subject in the CN+SCIADNI sample, and a bagged test prediction for the CNOASIS, SCIDELCODE, MCIADNI and MCIDELCODE samples. Across the CN+SCIADNI test samples (n = 357 after outlier exclusion), MRI and FDG-PET predicted chronological age with a mean absolute error (MAE) of 1.96 and 2.63 years, and a broad range of BAG spanning 16 and 18.7 years, respectively (see **Table 2**). Both, MRI- and FDG-PET-derived BAG were normally distributed and they were moderately strongly correlated (r = .288, *p* < 0.001). In the external CNOASIS sample (n=52 after outlier exclusion), bagged predictions of chronological age had an MAE of 2.23 and 2.03 years for MRI and FDG-PET, respectively, thus showing high generalization performance of the models to external datasets. SCIDELCODE individuals’ brains were estimated from FDG-PET to be, on average, 2.07 years advanced in age compared to their chronological age. MCIADNI individuals’ brains were estimated to be, on average, 1.51 or 1.07 years advanced in age when predicted from MRI or FDG-PET, and, consistently, MCIDELCODE individuals’ brains were estimated to be 1.42 years older than their chronological age. Bias correction eliminated the correlation between BAG and chronological age in the CN+SCIADNI, CNOASIS, both DELCODEsamples, although a marginal (α=0.1) correlation remained between BAG and chronological age in the CNOASIS sample (MRI: r = -.242, *p* = .08, FDG-PET: r = .266, *p* = 0.06).

Women showed lower BAG compared to men in CN+SCIADNI (tMRI = -6.98, *pMRI* < .0001, tFDG-PET = -1.98, *pFDG-PET* = .05), SCIDELCODE (tFDG-PET = -2.13, *p* = 0.04), MCIADNI (tFDG-PET = -3.85, *pFDG-PET* < .001; tMRI = -5.58, *pMRI* < .0001), and MCIDELCODE (tMRI = -2.73, *pMRI* < .008), especially on MRI-derived BAG. Carriership of the APOE-ε4 allele, genetically predisposing for Alzheimer’s disease, was associated with higher BAG in MCIADNI (only MRI: tMRI = 2.72, *pMRI*= 0.007). Years of education was not correlated with BAG in any of the samples.

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| **Table 2.** Precision of predicting chronological age from FDG-PET and MRI scans. | | | | | | |  |  |
|  | CN+SCIADNI | | CNOASIS | | MCIADNI | | SCIDELCODE | MCIDELCODE |
|  | MRI | FDG | MRI | FDG | MRI | FDG | FDG | MRI |
| *n* total | 357⁺ | 357⁺ | 52⁺ | 52⁺ | 596 | 596 | 88 | 80 |
| MAE | 1.96 | 2.63 | 2.23 | 2.03 | 2.62 | 2.51 | 2.64 | 2.62 |
| Range | [-6.91, 9.09] | [-8.72, 9.98] | [-5.44, 7.40] | [-6.70, 5.46] | [-9.07, 9.55] | [-10.91, 9.23] | [-5.49, 7.92] | [-4.64, 9.60] |
| ME | 0.05 | -0.001 | -0.71 | -0.04 | 1.51 | 1.07 | 2.07 | 1.42 |
| R² | .816 | .693 | .593 | .617 | .773 | .794 | .641 | .676 |
| *Notes.* +After outlier exclusion using CN train set (IQR > 6). Precision of bagged predictions are shown for all but the CN+SCIADNI samples. | | | | | | | | |

All final models were SVMs, and four out of five, and five out of five final used a linear kernel. To assess feature importance in the brain age prediction paradigm, we extracted all brain region’s weight coefficients as learned by these models. For non-linear kernels, weight coefficients are not available. Regional weight coefficients were strongly correlated within modalities (MRI: r = [.79, 0.89]), FDG-PET: r = [.74, .79], but average weight coefficients were not correlated between the two modalities (r = .048, *p* = .48), i.e. the regions used for brain age prediction in the two modalities were substantially different (see **Fig 3**).



