The preclinical phase of autosomal dominant genetic form of Alzheimer’s disease is characterized by accelerated brain aging that is independent from amyloid pathology

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Background and objectives

Overlaps exist between the neural systems vulnerable to aging and Alzheimer’s disease (AD). It is a matter of debate whether aging and AD progression are independent phenomena. We aimed at developing a model able to predict brain aging from resting-state functional connectivity (rsfMRI). We then used the difference between the predicted age and the chronological age to test whether presymptomatic autosomal dominant AD (ADAD) mutation carriers have premature aging (DIAN cohort). We also tested if the beta-amyloid (Aβ) status (positive or negative) contributes to the discrepancy between the age estimated from brain functions and the actual age. We repeated these analyses in asymptomatic individuals at risk of sporadic AD, while comparing APOE4 carriers to non-carriers (PREVENT-AD cohort).

Participants and Methods

Resting-state functional magnetic resonance imaging (rsfMRI) scans were collected in 1,350 cognitively normal participants from 18 to 94 years old by the DIAN, PREVENT-AD, Can-CAN, ADNI, and ICBM cohorts to train and test a “Brain Age” predictive model.

Cohorts

- Dominantly Inherited Alzheimer Network: a multinational longitudinal study, which enrolls individuals aged 16 and older who have a biological parent that carry a genetic mutation responsible for autosomal dominant AD (ADAD).
- cognitively normal mutation carriers and noncarriers were included in the present study.

- Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer’s Disease: a multinational longitudinal cohort which includes cognitively normal older individuals aged 60 and older with a family history of sporadic AD.

- Cambridge Centre for Ageing and Neurodegeneration: a large-scale longitudinal research project including cognitively normal older adults aged 60 years and older.

- Alzheimer’s Disease Neuroimaging Initiative: a multinational longitudinal study which recruits cognitively normal and impaired older individuals. Only cognitively normal older adults were included in the present study.

- International Consortium for Brain Mapping: a multinational study. Cognitively normal individuals aged 18 to 65 from the Montreal’s site enrolled in the 1000 Functional Connectomes Project’s repository were included in the present study.

Resting-state functional MRI (rfMRI)

Resting-state scans were all preprocessed with N4iR (http://niak.ximera-lab.org/)

Averaged BOLD signals were extracted using the Power and Petersen parcellation (Power et al., 2015). Some ROIs were removed due to low coverage resulting in a 212x226 Pearson correlation matrix.

26 graph metrics were then extracted using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010); https://sites.google.com/site/bctnet/

Neural Network was trained to predict age

Neural network were constructed using Matlab (https://www.mathworks.com/products/deep-learning.html)

Amyloid (Aβ) Positron emission tomography (PET)

Aβ scans were acquired in DIAN (18F-PBR tracer; H-141) and PREVENT-AD (18F-NIA0404 tracer; H-141). Standardized uptake value ratios (SUVR; ref. region: cerebellum grey matter) were averaged across frontal, temporal, parietal and posterior cortical cortices to obtain a global index of Aβ burden.

Neural Network development

Features (i.e. graph metrics) ranked by importance

Model was built on the training set, optimized based on its generalisability in the validation set and, finally, model’s predictions were analyzed on the testing set.

Brain Age Predictive Model

Root mean square error in the different sets as function of the number of features and network architecture

Increase in the number of features and architecture complexity introduced overfitting (i.e. lowest root mean square error in the training set but highest error in the validation set). The model using 39 features and 2 layers of 5 and 2 nodes was the one showing the better generalisability (i.e. providing the lowest error in the validation set and was selected for the final model).

Reliability and significance of the feature deposition for the different architectures.

Brain Aging in the preclinical phase of AD

Are genetic mutation and Aβ burden associated with accelerated brain aging in preclinical AD?

Are genetic risk factor and Aβ burden associated with accelerated brain aging in individuals at risk of sporadic AD?

Summary and conclusions

Using rsfMRI graph metrics, we developed a model that can predict brain aging across the whole lifespan.

Applying this model to predict brain aging in the context of preclinical AD revealed that the presymptomatic phase of ADAD is characterized by accelerated functional brain aging. This phenomenon is independent from, and might therefore precede, Aβ accumulation. In individuals at risk of sporadic AD, neither APOE4 genotype or Aβ burden was associated with accelerated brain aging. Further studies will be needed to understand better the factors modulating accelerated functional brain aging in the context of preclinical AD.

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