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Accelerated functional brain aging in pre-clinical familial Alzheimer’s disease

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Resting state functional connectivity (rs-fMRI) is impaired early in persons who subsequently develop Alzheimer’s disease (AD) dementia. This impairment may be leveraged to aid investigation of the pre-clinical phase of AD. We developed a model that predicts brain age from resting state (rs)-fMRI data, and assessed whether genetic determinants of AD, as well as beta-amyloid (Aβ) pathology, can accelerate brain aging. Using data from 1340 cognitively unimpaired participants between 18–94 years of age from multiple sites, we showed that topological properties of graphs constructed from rs-fMRI can predict chronological age across the lifespan. Application of our predictive model to the context of pre-clinical AD revealed that the pre-symptomatic phase of autosomal dominant AD includes acceleration of functional brain aging. This association was stronger in individuals having significant Aβ pathology.
The brain shows major changes over the course of aging. It is not fully understood how neurodegenerative diseases affect brain regions and networks that are also affected by normal aging. However, increasing evidence suggests that neural systems vulnerable to age are also vulnerable to Alzheimer’s disease (AD) and other neurodegenerative diseases. Recent availability of large-scale neuroimaging datasets has facilitated the application of machine learning techniques and enabled development of models that can predict behavior and characteristics of brain structure and function known to change with age. We investigated whether predicted brain age may be a relevant biomarker of neurodegenerative disease, inasmuch as disease may cause deviations from normal aging trajectories, and the factors that influence these deviations may be studied. As an example, brain age predictive models using data from structural magnetic resonance imaging (MRI) have shown accelerated biological aging in individuals who develop AD dementia. Similar phenomena are already apparent in others who have mild cognitive impairment (MCI) that progresses to dementia. Such inter-individual differences between predicted biological and chronological age have been studied in relation to lifestyle variables and to genetic determinants. It is currently unknown, however, whether accelerated brain aging precedes evidence of cognitive decline, and whether it can be detected in the pre-clinical phase of AD.

The dementia of AD is characterized by progressive cognitive decline that becomes sufficient to impair activities of daily living. Prior work has shown that brain changes characteristic of an AD process can be demonstrated two or three decades before symptom onset. Typically, this sequence begins with the accumulation of cerebral beta-amyloid (Aβ), followed by the deposits of hyperphosphorylated tau (neurofibrillary tangles), metabolic brain alterations, and other evidence of neurodegeneration that precede cognitive and functional symptoms. Functional brain alterations revealed by MRI measures of resting state connectivity become detectable almost synchronously with Aβ and tau measured by positron emission tomography (PET) and are therefore evident several years before atrophy can be detected by structural MRI. Conjunction of such functional and biological changes appears to extend throughout the development of AD from its pre-clinical to its dementia stages. These findings suggest that MRI measures of resting state functional connectivity may be a more sensitive modality than structural imaging for detection of brain changes in pre-clinical AD.

AD dementia symptoms appear only after massive, evidently irreversible brain changes. Therefore, a more promising approach, at least in theory, is to prevent such changes. However, AD prevention requires improved understanding of the pre-clinical phase of AD. Identification of individuals in this clinically silent phase of the disease is challenging because it is mostly unknown who will develop dementia during the lifespan. One way to circumvent this problem is the study of autosomal dominant AD (ADAD), a group of rare genetically determined variants of AD caused by mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1) or presenilin 2 (PSEN2) genes, all involved in Aβ production. Because these mutations are fully penetrant, progression to disease is predictable, making ADAD an ideal model for the study of the pre-clinical (i.e., pre-symptomatic) phase of AD.

Although it is impossible to determine with certainty who will develop dementia due to sporadic AD (sAD), some factors are known to increase the risk of its development. Prominent among these is the ε4 allele at the polymorphic APOE locus that encodes apolipoprotein E, known to be involved in Aβ clearance. More broadly, a strong family history of sAD dementia has also been associated with a 2- to 4-fold increased incidence of dementia. Individuals whose brains show Aβ pathology are also known to experience brain changes and related cognitive decline over time. Thus, asymptomatic individuals can be classified as being in the pre-clinical phase of the disease if they have Aβ pathology. Likewise, their risk of dementia is increased if they carry an APOE ε4 allele or other known genetic risk factor and/or if they have a strong family history of the disease. Here, we tested whether individuals in the pre-clinical phase of ADAD, or at risk of pre-clinical sAD, show evidence of accelerated brain aging prior to the symptoms predicted by their genetic risk or Aβ status.

We studied 1624 cognitively unimpaired participants between 18 and 94 years of age, recruited and scanned in different studies and centers. Within these, we developed a method that predicts brain age from rs-fMRI. We relied on measures of network integration and segregation, known as graph metrics, to represent global brain functioning and developed a neural net. Briefly, we trained this model initially on a cohort of cognitively unimpaired individuals ranging in age from 18 to 90 years old. We then validated its generalizability in another group of cognitively unimpaired individuals (in age from 19 to 79 years old) from another study/site. After such validation, we tested whether individuals with pre-clinical ADAD showed accelerated functional brain aging in comparison with their age-matched relatives without a causal mutation. Importantly, none of these latter participants had been involved in the development or validation of the brain age model. In these same individuals, we also tested whether Aβ pathology was a further predictor of brain age. Finally, in a cohort of asymptomatic individuals having a parental or other strong family history of sAD, we tested whether APOE ε4 and/or Aβ pathology were associated with predicted functional brain age.