**Fig 3** **Feature importance for brain age prediction.** a) Average weights of support vector regression across three linear SVR for brain age prediction using FDG-PET. Weights were highly correlated across models (r > 0.8). b) Average weights of support vector regression across five linear SVR for brain age prediction using MRI. Weights were highly correlated across models (r > 0.7).

**3.3 BAG and Cognitive Performance**

Partial correlations between BAG and composite scores for memory (ADNI-MEM) and executive function scores (ADNI-EF) were calculated to evaluate whether BAG is associated with cognitive performance in the two modalities using the ADNI samples. To adjust for multiple comparisons, threshold levels of significance were adjusted by Bonferroni correction (α = .025), while p-values below .10 were considered “marginal” and are reported for interpretability. Age, sex, years of education and APOE-ε4 were entered as covariates.

In CN, ADNI-MEM (*p* = .64) and ADNI-EF (*p* = .13) scores were normally distributed as assessed with the Shapiro Wilk test, thus, Pearson correlations were computed. Higher MRI-derived BAG was associated with lower ADNI-EF scores (r = -.137, *p*= .01). A marginal, negative correlation was observed between FDG-PET-derived BAG and ADNI-MEM scores (r = -.100, *p* = .06).

In MCI, ADNI-MEM (*p* = .004) and ADNI-EF (*p* = .05) were not normally distributed as assessed with the Shapiro Wilk test, thus, Spearman-rank correlations were assessed. Both, MRI- and FDG-PET-derived BAG were significantly negatively correlated with ADNI-MEM (rhoMRI = -.379, *pMRI <* .0001; rhoFDG-PET = -.237, *pFDG-PET* < .0001) and ADNI-EF (rhoMRI = -.272, *pMRI <* .0001; rhoFDG-PET = -.243, *pFDG-PET*  < .0001).

**3.4 BAG and AD Neuropathology**

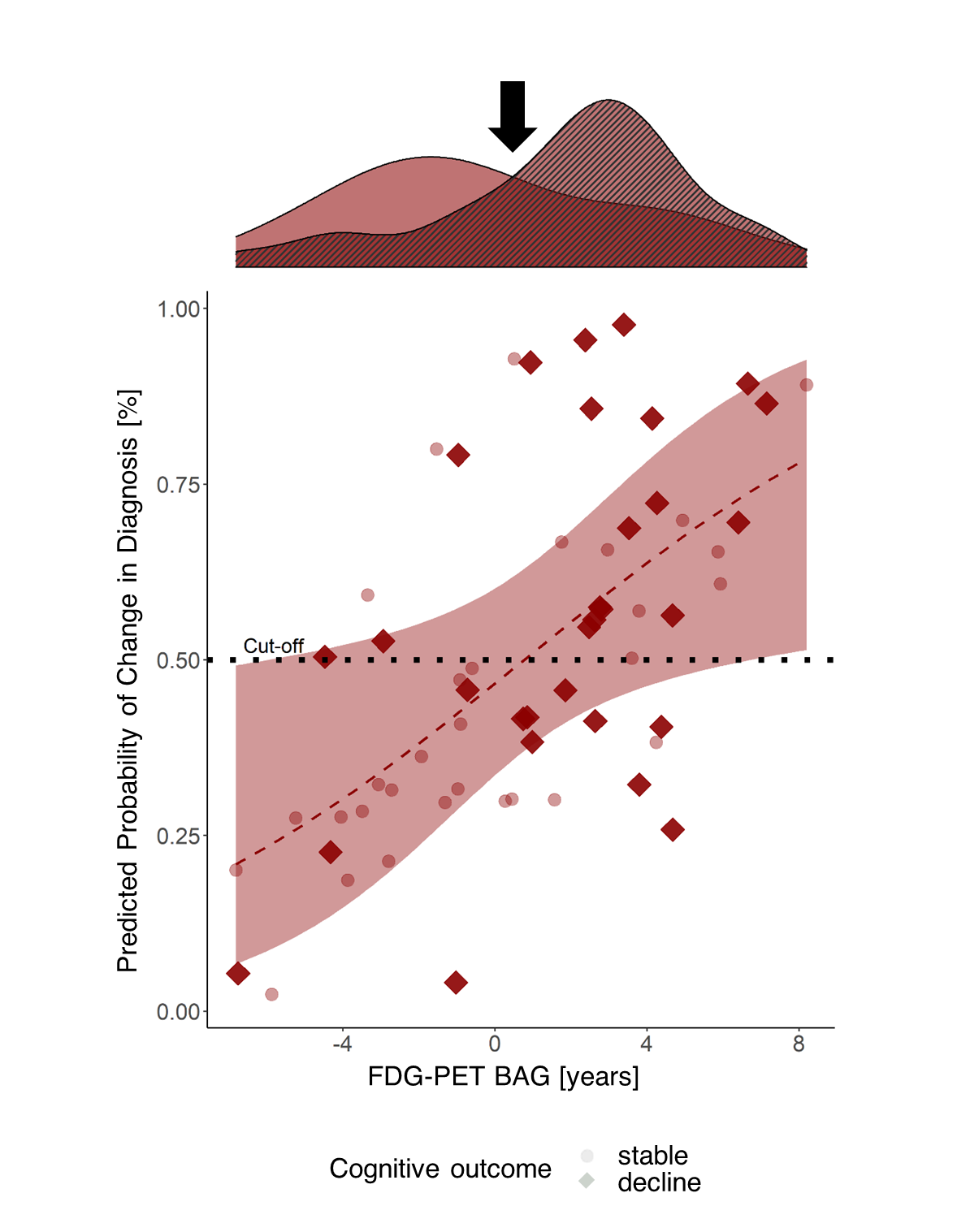
Partial correlations between BAG and PET amyloid status (global AV45), CSF β-amyloid1–42 (CSF Aβ1-42), CSF total-tau (CSF Tau) and CSF phospho-tau181 (CSF pTau181) were calculated to evaluate whether BAG is associated with AD neuropathology in the two modalities using the ADNI sample. To adjust for multiple comparisons, threshold levels of significance were adjusted by Bonferroni correction (α = .0125), while p-values below .05 were considered “marginal”. Again, age, sex, years of education and APOE-ε4 were entered as covariates. None of the neuropathological indicators were normally distributed in either CN or MCI, therefore Spearman-rank correlations were computed.

