Prediction of brain age using resting-state functional connectivity reveals accelerated aging in the preclinical phase of autosomal dominant Alzheimer’s disease, irrespectively of 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 function 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 of age provided by the DIAN, PREVENT-AD, Cam-CAN, ADNI, and ICBM cohorts to train and test a “Brain Age” predictive model.

Cohorts

Dominantly Inherited Alzheimer Network is a multisite longitudinal study which enrolls individuals aged 18 and older who have a biological parent who carries 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 is a non-syndromic longitudinal cohort which includes cognitively normal older individuals aged 55 and older with a family history of sporadic AD.

Cambridge Centre for Aging and Neuroscience is a large-scale mesoscale research project including cognitively normal individuals aged 25 to 85 years of age.

Alzheimer’s Disease Neuroimaging Initiative is a multisite longitudinal study which enrolls cognitively normal and impaired older individuals. Only cognitively normal older adults were included in the present study.

International Consortium for Brain Mapping is a multisite study. Cognitively normal individuals aged 19-69

Resting-state functional MRI (rsfMRI)

Resting-state scans were all preprocessed with NIAK (http://niai.simexp-lab.org/)

Brain Aging in the preclinical phase of AD

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

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

Brain Age Predictive Model

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

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

Summary and conclusions

Using rsfMRI graph metrics, we developed a model that can predict brain age 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 nor 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.