Our results showed, first, that pre-symptomatic carriers of ADAD mutations (DIAN cohort) had evidence of accelerated functional brain aging. Importantly, this finding was stronger in individuals who already accumulated significant Aβ pathology as evidenced by PET imaging. In the cohort at elevated risk of sAD (PREVENT-AD cohort), neither APOE ε4 status nor PET evidence of Aβ pathology was associated with apparent accelerated brain aging but individuals closer to their parental age of onset tended to show accelerated brain aging. Secondary analyses in a third independent cohort including a small subset of individuals diagnosed with either sAD dementia or MCI (ADNI cohort) confirmed the expected acceleration in functional brain aging in patients vs. cognitively normal older adults, suggesting that functional brain age is accelerated in cognitively impaired individuals with sAD and therefore validating the sensitivity of our model to sporadic AD-related processes. We conclude that asymptomatic persons with strong genetic determinants show a characteristic pattern of functional brain changes that are associated with accelerated biological brain aging. The biological development of AD is therefore characterized by a pattern of advanced brain aging that can be detected prior to symptom onset, at least in individuals having rare genetic mutations that cause AD and significant Aβ pathology.

Results

Separation of the multisite data into a training, validation, and test sets. We gathered rs-fMRI data from 1624 cognitively unimpaired participants between 18 and 94 years of age, provided by the Dominantly Inherited Alzheimer Network (DIAN), the Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer’s Disease cohort (PREVENT-AD), the Cambridge Centre for Ageing and Neuroscience (CamCAN), the
To select the optimal neural network architecture for our brain age model, we chose the optimal neural net after having built different neural networks with increasing complexity, such that features of more complex models were used as input into the subsequent neural network models, to build our predictive brain age model.

### Building the Brain Age model and improving its generalizability.

We chose the optimal neural net architecture after having built different neural networks with increasing complexity, varying in number of input features (5, 10, 15, 20, or 25 most important graph metrics, ranked as described previously), hidden layers, and hidden layer units. Importantly, each graph metric was only entered once as input for each neural network architecture tested, and the inputs were kept constant across the model’s iterations, such that features of more complex models always included the features of the simpler ones. We used an average of three determinations of rmse to assess the performance for each model. The different neural networks were applied separately in the training and validation set (Fig. 2b). To test the relevance of the metrics’ ranking, we assessed also the performance of neural nets on the training data when including the metrics randomly (null model, see Fig. 2b, right panel) and compared it to the models created based on ranked metrics (Fig. 2b, left panel). This null model suggested that the neural network performed better when features were ordered using SVM weights and ensemble feature importance, at least in simpler models.

To select the optimal neural network architecture for our brain age model, we generated the different models using the training set and evaluated which of these provided the best generalizability.
to the validation set (i.e., avoiding overfitting). Thus, the validation set helped us to determine the best balance between improved age prediction and good generalizability. In general, increasing model complexity (more features and hidden layers/units) led to better performance in the training set (Fig. 2b, left panel). However, as expected, too much complexity resulted in overfitting as evidenced by improved performance in the training set, resulting in poorer fit in the validation set (Fig. 2b, middle panel). The model that produced the lowest rmse in the validation set (averaged rmse over 3 iterations = 13.89) had 10 inputs (i.e., the 10 most important metrics, see Fig. 2a) and 2 hidden layers (5 units in the first layer and 2 in the second). The performance of this specific model was similar to that obtained in the training set (averaged rmse over 3 iterations = 13.75). This model was thus applied to the remaining unseen data (test set) to test whether genetics or AD pathology accelerated apparent functional brain aging. Subgraph centrality, clustering/modularity coefficients, and small-worldness were among the selected graph metrics (10 first metrics Fig. 2a). For reference, the covariance matrix of the 10 selected graph metrics is presented as Supplementary material (Supplementary Fig. 1).

Fig. 1 Methodology overview. a Multiple cohorts covering the lifespan were included in the study. They were separated into a training and validation set, both used to develop the predictive brain age model, and a test set in which our model was applied. b All participants underwent resting state functional magnetic resonance imaging that was processed with a uniform pipeline. Functional connectivity matrices were generated from the Power atlas\textsuperscript{82}, from which graph metrics were calculated. Graph metrics were the input in our brain age model, and thus all possible metrics were of interest. c The first step toward building the model was to rank the different graph metrics from the most to least related to aging in our training set, to determine an order of importance to our model inputs using both support vector machine and regression tree ensemble algorithms. Neural networks were then tested to identify the best brain age model. Different architectures were tested, and the model applied in the training set that best generalized to the validation set was chosen as the final model (see Fig. 2). d The model was applied to the left-out test set and our measure of interest was the predicted age difference (PAD). Mut−: mutation non-carriers, Mut+: mutation carriers, MRI: magnetic resonance imaging, PAD: predicted age difference.