In CN+SCIADNI, higher MRI- and FDG-PET-derived BAG were both correlated with a decrease in CSF Aβ1-42 (rhoMRI = -.152, *pMRI* .012; rhoFDG-PET = -.152, *pFDG-PET* = .012), but none of the other pathological variables. In MCIADNI, both, higher MRI- and FDG-PET-derived BAG were associated with enhanced amyloid accumulation, as reflected by significant negative correlations with CSF Aβ1-42 (rhoMRI = -.232, *pMRI <* .0001; rhoFDG-PET = -.144, *pFDG-PET* = .002), and (marginal) positive correlations with global AV45 (rhoMRI = -.272, *pMRI <* .0001; rhoFDG-PET = -.1, *pFDG-PET*  = .026). Moreover, higher MRI-derived BAG was marginally associated with higher levels of CSF pTau181 (rhoMRI = .093, *pMRI* = .048).

**3.5 BAG and Cognitive Outcome**

To assess the potential of BAG from the two modalities to serve as an indicator of cognitive outcome, and to calculate thresholds for elevated risk of cognitive decline in CN and MCI, cognitive outcome after two years was predicted from MRI- and FDG-PET-derived BAG, APOE-e4 carriership, CSF amyloid status and years of education. We applied 10-fold cross-validated logistic regression in a subsample containing all decliners, and an equal number of stables matched in age and sex for both, CN and MCI. Predictors were considered significant at α = .05. As amyloid status was not available for all individuals, analyses were conducted in two ways: once including individuals with missing amyloid information (NA values coded as 0, and amyloid negativity coded as reference; “whole samples”), and once excluding these individuals (“complete samples”, results in Supplementary Materials).

