

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 phenomenon. We aimed at developing a model able to predict brain aging from restingsate 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 betaamyloid (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 noncarriers (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 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 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 is a monocentric longitudinal cohort which includes cognitively normal older individuals aged 55 and older with a family history of sporadic AD.



Cambridge Centre for Ageing and Neuroscience is a large-scale monocentric research project including cognitively normal individuals aged 18 to 88 years old.



ADN

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 to 85 form the Montreal's site archived in the 1000 Functional Connectomes Project's repository were included in the present study.

Resting-state functional MRI (rsfMRI)

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



Averaged BOLD signals were extracted using the Power and Peterson parcellation (Power et al., 2011). Some ROIs were removed due to low coverage resulting in a 238x238 Pearson correlation matrix.

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

M Brain Connectivity Toolbox



Amyloid (Aβ) Positron emission tomography (PET)

A β scans were acquired in DIAN (C¹¹-PIB tracer; N=145) and PREVENT-AD (F¹⁸-NAV4694 tracer; N=61).

Standardized uptake value ratios (SUVR; ref. region: cerebellum grey matter) were averaged across frontal, temporal, parietal and posterior cingulate cortices to obtain a global index of AB burden.

Funding









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Neural Network development

Data sets. Sample size [age-range]

Cohorts		Training set	Validation set	Testing set
	DIAN mut. noncarriers	105 [19-69 уо]	-	30 [18-61 yo]
antly Inherited	DIAN mutation carriers	-	-	128 [20-58 yo]
J-AD Group	PREVENT-AD	Зб [55-78 уо]	-	257 [55-84 yo]
Cantol Control	CamCAN	602 [18-87 yo]	-	100 [18-88 уо]
	ADNI	30 [65-90 уо]	_	15 [66-94 yo]
	ІСВМ	-	47 [19-79 yo]	-
	Total sample	773 [18-90 yo]	47 [19-79 yo]	530 [18-94 yo]



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

Model performance – Brain Age prediction against actual age across data sets



Brain Aging in the preclinical phase of AD

PREVENI-AD

DIAN Dominantly Inherited Alzheimer Network Predicted A 38.10 ± 14.43

Mutation Mutation noncarriers carriers Predicted age was overestimated in DIAN

mutation carriers while it was underestimated in noncarriers.

43.27 ± 16.96*+ Predicted Age Mutation noncarriers carriers carriers The overestimation in mutation carriers was not related to the presence of $A\beta$ deposition.

Different from mutation noncarriers at t^{p} <.10, *p<.05, **p<.001; Different from mutation carriers AB- at t^{p} <.05, $t^{+}p$ <.001, ns: not significant

in preclinical ADAD?







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Brain Age Predictive Model

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

- 1) Sub-graph centrality 2) Positive weighted clustering coefficien
- 3) Binarized assortativity 4) Weighted modularity coefficient
- 5) Small worldness
- 6) Flow coefficient
- 7) Betweenness centrality 8) Negative weighted participation coeffici
- 9) Positive weighted diversity coefficier
- 10) Negative weighted clustering coefficien
- 11) Eigen vector centrality 12) Binarized efficiency
- 13) Weighted assortativity
- 14) Negative weight gateway coefficient 15) Binarized clustering coefficient
- 17) Binarized modularity coefficient 18) Participation coefficient
- 19) Negative weighted diversity coefficient
- 20) Positive weighted participation coefficient
- (1) Characteristic path diamete 2) Characteristic path eccentricit

26) Characteristic path efficiency

- 3) Characteristic path radius
- 24) Positive weighted gateway coefficient
- 25) Characteristic path lambda



in the training set but highest error in the validation set).

Are genetic mutation and A β burden associated with accelerated brain aging

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





Predicted age was overestimated in the PREVENT-AD with no difference between APOE4 carriers (the main genetic risk factor of sporadic AD) and noncarriers.



Predicted age overestimation in the PREVENT-AD did not differ either between A β positive and negative individuals.

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Increase in the number of features and architecture complexity introduced overfitting (i.e. lowest root mean square error

The model using 10 features and 2 layers of 5 and 2 nodes was the one showing the better generalizability (i.e. providing the lowest error in the validation set) and was selected for the final model.

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, $A\beta$ accumulation.

In individuals at risk of sporadic AD, neither APOE4 genotype or $A\beta$ 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.