Performance of the final brain age model. We show the association between chronological age and the model-predicted brain age.
**Fig. 2 Features ranking and neural networks performance.**

**a** Scatter plots of SVM model weights (y-axis) and ensemble tree feature importance (x-axis). Model weights are absolute value, and normalized such that 1 indicates highest importance. Numbers next to data points indicate their rank (i.e., 1 = highest average rank between both SVM and ensemble models; orange dots correspond to the top 10 features, blue dots represent lower-ranked features).

**b** Root mean square error of different neural network models with inputs sorted according to rank for the training set (left), and the validation set (middle). Values were averaged over 3 iterations of the models. Neural networks trained with randomly-ranked inputs served as our null models (right). The x-axis indicates the number of inputs into the model (number of graph metrics) while the y-axis indicates the network architecture. For example, 5 means 1 hidden layer with 5 units, 5 2 means 2 hidden layers, the first one with 5 units and the second with 2 units. Darker (blue) colors indicate higher accuracy, while lighter (yellow) colors indicate lower accuracy. The red square identifying the model that provides the better generalizability in the validation set (lowest rmse) contains 2 hidden layers of 5 and 2 units, and uses the 10 highest-ranked graph metrics as input. The same neural network trained on randomly-ranked inputs (null model, gray square) provides lower accuracy.

**c** Brain age model performance across datasets. Correlations between chronological age (x-axis) and age predicted by the neural network (y-axis) are represented for the training (n = 773), validation (n = 46) and test (n = 521) sets. Statistical values (c) were obtained from Pearson’s correlations (two-sided test, with no adjustment). Source data are provided as a Source data file. SVM: support vector machine, rmse: root mean square error, mae: mean absolute error.
Fig. 3 Predicted age difference in DIAN and PREVENT-AD. Density plot of chronological age vs predicted age in the test set participants in DIAN (n = 154) (a). Brain age is overestimated in autosomal dominant mutation carriers (n = 125) compared to non-carriers (n = 29) (b). The overestimation in mutation carriers is in part due to Aβ, with a difference between mutation noncarriers (n = 29) and Aβ+ mutation carriers (n = 39) only (Aβ− mutation carriers (n = 75) did not differ from the other groups) (c), and an association between Aβ load and predicted age difference across the whole cohort (n = 154) (d). Light (yellow) colors represent DIAN mutation non-carriers and darker (orange) colors represent DIAN mutation carriers. Density plot of chronological age vs predicted age in the test set participants in PREVENT-AD (n = 256) (e). In individuals at risk of sporadic Alzheimer’s disease, brain age is overestimated irrespectively of APOE ε4 genotype (f). Light (salmon) colors represent PREVENT-AD APOE ε4 non-carriers (n = 147) and darker (dark orange) colors represent PREVENT-AD APOE ε4 carriers (n = 108). For b, c and f the interquartile range (25th Percentile, Median and 75th Percentile), the whiskers (lines indicating variability outside the upper and lower quartiles minimum value) and the individual dots are presented. For d, shaded (gray) area represents confidence intervals (95%). Statistical values were obtained from general linear models (b, c, f) or partial Pearson’s correlations (d), controlling for chronological age, without further adjustment (two-sided tests). Aβ: beta-amyloid, Aβ−: amyloid-negative, Aβ+: amyloid-positive; APOE4: apolipoprotein E4, PIB: Pittsburgh compound B, SUVR: standardized uptake value ratio. Source data are provided as a Source data file.

age for each dataset in Fig. 2c. As expected, predicted age was correlated with chronological age in the training set (R² = 0.53, p < 0.0001; rmse = 14.01, mean absolute error [mae] = 11.00; Fig. 2c left) and the validation set (R² = 0.49, p < 0.0001; rmse = 13.84; mae = 11.90; Fig. 2c middle). Of note, the neural network model outperformed the simpler models used in our feature ranking step (rmse = 16.45 for SVM and 16.45 for tree ensemble, see above). Importantly, the model was able to predict chronological age from functional brain properties in the test set (R² = 0.36, p < 0.0001; rmse = 13.24; mae = 11.58; Fig. 2c right). Notably, the same was true when restricting the analyses to the CamCAN cohort, considered as a lifespan dataset representative of healthy aging (R² = 0.26; p < 0.001; rmse = 16.70; mae = 14.32).

Functional brain aging and pre-clinical Alzheimer’s disease. To assess the characteristics of functional brain aging in pre-clinical AD and evaluate whether genetic determinants/risk and Aβ pathology were related to accelerated brain aging, we calculated the predicted age difference or PAD (Fig. 1d). This was computed as predicted brain age minus chronological age for each participant in the test set. PAD deviation from zero should not be interpreted in isolation due to the potential existence of site/cohort effects, and we, therefore, interpret group comparisons only within cohorts.