Two hundred seventy eight individuals from the CN+SCIADNI sample remained stable until year two, while 30 obtained a diagnosis of cognitive impairment (MCI or dementia) within two years. Consequently, a subsample of 30 stables and all 30 decliners constituted the subsample for prediction of cognitive outcome in CN. We found that, holding all other predictor variables constant, FDG-PET-derived BAG and APOE-ε4 carriership significantly predicted cognitive outcome after two years. The odds of a change in diagnosis for the worse within two years were increased by 29% (95% CI [1.079, 1.604], *p* = .010) for every FDG-PET-derived BAG year. Moreover, these odds were also increased by 835% (95% CI [1.496, 71.814], *p* = .028) for APOE-ε4 carriers, compared to non-carriers. To obtain a cut-off for cognitive outcome, we fit a logistic regression model on the predicted probability of receiving an MCI/Dementia diagnosis within two years against FDG-PET BAG. The intersection of the curve with 50% probability of receiving such a diagnosis was at 0.78 years FDG-PET BAG (see **Fig. 4**). This suggests that if the brain age of a cognitively unimpaired individuals is advanced by 0.78 years, they have an elevated risk of cognitive decline. In the XX current subsample XX + CN+SCIADNI sample of all 308 individuals who were either stable or decliners by year 2, including the subsample used to derive the cut-off, this threshold yielded a specificity of 73.3% and a sensitivity of 62.5%. To validate the cut-off in an external dataset, we applied it to the SCIDELCODE cohort (ndecliners= 8, nstables = 80), where we obtained a specificity of 87.5% and a sensitivity of 33.8%. Indicating that when FDG-PET BAG is 0.78 years or higher, cognitively unimpaired individuals have a high risk of cognitive decline, risk assessment of individuals with an FDG-PET BAG below this cut-off requires further investigation.

