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 phenomenon. We aimed at developing a model able to predict brain aging from resting-sate 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 *APOE*4 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 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.

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.

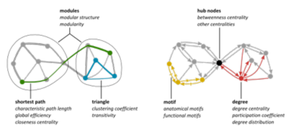
Resting-state functional MRI (rsfMRI)

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.

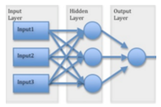
26 graph metrics were then extracted using the Brain Connectivity Toolbox (Rubinov & Sporn, 2010; https://sites.google.com/site/bctnet/)

Brain Connectivity Toolbox



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 (C^{11}-PIB tracer; N=145) and PREVENT-AD (F^{18}-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 Aβ burden.

Brain Age Predictive Model

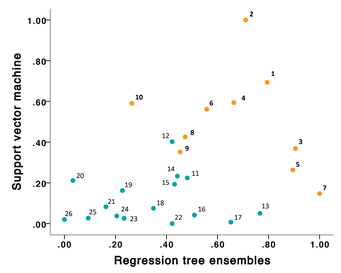
Neural Network development

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]**

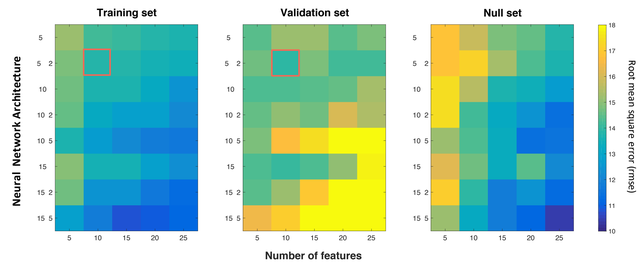
Model was built on the training set, optimized based on its generalizability in the validation set and, finally, model's predictions were analyzed in the testing set.

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



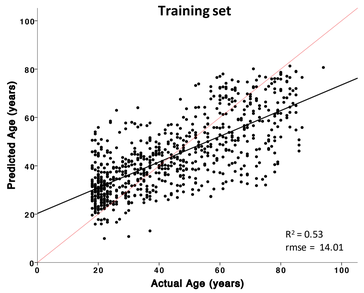
1) Sub-graph centrality
2) Positive weighted clustering coefficient
3) Binarized assortativity
4) Weighted modularity coefficient
5) Small worldness
6) Flow coefficient
7) Betweenness centrality
8) Negative weighted participation coefficient
9) Positive weighted diversity coefficient
10) Negative weighted clustering coefficient
11) Eigen vector centrality
12) Binarized efficiency
13) Weighted assortativity
14) Negative weight 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

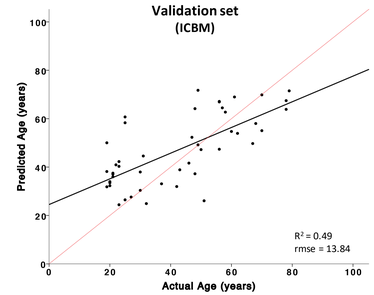
Root mean square error in the different sets as function of the number of features and network architecture



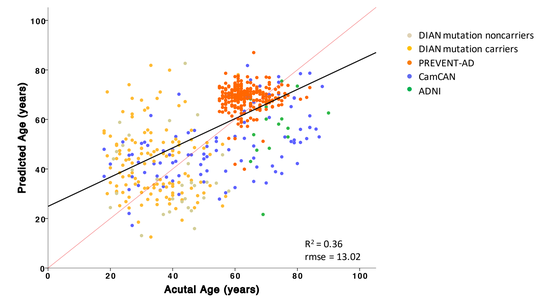
Increase in the number of features and architecture complexity introduced overfitting (i.e. lowest root mean square error in the training set but highest error in the validation set).
The model using 10 features and 2 layers of 5 and 2 nodes was the one showing the better generalizability (i.e. providing 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





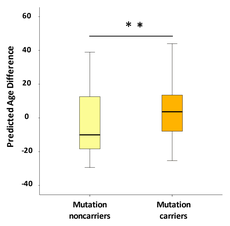
Brain Age prediction across groups - Test set



Brain Aging in the preclinical phase of AD

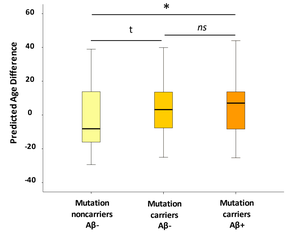
Are genetic mutation and Aβ burden associated with accelerated brain aging in preclinical ADAD?

	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[†]



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

	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	35.78 –15.81	35.99 ± 12.78	43.27 ± 16.96*†

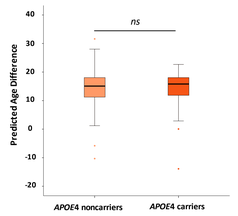


The overestimation in mutation carriers was not related to the presence of Aβ deposition.

*Different from mutation noncarriers at [t]p<.10, *p<.05, **p<.01; Different from mutation carriers Aβ- at [†]p<.05, [††]p<.001, ns: not significant*

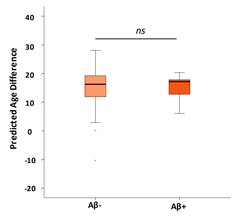
Are genetic risk factor and Aβ burden associated with accelerated brain aging in individuals at risk of sporadic AD?

	PREVENT-AD *APOE*4 noncarriers	PREVENT-AD *APOE*4 carriers
Sample size	147	109
Actual Age	64.02 ± 5.71	62.94 ± 4.81
Predicted Age	78.70 ± 5.85	77.56 ± 5.58



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.

	PREVENT-AD Aβ-	PREVENT-AD Aβ+
Sample size	50	11
Actual Age	62.88 ± 4.27	65.45 ± 6.22
Predicted Age	77.96 ± 6.32	80.51 ±4.36



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

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 *APOE*4 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.

Funding

Authors have no disclosure.
Acknowledgments: We would like to thank all the participants, the collaborators from the DIAN and PREVENT-AD studies and all members of the Villeneuve lab who contributed to this study.

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