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 functional connectivity and the actual age. We repeated these analyses in asymptomatic individuals at risk of sporadic AD, assessing both the effect of *APOE*4 genotype and Aβ burden (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 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 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.

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.

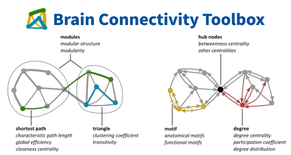
International Consortium for Brain Mapping is a multisite study. Cognitively normal individuals aged 19 to 85 form the Montreal's site archived in the 1000 Functional Connectomes Project's repository were included in the present study.

Resting-state functional MRI (rsfMRI)

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

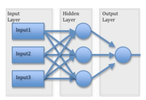
Averaged BOLD signals were extracted using the Power and Peterson parcellation (Power et al., 2011). Some ROIs were removed due to low coverage resulting in a 238x238 Pearson correlation matrix.

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



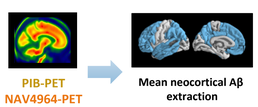
Neural Network was trained to predict age

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



Amyloid (Aβ) Positron emission tomography (PET)

Aβ scans were acquired using C^{11}-PIB in DIAN (N=145) and F^{18}-NAV4694 in PREVENT-AD (N=62).
Standardized uptake value ratios (SUVR; reference region: cerebellum grey matter) were averaged across frontal, temporal, parietal and posterior cingulate cortices to obtain a global index of Aβ burden.



Brain Age Predictive Model

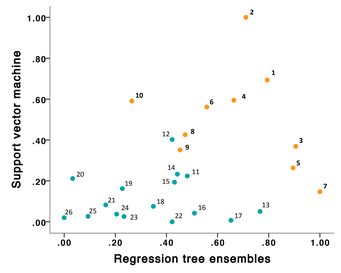
Neural Network development

Data sets. Sample size [age-range]

Cohorts		Training set	Validation set	Testing set
DIAN	DIAN mut. noncarriers	105 [19-69 yo]	-	30 [18-61 yo]
DIAN	DIAN mutation carriers	-	-	128 [20-58 yo]
PREVENT-AD	PREVENT-AD	36 [55-78 yo]	-	257 [55-84 yo]
CamCAN	CamCAN	602 [18-87 yo]	-	100 [18-88 yo]
ADNI	ADNI	30 [65-90 yo]	-	15 [66-94 yo]
ICBM	ICBM	-	47 [19-79 yo]	-
	Total sample	**773 [18-90 yo]**	**47 [19-79 yo]**	**530 [18-94 yo]**

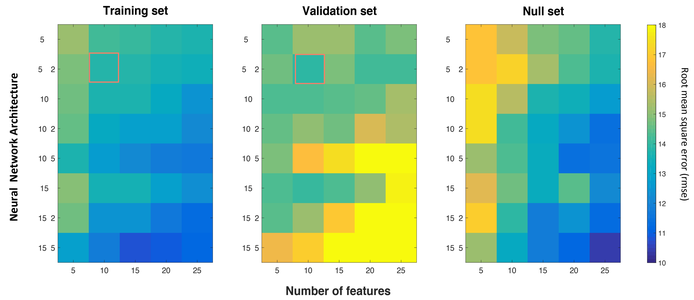
Model was built on the training set, optimized based on its generalizability in the validation set and, finally, the model's predictions were analyzed in the testing set.

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



1) Sub-graph centrality
2) Positive-weighted clustering coefficient
3) Binarized assortativity
4) Weighted modularity coefficient
5) Small worldness
6) Flow coefficient
7) Betweenness centrality
8) Negative-weighted participation coefficient
9) Positive-weighted diversity coefficient
10) Negative-weighted clustering coefficient
11) Eigen vector centrality
12) Binarized efficiency
13) Weighted assortativity
14) Negative-weighted gateway coefficient
15) Binarized clustering coefficient
16) Resilience
17) Binarized modularity coefficient
18) Participation coefficient
19) Negative-weighted diversity coefficient
20) Positive-weighted participation coefficient
21) Characteristic path diameter
22) Characteristic path eccentricity
23) Characteristic path radius
24) Positive-weighted gateway coefficient
25) Characteristic path lambda
26) Characteristic path efficiency