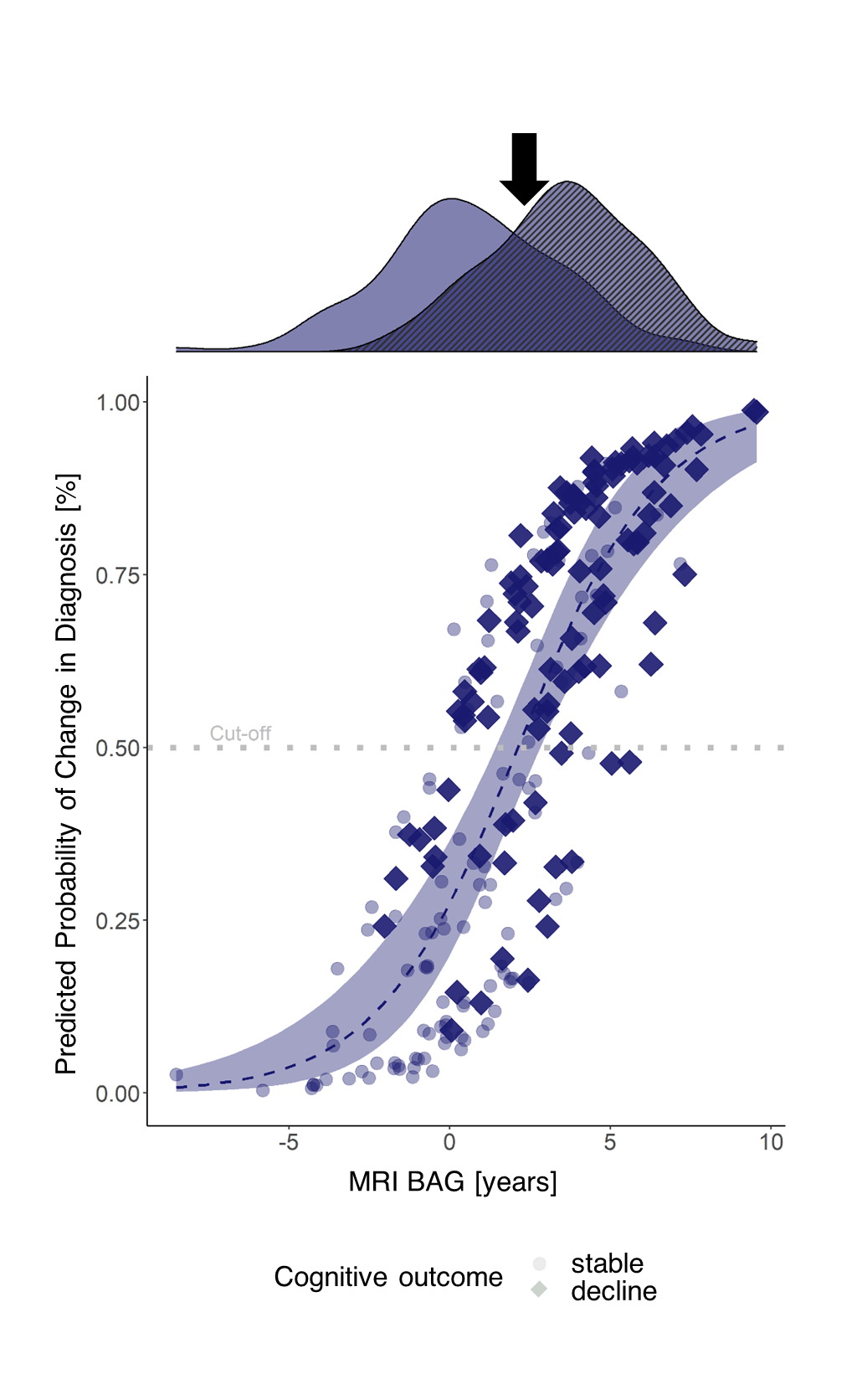


**Fig. 4** **Cross-validated probability of a change in diagnosis from CN to MCI/Dementia within two years after a baseline diagnosis by PET-BAG.** The gray lines depict smoothed probability curves yielded from logistic regression predictions. Transparency of stable individuals is increased for visibility. a) CD predicted from FDG-BAG only. Higher PET-BAG was the only significant predictor of CD in sample one. The PET-BAG-derived threshold for CD in sample 1 (50% probability of CD; dotted line) was .3 years (as indicated by dotted line and black arrow). The density plots show that most stables show a lower BAG, while most decliners have a higher BAG. b) CD predicted from FDG-BAG and amyloid status. Amyloid positivity and marginally FDG-PET predicted CD in sample two. The PET-BAG-derived decision boundary in sample 2 was .4 years. DX = diagnosis.

After removing those individuals who did not have information on amyloid status available (n=6), a complete sample of 24 decliners remained, thus constituting a sample size of 48. Results from the complete samples were largely consistent with results obtained from the whole samples and can be found in the Supplementary Materials, section “Prediction of Cognitive Outcome”.

Three hundred forty eight MCI patients remained stable until year two, while 113 MCI patients converted to dementia. Consequently, a subsample of 113 stables and all 113 decliners constituted the subsample for prediction of cognitive outcome in MCI. Holding all other predictor variables constant, MRI-derived BAG, a positive amyloid status in CSF, and APOE-ε4 carriership significantly predicted cognitive outcome after two years. With every one-year increase in BAG on MRI, the odds of converting to MCI or dementia were increased by 52% (95% CI [1.304, 1.788]), while a positive amyloid status and APOE-ε4 carriership increased those odds by 411% (95% CI [1.632, 11.255]) and 303% (95% CI [1.495, 6.254]), respectively. To obtain a cut-off for cognitive outcome, we fit a logistic regression model on the predicted probability of converting to dementia within two years against MRI BAG. The intersection of the curve with 50% probability of receiving such a diagnosis was at 2.23 years MRI BAG (see **Fig. 5**). Again, this suggests that if the brain age of an MCI patient is advanced by at least this cut-off value, they have an elevated risk of conversion to dementia. In the current MCIADNI subsample, stratification by this cut-off yielded a specificity of 70.8% and a sensitivity of 72.5%. In the sample of all individuals where an estimation of cognitive outcome was possible (n=461), the cut-off yielded a specificity of 70.8% and a sensitivity of 70.4%. In the MCIDELCODE sample (nstables = 41, ndecliners = 28), the cut-off had a specificity of 67.9% and a sensitivity of 73.2%.