Analyses considered DIAN (Fig. 3a–d) and PREVENT-AD (Fig. 3e, f) participants from the test set (Table 2). We tested whether genes predisposing to AD, either the ADAD mutation carriers or the broader familial risk of sAD, were associated with accelerated brain aging. To do so, we compared PAD between mutation carriers vs non-carriers from DIAN, and APOE ε4 carriers vs non-carriers from PREVENT-AD. Considering the tendency of the model to overestimate younger ages and underestimate older ages, all subsequent analyses were controlled for chronological age (see ref. 14 for a similar procedure). The model’s prediction in DIAN mutation carriers overestimated their chronological age (i.e., positive PAD = 8.19 years) in contrast to mutation non-carriers (i.e., negative PAD = −3.54 years; F1,152 = 4.88, p = 0.03; Table 3 and Fig. 3a, b). Overall, the predicted age in the PREVENT-AD cohort overestimated the chronological age by ~5 years (Fig. 3e), but APOE ε4 status was not associated with differences in this PAD (F1,253 < 1; p = 0.49, Table 3 and Fig. 3f).

Given the importance of Aβ deposition in the cascade of events leading to AD dementia, we investigated whether Aβ burden is related to functional brain aging. We assessed the effect of Aβ deposition, measured by PET, on the PAD in both the DIAN and PREVENT-AD cohorts. Aβ-PET was acquired using 11C-PIB in DIAN and 18F-NAV4694 in PREVENT-AD, and Aβ burden was determined for each cohort according to their own processing
Table 2 DIAN and PREVENT-AD test set characteristics.

<table>
<thead>
<tr>
<th></th>
<th>DIAN mutation non-carriers</th>
<th>DIAN mutation carriers</th>
<th>PREVENT-AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>29</td>
<td>125</td>
<td>256</td>
</tr>
<tr>
<td>Chronic Age (years; mean ± SD)</td>
<td>38.90 ±11.55</td>
<td>34.33 ±9.66</td>
<td>63.51 ±5.37</td>
</tr>
<tr>
<td>Sex Ratio F/M (%)</td>
<td>18/11 (62%/38%)</td>
<td>68/57 (54%/46%)</td>
<td>189/67 (74%/26%)</td>
</tr>
<tr>
<td>Education (years; mean ± SD)</td>
<td>14.41 (2.13)</td>
<td>14.89 (3.10)</td>
<td>15.65 (3.51)</td>
</tr>
<tr>
<td>EYO (years; mean ± SD)</td>
<td>-8.56 ± (10.85)</td>
<td>-14.18 ± (8.94)</td>
<td>-10.42 ± (7.21)</td>
</tr>
<tr>
<td>APOE4 carriers (%)</td>
<td>11 (38%)</td>
<td>36 (29%)</td>
<td>108 (42%)</td>
</tr>
<tr>
<td>Aβ-positive (%)</td>
<td>0 (0%)</td>
<td>39 (34%)</td>
<td>14 (22%)</td>
</tr>
<tr>
<td>MMSE or MoCA (mean ± SD)</td>
<td>29.36 ±1.03</td>
<td>29.02 ±1.27</td>
<td>28.11 ±1.52</td>
</tr>
</tbody>
</table>

* Aβ-amyloid, Aβ+- amyloid-positive, Aβ- amyloid-negative, APOE apolipoprotein E, EYO Estimated Years to Symptom Onset, MMSE Mini-Mental State Examination, MoCA Montreal Cognitive Assessment, SD standard deviation.
* EYO in DIAN was calculated based on the parental age at onset. EYO of PREVENT-AD was calculated only for individuals with a parental history of AD, data was available for 241 participants.
* APOE genotyping was missing for 1 PREVENT-AD participant.

To account for inter-individual differences in the way people age, combined with larger and more available datasets, machine learning methods can improve our understanding of brain function and our ability to predict health trajectories from brain properties. Previous models of brain aging have been informed primarily by characteristics of brain structure. Accelerated structural brain aging has been found in individuals with MCI and AD dementia. However, functional brain abnormalities are generally detectable prior to structural changes in the AD continuum, the latter being typically more proximate to the expression of clinical symptoms. Here we developed a model that could easily predict brain age across the entire adult human lifespan (ages 18–94). This model relied on topological properties of graphs constructed from rs-fMRI and demonstrates the feasibility of predicting brain age from rs-fMRI using global measures of network integration and segregation. Applying our predictive functional model to ADAD in the DIAN cohort, we observed that brain aging was apparently accelerated in individuals with pre-clinical ADAD. This association was especially clear in individuals who had PET evidence of Aβ deposition. Among individuals at elevated risk of sAD (PREVENT-AD cohort), neither APOE e4 nor Aβ was associated with accelerated brain aging. However, asymptomatic individuals who were closer to their expected age of symptom onset tended to show accelerated brain aging. The latter observation was corroborated by observations that symptomatic individuals with sAD showed accelerated brain aging when compared to asymptomatic individuals at risk (ADNI cohort, secondary analyses).