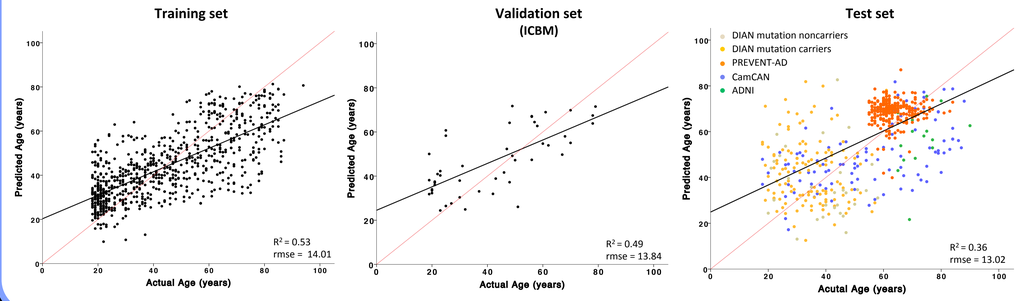
Root mean square error in the different sets as function of the number of features and network architecture



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 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.

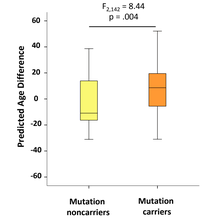
Model performance – Brain Age prediction against actual age across data sets



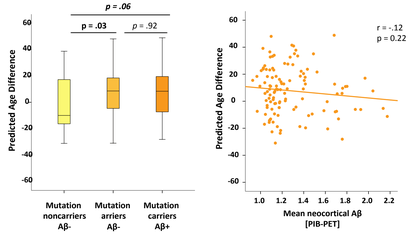
Brain Aging in the preclinical phase of AD

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

	DIAN mutation noncarriers	DIAN mutation carriers
Sample size	30	128
Actual Age	39.07 ± 11.39	34.27 ± 9.56*
Predicted Age	36.92 ± 15.61	42.36 ± 14.43[†]



	DIAN mutation noncarriers Aβ-	DIAN mutation carriers Aβ-	DIAN mutation carriers Aβ+
Sample size	28	77	40
Actual Age	38.86 ± 11.74	33.01 ± 8.96**	38.20 ± 9.39[††]
Predicted Age	37.89 –15.43	40.83 ± 12.89	45.68 ± 16.30*[†]



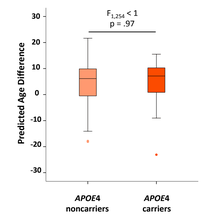
Predicted age was overestimated in DIAN mutation carriers while it was under-estimated in noncarriers.

The overestimation in mutation carriers was not associated with Aβ status or load.

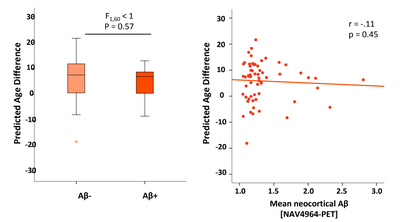
*Different from mutation noncarriers at [†]p<.10, *p<.05, **p<.01; Different from mutation carriers Aβ- at [††]p<.05, [†]p<.01, ns: not significant*

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

	PREVENT-AD *APOE*4 noncarriers	PREVENT-AD *APOE*4 carriers
Sample size	148	108
Actual Age	63.93 ± 5.75	63.05 ± 4.78
Predicted Age	68.96 ± 5.14	68.46 ± 5.01



	PREVENT-AD Aβ-	PREVENT-AD Aβ+
Sample size	51	11
Actual Age	62.82 ± 4.25	65.45 ± 6.22
Predicted Age	68.89 ± 6.07	70.09 ± 3.09



Predicted age was overestimated in the PREVENT-AD with no difference between *APOE*4 carriers (the main genetic risk factor of sporadic AD) and noncarriers.

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

Summary and conclusions

Using resting-state fMRI 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 *APOE*4 genotype or Aβ burden was associated with accelerated brain aging.

Further studies will be needed to better understand the factors modulating accelerated functional brain aging in the context of preclinical AD.

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