**MANUSCRIPT DRAFT**

**COMPARISON OF STRUCTURAL AND METABOLIC BIOMARKERS OF NEURODEGENERATION FOR BRAIN AGE PREDICTION USING MACHINE LEARNING**

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‘ = impact factor > 4, \* = published numerous work on brain age

**Abstract**

XXX (will do this at the end)

**Introduction**

“Brain-age prediction uses machine learning to estimate an individuals apparent brain aging based on structural and functional brain characteristics derived from neuroimaging, commonly magnetic resonance imaging (MRI). Subtracting chronological age from estimated brain age provides a measure of the difference between an individuals predicted and chronological age; the *brain age delta*. For instance, if a 60 year old individual exhibits a brain age delta of -5 years, their typical aging pattern resembles the brain structure of a 55 year old, i.e., their estimated brain age is younger than what is expected for their chronological age. Individual variation in delta estimations have been associated with a range of biological and cognitive variables. brain-age estimation also involves a **frequently observed bias:** brain age is overestimated in younger subjects and underestimated in older subjects, while brain age for participants with an age closer to the mean age (of the training dataset) are predicted more accurately”

Brain-predicted age (BPA)

Chronological age (CA)

Brain-predicted age difference (BPAD)

mean absolute error (MAE)

* **First paragraph: aging of the brain**
  + late-life adult brain shrinks with increasing age
  + changes at all levels from metabolism to morphology
  + incidence of stroke, white matter lesions, and dementia also rise with age
  + thus, abnormal brain age could be used as a biomarker for proneness to neurodegenerative diseases, such as Alzheimer’s disease
  + however, state-of-the-art machine learning models of normal brain aging are mostly based on structural MRI, thereby restricting brain age prediction to changes in morphology
  + young-old, middle-old, oldest-old → different risk factors associated with being of high age [Suzman 1985], but inherent resilience against age-related detrimental factors may be in place which allows reaching such high age, e.g. “Overall, there is evidence that pathological substrates of cognitive deterioration in the oldest-old are different from those observed in the younger-old. Microvascular parameters such as mean capillary diameters may be key factors to consider for the prediction of cognitive decline in the oldest-old. Neuropathological particularities of the oldest-old may be related to “longevity-enabling” genes” [von Gunten 2010]
* **Second paragraph: MRI - FDG-PET comparison**
  + FDG-PET unravels the molecular changes in cell metabolism of the brain
  + structural MRI depicts anatomical changes, such as atrophy
  + FDG-PET, as compared to MRI captures first AD-related changes earlier and more accurately [1,2,3]
  + FDG-PET displays greater and more consistent changes as compared to structural MRI at early stages of AD [3]
  + therefore, FDG-PET possibly yields previously unexplored information about brain age
* **Third paragraph: What is a good brain age model**
  + brain age = neuroimaging-predicted chronological age
  + brain-predicted age difference (BPAD) = brain age - chronological age
  + ...
* **Fourth paragraph: Aim of the study**
  + 1) to find suitable bias-correction for FDG-PET and T1-weighted MRI
  + 2) to **compare the predictive value** of FDG-PET and MRI for brain age in CN
  + 3) to assess **BPAD in individuals with MCI**
  + 4) to associate **BPAD with neuropsychology and neuropathology**

**Method**

**Participants - ADNI**

Baseline T1-weighted MRI (T1w MRI) and  18F-Fluorodesoxyglucose-PET (18F-FDG-PET) scans of 370 cognitively normal (CN) elderly (65 years+) individuals 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 AD. We required the time interval between T1w MRI and 18F-FDG-PET scans to not exceed 12 months. The ADNI dataset was split into 70% training and 30% testing set.

XX MCI XX

**Participants - OASIS**

To test our algorithms in an external dataset, we additionally considered 60 CN elderly  participants from the Open Access of Imaging Studies-3 (OASIS-3) database (https://www.oasis-brains.org/) [1]. Given the small sample size of participants who received both an sMRI and 18F-FDG-PET within 12 months, we eliminated this time constraint for the OASIS test set.