We developed the described model in participants from different cohorts and sites, and validated its generalizability in an independent monocentric dataset. While there is undoubtedly a cost to (internal) accuracy when optimizing model (external) generalizability, this external validation step is a major strength of this work. While modest in size, the validation set represented a completely independent dataset that covers the entire adult lifespan. Although we cannot exclude the possibility that a larger multicenter validation cohort might have led to selection of a slightly different network architecture, we note that our model’s mse was very similar between the validation and the test sets. Importantly, the test set was never used in the development/
validation of the brain aging model. Also, the model was not modified any further after the hypotheses were tested, i.e., hypotheses were only tested once using a model that appeared (from development and validation work) to be optimal. This approach ensured that our results regarding brain aging in pre-symptomatic AD were independent of the way the model was built.

To assess information integration in the brain, we relied on global brain function while applying graph metrics\textsuperscript{46}. This approach provides a holistic view of brain function that has been shown previously to change through aging and AD\textsuperscript{43}. Graph theory has the advantage that it quantifies and simplifies the many “moving parts” of dynamic systems inasmuch as every connection is defined by its relation to all others. We also used feature selection as an intermediate step to simplify the final model. We suggest that our approach using graph theory and feature selection are steps in the right direction toward interpretability of complex models. We are encouraged that the 10 graph metrics suggested as most important by these algorithms provided much lower error in our final neural network model in comparison to random choice of graph metrics. Of note, models using individual functional connections as inputs are also possible, but such models have been shown to require multiple dozens\textsuperscript{45} or hundreds\textsuperscript{40} of functional connections whose inter-relationships are not defined.

Compared with structural predictive models, previous modeling approaches using rs-\textsuperscript{1}H-MRI data have found higher error\textsuperscript{7,19,46,47}. These observations could partly be attributable to known characteristics of rs-\textsuperscript{1}H-MRI data. Such data are typically noisier and experience more dynamic changes than structural data, and they may be more sensitive to multi-site effects. Despite these difficulties, we attempted to derive our brain age model from rs-fMRI because this modality appears better suited to study the pre-clinical phase of AD. An extensive literature suggests that connectivity disruption appears early in the course of sAD as well as in “normal” aging\textsuperscript{48-53}. Moreover, training, validating, and testing our predictive model across multiple cohorts also increased the error of our model compared to the previous studies\textsuperscript{3,7,11,13,14}. Yet, inclusion of data from different sites should logically improve the generalizability of the model, a key strength when the model is applied to new data from different cohorts\textsuperscript{7,54}. Finally and importantly, brain age models tend to overestimate younger ages and underestimate older ages\textsuperscript{19,55}. While some researchers apply an age-bias correction procedure to their model\textsuperscript{19}, we are showing the non-adjusted model and used chronological age as a nuisance variable in our PAD analyses instead of applying this correction prior to the PAD calculation. In sum, while we recognize that the error of our model is higher than most previous brain age models, it was derived from rs-fMRI data, no age-bias correction was applied to test the model accuracy, and we suggest that it is more generalizable than previous models. Crucially, it also appears to be sensitive to the questions of interest here.

Applying our model in the context of AD, we found evidence of accelerated functional brain aging in individuals in the pre-clinical phase of dominantly inherited AD. ADAD is widely believed to be a disease caused by overproduction of \( \beta \)-amyloid, and studies of ADAD have shown that biomarkers such as CSF-A\( \beta \) start changing in mutation carriers as early as 25 years before symptom onset\textsuperscript{22}. This is followed by the accumulation of fibrillar A\( \beta \) deposition as measured by PET imaging, alongside changes in concentrations of \textit{tau} in the CSF and cerebral atrophy. Later changes include glucose hypometabolism and episodic memory decline and global cognitive decline\textsuperscript{22}. Studies employing rs-\textsuperscript{1}H-MRI in this disease are relatively rare, however, and have considered the entire ADAD spectrum\textsuperscript{48,56-58}. One of these studies

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### Table 3 Model’s prediction according to the presence of genetic mutation/risk and \( \beta \)-amyloid pathology in DIAN and PREVENT-AD cohorts (test set only).

<table>
<thead>
<tr>
<th>Cohort</th>
<th>( \beta )-Amyloid Negative</th>
<th>( \beta )-Amyloid Positive</th>
<th>( \beta )-Amyloid Negative</th>
<th>( \beta )-Amyloid Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAN</td>
<td>( \beta )-Amyloid Negative</td>
<td>( \beta )-Amyloid Positive</td>
<td>( \beta )-Amyloid Negative</td>
<td>( \beta )-Amyloid Positive</td>
</tr>
<tr>
<td>Mutation Non-Carriers</td>
<td>29</td>
<td>125</td>
<td>38</td>
<td>90</td>
</tr>
<tr>
<td>Predicted Age Difference (( \beta )-Amyloid Negative)</td>
<td>3.54</td>
<td>-3.54</td>
<td>8.40</td>
<td>b</td>
</tr>
<tr>
<td>Predicted Age Difference (( \beta )-Amyloid Positive)</td>
<td>6.62</td>
<td>b</td>
<td>5.90</td>
<td></td>
</tr>
<tr>
<td>Predicted Age Difference (( \beta )-Amyloid Negative) &amp; (( \beta )-Amyloid Positive)</td>
<td>3.54</td>
<td>(b)</td>
<td>8.40</td>
<td>(b)</td>
</tr>
<tr>
<td>Predicted Age Difference (( \beta )-Amyloid Negative) &amp; (( \beta )-Amyloid Positive)</td>
<td>6.62</td>
<td>(b)</td>
<td>5.90</td>
<td>(b)</td>
</tr>
</tbody>
</table>

\( \beta \)-amyloid-negative, \( \beta \)-amyloid-positive, predicted age difference, standard deviation.