Three hundred sixty nine MCI patients had full information on all considered variables, thus constituting the decliner group of the complete samples. Results from the complete samples were largely consistent with results obtained from the whole samples and can be found in the Supplementary Materials. Finally, given the correlation observed between FDG-PET- and MRI BAG, we additionally assessed logistic regression models with unimodal BAG29. Considered in separate models, both MRI- and PET-BAG very significantly predicted Cognitive Outcome in MCIADNI, while only FDG-PET predicted cognitive outcome in CN+SCIADNI (see Supplementary Tables S2 and S3 for estimates of logistic regression in whole samples).



**Fig. 5 Cross-validated probability of cognitive decline within two years after a baseline diagnosis of MCI by MRI-BAG.** The gray lines depict smoothed probability curves yielded from logistic regression predictions. Transparency of stable individuals is increased for visibility. a) The MRI-BAG-derived cut-offs for CD in sample 1 (dotted line) was 2.3 years. This cut-off differed as a function of APOE-ε4 carriership, where APOE-ε4 carriers showed a considerably lower cut-off. b) The MRI-BAG-derived decision boundary in sample 2 was 2.5 years. Again, APOE-ε4 carriers displayed a lower cut-off of MRI-BAG for CD. Density plots show that CD is well predictable from MRI-BAG among APOE-ε4 (non-)carriers. DX = diagnosis.

**TODO investigate memory and pathology after cognitive outcome as “profile” of elevated brain age?**

**4 Discussion**

While numerous works exist on the relationship between brain age and neurodegenerative diseases, thresholds and recommendations for BAG as an individual-level biomarker of cognitive decline were only sparsely investigated. However, such guidelines are necessary in order to provide guidelines to clinicians, and thus to effectively integrate measures of brain age into clinical practice. Our main findings were three-fold: We found that 1) FDG-PET predicts brain age equally well as MRI, 2) FDG-BAG can serve as a prognostic marker of cognitive decline providing information complementary to MRI-BAG, and 3) that risk of cognitive decline within the following years is elevated with an FDG-BAG of XX in CN and an MRI-BAG of XX in MCI. XX We further demonstrated that FDG-BAG is superior in representing AD neuropathology and risk of cognitive decline in CN. MRI-BAG, on the other hand, was more closely associated with a decline of executive function within the range of a CN diagnosis, as well as memory function, AD neuropathology and cognitive decline in MCI. Importantly, we identified that CN with an FDG-BAG > 0 are at elevated risk for cognitive decline, while the cut-off for MCI lies around an MRI-BAG of 2.4 years.

Congruent with previous work, our findings underline that FDG-PET shows greater and more consistent changes early in the AD continuum (e.g. a decrease of Aβ1-42 in CSF), whereas MRI is superior in delineating AD-related changes with an AD diagnosis (e.g. onset of tau-related neurodegeneration)8. Among the CN population, our results may be most relevant to individuals experiencing subjective cognitive impairment (SCI). Persons with SCI recognize cognitive deficits before they become objectively measurable. These individuals were shown to be more likely to develop MCI or AD compared to CN without SCI30. Differences on MRI brain age between CN and SCI have previously been shown, as SCI demonstrated a BAG advanced by 1.1 years3. However, as we have shown here, for individuals without objective cognitive impairment, FDG-BAG serves as a better biomarker to measure neuropathological variability and risk of CD. Individuals presenting to a memory clinic with SCI could in the future be recommended an FDG-PET. Should their brain age exceed their chronological age, our current results yield a justification for a need of close monitoring of symptoms and potential therapeutic interventions.