**Acquisition & Preprocessing of Biomarkers of Neurodegeneration**

XX Acquisition XX

First, T1-weighted images were preprocessed 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 (v7771) using Matlab (R2017b) and compiled for containerization in Singularity (2.6.1)

18F-FDG-PET scans in both samples were acquired dynamically 30-60 minutes (6x5min frames) after injection with an average dose of 185 MBq (5mCi). 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)): First, each individual’s 18F-FDG-PET scan was averaged across frames. Second, all 18F-FDG-PET scans were aligned to the anterior commissure/posterior commissure. Third, all 18F-FDG-PET scans were co-registered and normalized to an MRI template. Lastly, standardized uptake value ratios (SUVr) were calculated (reference: pons [2]).

**Estimation of brain-predicted age**

Mean gray matter volume (GMV) and SUVr were extracted for T1w MRI and 18F-FDG-PET, respectively, using a composite atlas containing 200 cortical (Schaefer atlas [3]) and 16 sub-cortical regions (Tian atlas [4]). Next, the ADNI data of CN individuals was split in a stratified manner into a train (70%) and a test set (30%). Through stratification, the original proportions of young-old (65 - 74 years), middle-old (75 - 84 years) and oldest-old classes (85 years+) [5] in the whole ADNI dataset were maintained in the train and test set. For data quality assurance across modalities, all 216 regions’ interquartile ranges (IQR) were calculated on the train set. Subjects from the train set, as well as the ADNI and OASIS test set, with a mean regional GMV and/or SUVr outside of three times a region’s IQR (“extreme outlier”) were excluded from both the T1w MRI and the 18F-FDG-PET dataset (n=XX).

To estimate BPA using T1w MRI and 18F-FDG-PET, we compared relevance vector regression (RVR) and support vector regression (SVR). These machine learning models are prominently used for brain age prediction and are especially suited for training on small datasets [6]. Optimal hyperparameters were determined using five-fold stratified cross-validation using scikit-learn [7] (for a list of hyperparameters, see Supplementary Materials Table 1). During each iteration of cross-validation, four parts of the training data were first scaled (by removing the median and scaling the data according to the IQR) and then used to fit the models. The respective scaling parameters were subsequently applied to the validation set (fifth part of training data). The fitted models were used to predict CA from either neuroimaging modality in the validation set. As a result of 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 sets.

**Bias-correction**

BPA is subject to a frequently reported bias, in which BPA of older individuals is under- and BPA of younger individuals is overestimated [XX], regardless of which data or method is used [8]. Several methods exist to correct for this bias, which can be broadly summarized into *methods including chronological age in the correction* and *methods not including chronological age in the correction* [9]. While the first set of methods reduces the MAE and variance between CA and BPA, the latter increases it. To obtain an in-depth understanding of the effect of both methods on the prediction of CA from T1w MRI and 18F-FDG-PET, we implemented both kinds of methods and compared MAE and R² between them and uncorrected predictions, thus aiming to replicate the results from Beheshti et al. [10] with our data from two different neuroimaging modalities. Bias-correction methods were implemented using five-fold cross-validated predictions of the whole train set.

For a bias-correction procedure with CA, we used the method proposed by Beheshti and colleagues [10], where a linear regression model is fit on BPAD versus CA, yielding a slope (ɑ) and an intercept (β). Bias-free brain age is then calculated as:

The second bias-correction procedure we assessed was a bias-correction procedure without CA proposed by Cole et al. [11], which Beheshti et al. compared their proposed algorithm to. In this method, a linear regression model is fit on BPA versus CA. Without CA, bias-free brain age is then calculated as:

**Validation of brain-predicted age results**

* **Comparison of Predictive Value of** 18F-FDG-PET and T1w MRI for Brain Age Prediction
* **Brain age prediction (feature extraction, features importance, features interaction etc)**
* **Neuropsychology/neuropathology correlations**

**Results**

* **Participant Characteristics**

Gender/Age/MMSE

**Discussion**

Oldest-old (>85) in CN vs MCI?

* Superaging: do not show the typical patterns of brain atrophy in certain regions [Sun 2016] or resistance to pathology [Hoenig 2020].

**Conclusion**

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