\( a \) A\( \beta \)-PET data was missing for 2 mutation non-carriers. To avoid further reducing the number of individuals in this group, they were both exceptionally kept for the corresponding analysis and their A\( \beta \)-negativity was determined based on (i) their CSF data (available for both of them) and (ii) the unlikelihood that they have detectable A\( \beta \) pathology on PET considering their young age and the absence of ADAD mutation.

\( b \) indicates a significant difference from DIAN mutation noncarriers (< .05); of note, no differences were found between DIAN mutation carriers A\( \beta \)-\( \beta \), neither in PREVENT-AD when comparing APOE4 carriers or non-carriers to A\( \beta \)-A\( \beta \), nor in DIAN ADAD carriers A\( \beta \)-A\( \beta \) to A\( \beta \)-non-carriers.
compared asymptomatic mutation carriers and non-carriers and suggested reduction in Default Mode Network functional connectivity among asymptomatic carriers. This finding is concordant with literature on sAD suggesting that change in rs-fMRI is one of the earliest biomarkers of the disease53,54. Our rs-fMRI predictive model implied that functional brain age of ADAD presymptomatic mutation carriers (DIAN) exceeded their chronological age by about 10 years (based on the findings in non-carriers). This observation alone suggests that the presymptomatic phase of ADAD is accompanied by accelerated brain aging. The relative importance of Aβ burden on accelerated brain aging was less clear. While no association was found between Aβ burden when restricted to DIAN mutation carriers, the difference between mutation carriers and non-carriers was stronger (i.e., significant only) in those with fibrillar Aβ as detected with PET imaging. The observations of accelerated brain aging in carriers may therefore not be entirely attributable to the accumulation of Aβ. While Aβ is often hypothesised to be the starting point of the AD neuropathological cascade, tau is believed to be more toxic60,61, and might therefore be more closely associated with accelerated aging. Mutated genes in ADAD could also have life-long effects on the brain that are not fully dependent on Aβ accumulation. Consistent with this view, a previous study in PSEN1 mutation carriers from the Columbian cohort showed early changes in brain function before evidence of cerebral Aβ plaque accumulation62. Finally, we cannot exclude the possibility that some Aβ-negative individuals would in fact be Aβ accumulators63,64, or present other forms of Aβ that cannot be detected through PET. What seems to be clear is that AD genetic mutations influence functional brain properties in pre-clinical ADAD. The exact mechanisms that drive this accelerated brain aging will need further investigation.

When investigating the characteristics of PAD in individuals with a family history of sAD (PREVENT-AD), we did not find differences between APOE ε4 carriers and non-carriers, nor associations with Aβ burden (for similar results with structural and metabolic brain age, see refs. 11,65). These findings do not necessarily contradict an extensive literature suggesting association between APOE ε4 status, Aβ, and rs-fMRI44,66–69. They seem instead to suggest that we are capturing different constructs. While the previous studies tested the direct effect of these two factors on rs-fMRI metrics, we tested the associations between these AD risk factors and a proxy of biological aging derived from rs-fMRI. While we found no association between Aβ and PAD, we did observe, however, an association between EYO and PAD such that PREVENT-AD participants who were closer to their parents’ age of onset tended to have older predicted brain age when compared with others. In the same cohort, EYO had previously been associated with functional changes mimicking brain changes characteristic of AD dementia70.