Early detection of pathological abnormality is among the most crucial concepts in preventing AD. According to the *amyloid cascade hypothesis*, amyloid deposition is the causative agent of AD, causing a downstream effect of tau deposition, neurodegeneration and dementia31. Several promising anti-amyloid therapies are currently under assessment or have recently been approved for the treatment of MCI and early AD. The inclusion of BAG into clinical trials of AD could have several advantages. First, we have shown that BAG serves as a biomarker of cognitive decline in both, CN and MCI. Since cognitive decline is often an outcome factor of these trials, the notion of BAG could help to identify those individuals who are most at risk of cognitive decline, thereby strongly reducing the number of participants and thus cost of treatment trials. Secondly, BAG is an established summary marker of brain health32. Brain age prediction algorithms are trained on a cognitively normal cohort and we have shown that BAG reliably detects current and pending deviations from normal cognitive performance. Thus, it also appears possible to consider BAG itself as an outcome variable of neuroscientific clinical trials, potentially reflecting drug action on the whole brain above and beyond variables of interest. Importantly, given that it is hardly possible to restore brain structures lost to neurodegeneration, MRI brain age is unlikely to decrease, but only to decelerate. On the other hand, it appears possible that a decreased metabolism can be strengthened and increased again by certain interventions, thus underlining the here postulated importance of choice of modality for brain age prediction.

Lee: FDG-PET scans were pre-processed using partial volume correction and are thus influenced by MRI information 🡪 fallacy as not really a comparison. Our study confirms findings except find stronger difference in associations between AD biomarkers, cognitive decline, … BPA not correlated in CN

In the MCI population, differential cut-offs were identified for APOE-ε4 carriers and non-carriers, with cut-offs for APOE-ε4 carriers being as low as 0.7 years on MRI, which is well below the average BAG of this group identified here (1.57 years on MRI). Post-hoc analyses confirmed that APOE-ε4 carriers also showed a higher MRI-BAG (2.11 years) compared to APOE-ε4 non-carriers. These findings support the notion that BAG increases more strongly in APOE-ε4 carriers5. The APOE lipoprotein is involved in lipid transport, metabolism, inflammatory response signaling and pathology clearance mechanisms, for example of cerebral amyloid33. In our analyses, APOE-ε4 carriership was a significant predictor of CD in both MCI samples, while amyloid status only predicted cognitive decline in one sample. This was likely attributable to the fact that we investigated decline from MCI to dementia, rather than AD, in order to retain a considerable sample size of decliners. While APOE is associated with a variety of neurological conditions, amyloid is rather AD-specific. Together, these findings underline the pivotal role of genetic predisposition for several dementias and other neurological conditions in individuals carrying at least one ε4 allele33–37, and are in favor of the combined observation of genetic and neurodegenerative patterns for disease risk assessment38.

Some limitations should be acknowledged. Only one of two samples evidenced usability of BAG for prediction of CD in CN. The purpose of using two different matched samples was to obtain an indicator of reliability of the obtained results. The different results on the two samples could be due to the small sample size of decliners. Therefore, the implementation of FDG-BAG as a biomarker in CN requires confirmation by future studies including a larger sample of decliners. Moreover, it is not a straightforward to acquire FDG-PET scans from a CN population, as PET scans require logistic availability, comparably high cost, and the injection of a radioactive tracer. However, whether the multi-dimensional feature space of FDG-PET can be replaced by easier accessible fluid biomarkers of neurodegeneration, and whether they would reflect brain aging, is questionable. Finally, our definition of CN only required for the absence of objective cognitive impairment, but not normality according to specific biomarkers, thus some participants with underlying amyloid pathology were included into our training sample. However, here the choice was to train our models to capture potential pathological heterogeneity of cognitively normal individuals to obtain a realistic estimate of brain aging.

In conclusion, we have shown that FDG-PET and MRI can and must both be used for brain age prediction: While FDG-PET better captures deviations from normal aging in CN, MRI is the superior modality in individuals with MCI. We have developed BAG cut-offs for estimation of risk in CN and MCI, which could support the identification of patients in need of frequent monitoring at an early time point, as well as support clinical trials, both methodologically, and financially.

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**Statements & Declarations**

**Author Contributions**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ED and GA, in support of KP and MH. KP, TvE, SE and AD jointly supervised this work. 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.

**COMPETING INTERESTS**

MH reports no conflict of interest.

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Maybe mention SFB?

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1. 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> [↑](#footnote-ref-1)
2. Mean and standard deviation indicated from absolute difference in days [↑](#footnote-ref-2)
3. An outlier exclusion procedure was included in our cross-validation approach. Outlier ranges were estimated based on the training set and test subjects falling in these ranges were subsequently excluded from brain age prediction. [↑](#footnote-ref-3)