While our focus was the pre-clinical phase of the disease, we performed post-hoc analyses using rs-fMRI data from a small subset of ADNI patients. We found accelerated functional aging in persons with symptomatic sAD (MCI or dementia) when compared with others who were asymptomatic, but at increased risk of sAD (APOE ε4 participants from our test set). These additional analyses suggest accelerated functional brain aging in individuals with clinical sAD and further confirm the validity of our brain age model. Several limitations should be mentioned. These relate both to the model and to the cohorts used to test our hypotheses. First, our choice not to update or tweak the model after it was used to test our hypotheses (a main strength of our approach) left us with a few small errors when constructing the model (e.g., two PREVENT-ADAPOE ε4 carriers were included in the training set). While these oversights were unlikely to have affected the final results (APOE ε4 carriers from other cohorts without genotype data were presumably included in the training set), they nevertheless pose a small threat to the integrity of the model. Second, we also cannot exclude the possible influence of collinearity when determining the age predictive graph metrics. The SVM and the tree ensemble were however mostly in agreement, and it’s unlikely that multicollinearity would have had equal influence on these two very different algorithms. Also, while we made great efforts to increase the generalizability of our predictive model, most of the participants included in this study were Caucasian (see Supplementary Methods), stressing the need to increase diversity in both lifespan and AD cohorts. Functional brain age was also found to exceed chronological age in the PREVENT-AD cohort, while this was not the case in other sites/cohorts of similar ages. While it is tempting to interpret these results as resulting from the participants’ family history, we think it reflects largely a site effect. To minimize such possible site effects, we drew on data from a variety of cohorts and sites, validated the model on a completely independent validation set (new sites) and applied similar preprocessing methods to all data. No further harmonization procedure was applied. The site effects are inherently related to the different age composition of the sites (or cohorts, see Fig. 1), and thus harmonizing by sites would have removed the age difference between participants (see Supplementary Fig. 2 for an example of sites correction using ComBat; https://github.com/Jfortin1/ComBatHarmonization). While the possibility of site effects limits our ability for direct comparisons across cohorts, it cannot reasonably threaten the integrity of our main findings, which resulted from within-cohort comparisons. One obvious limitation of inference from the PREVENT-AD data compared to those from DIAN, is that we cannot know which participants will later develop AD dementia. The lack of evidence for accelerated brain aging in PREVENT-ADAPOE ε4 carriers (vs non-carriers) might reflect nothing more than the known fact that not all APOE ε4 carriers will develop AD dementia (i.e., are in the pre-clinical phase of the disease) while some non-carriers will develop the disease. The subsample of PREVENT-AD participants having Aβ pathology in the test set was also relatively small, which could likely limit inference.

In sum, using rs-fMRI graph metrics, we developed a model that can predict brain age across the whole human lifespan. Applying this model to predict brain aging in the context of preclinical AD revealed that the pre-symptomatic phase of ADAD is characterized by accelerated functional brain aging. Whether a similar relationship holds for pre-clinical sAD and by which underlying mechanisms AD accelerates brain aging will require further evaluation.

Methods

Cohorts and participants

Dominantly Inherited Alzheimer Network—DIAN. DIAN is a multisite longitudinal study71, which enrols individuals age 18 and older who have a biological parent that carries a genetic mutation responsible for ADAD. They all underwent clinical and cognitive assessments, genetic testing, and imaging (magnetic resonance imaging [MRI] and amyloid positron emission tomography [PET]). Data has been obtained after request and IRB approval (information can be found at dian.wustl.edu/our-researchobservational-study/). Baseline data from cognitively unimpaired mutation carriers and non-carriers archived in the DIAN data freeze 10 (January 2009 to May 2016) were used in the present study. All selected individuals had a Clinical Dementia Rating (CDR)72 scale of 0. Baseline data from 280 cognitively unimpaired individuals (mutation carriers and non-carriers) aged between 18 and 69 years old, for whom structural MRI and rs-fMRI data were available, have been included.

Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer’s Disease—PREVENT-AD. The PREVENT-AD (Douglas Mental Health Institute, Montreal) is a monocentric longitudinal cohort73. Briefly, 399 cognitively unimpaired older individuals with a family history of sAD (at least one parent or multiple siblings) were enrolled between September 2011 and November 2017.
Inclusion criteria included (i) being 60 or older; 55–59 for individuals who were less than 15 years from the age of their relative at symptom onset, (ii) being cognitively normal; and (iii) no history of major neurological or psychiatric disease. Normal cognition was defined as a CDR of 0 and a Montreal Cognitive Assessment (MoCA) \( \geq 24 \). In the few cases of ambiguous results (3 participants having a CDR of 0.5 and 1 participant with a MoCA of 23 in the present sample), participants were further evaluated with a more extensive neuropsychological test battery, which was carefully reviewed by neuropsychologists and physicians to ensure normal cognition. Participants underwent clinical and cognitive examinations, blood tests, and MRI annually. Data from the present study were archived in the Data Release 5.0 and are partially available at https://openpreventingdementia.io/can/. PET scans were acquired in a subset of participants between February 2017 and July 2019. Three hundred and fifty-three participants, aged 55–84, for whom baseline structural MRI and rs-fMRI data were available were included in the present study.

**Cambridge Centre for Ageing and Neurosciences—CamCAN.** The Cambridge Centre for Ageing and Neurosciences (Cam-CAN; http://www.cam-can.org/) is a large-scale collaborative research project, launched in October 2010, using epidemiological, behavioral, and neuroimaging data to characterize age-related changes in cognition and brain structure and function, and to uncover the neurocognitive mechanisms that support healthy cognitive ageing. In the present study, 648 individuals aged between 18 and 88, with structural MRI and rs-fMRI data were included.

**Alzheimer’s Disease Neuroimaging Initiative—ADNI.** ADNI data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) \(^76\). ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, clinical, and neuropsychological assessments can be combined to measure the progression of MCI and early AD. Considering the focus on preclinical AD, forty-nine cognitively unimpaired individuals with structural MRI and rs-fMRI data were included in the present study. An additional 106 (100 after quality control) individuals with MCI or dementia and structural MRI and rs-fMRI data were included in post hoc analyses to validate the model in cognitively impaired AD individuals.

**1000-Functional Connectomes Project (Cambridge site)—FCP-Cambridge.** The 1000-Functional connectomes project (FCP) is a large initiative that gathers functional data from cognitively unimpaired adults recruited worldwide (33 sites) and makes it publicly available to facilitate discovery science of brain function (http://fcon_1000.projects.nitrc.org/fc/CpcTable.html) \(^77\). We used the large dataset from Cambridge-Buckner that includes 198 subjects between 18 and 30 years old, all collected at the Cambridge site ([FCP-Cambridge], PI: Buckner, R.L.).

**International Consortium for Brain Mapping—ICBM.** The ICBM dataset is publicly available as part of the 1000-FCP repository (see above) \(^78\). The ICBM was used as an independent sample of healthy controls, led by Principal Investigator Michael W. Weiner, MD.

**Validation, and test sets. In order to reach the most accurate model of   **

**MRI acquisition and processing.** DIAN: DIAN imaging data was acquired at multiple sites on 3T scanners by applying ADNI parameters and procedures \(^22\), \(^27\). T1-weighted MRI (used for rs-fMRI processing) were acquired with the following parameters: repetition time (TR) = 2400 ms, echo time (TE) = 16 ms, flip angle = 8°, acquisition matrix = 256 × 256, voxel size = 1 × 1 × 1 mm. Eyes-open rs-fMRI images were acquired using the following parameters: TR = 2230 ms or 3000 ms; TE = 30 ms, flip angle = 80°, voxel-size = 3.3 × 3.3 × 3.3 mm, field of view (FOV) = 212, 140 volumes; acquisition lasting ~5 min or 7 min. PREVENT-AD: DIAN data were acquired on a 3T Magnetom Tim Trio (Siemens) scanner. T1-weighted images were obtained using a GRE sequence with the following parameters: TR = 2.94 ms; TE = 0.52 ms; flip angle = 8°; acquisition matrix = 256 × 256; voxel size = 1×1×1 mm; 176 slices. For resting state fMRI scans, two successive functional T2*-weighted scans were collected eyes-closed with a blood oxygenation level-dependent (BOLD) sensitive, single-shot echo planar sequence with the following parameters: TR = 2000 ms; TE = 30 ms; flip angle = 90°; matrix size = 64 × 64; voxel size = 3 × 3 × 3 mm; field of view = 150 volumes, acquisition time = 5min45s. For consistency with the other cohorts that only had one run, only the first run was considered for each participant.

**CamCAN:** Images were acquired on a 3T Magnetom Tim Trio (Siemens). T1-weighted MRI were acquired using the following parameters: 3D MPRA GE, FA = 2. TR = 2250 ms; TE = 131 ms; flip angle = 90°; acquisition matrix = 100 × 100 × 1 mm isotropic; FOV = 256 × 240 × 192 mm; acquisition time = 4 min 32 s. Rs-fMRI data were acquired eyes closed using a T2* GE EPI sequence with the following parameters: TR = 1970 ms; TE = 30 ms, flip angle = 78°; voxel-size = 3 × 3 × 4.4 mm; FOV = 192 × 192 × 261 volumes of 32 axial slices 3.7 mm thick with a 0.74 mm gap, acquisition time = 8 min 40 s.
ADNI: Data were acquired at multiple sites, following the ADNI protocol. Structural images were acquired using a 3D MP-RAGE T1-weighted sequence with the following parameters: TR = 2300 ms; TE = 9.4 ms; flip angle = 9°; voxel size = 1.1 × 1.1 × 1.2 mm; FOV = 256 × 240 mm; 170 slices. The rs-fMRI images were obtained, open eyes, using a T2 weighted echo-planar imaging sequence with the following parameters: TR = 3000 ms; TE = 30 ms; flip angle = 80°; 88 slices of 3.3 mm; 140 volumes; acquisition lasting ~5 min. FCP-Cambridge: Images were acquired using a Siemens 3T Trio scanner. High-resolution T1-weighted images were acquired as follows: MP-RAGE TR = 2200 ms, TE = 1.04–7.01 ms, flip angle = 7°; voxel size = 1.2 × 1.2 × 1.2 mm, FOV = 230 mm, 144 sagittal slices. Rs-fMRI were acquired, open eyes, with the following parameters: TR = 3000 ms; TE = 30 ms; flip angle = 80°; voxel size = 3 × 3 × 3 mm, FOV = 216 mm, 47 axial slices, 124 volumes, lasting ~6 min. ICBM data was acquired on a Siemens Sonata 1.5 T MR scanner at the MRI. The rs-fMRI was scanned as follows: TR = 2200 ms, TE = 92 ms, flip angle = 30°, 256 × 256 matrix with a 1 × 1 mm resolution, 176 contiguous sagittal slices covering the whole-brain, slice thickness = 1 mm. Three rs-fMRI runs were acquired eyes-closed with the following parameters: 2D echo-planar BOLD Mosaic sequence, TR = 2000 ms, TE = 50 ms, flip angle = 90°, 64 × 64 matrix with a 4 × 4 mm resolution, 23 contiguous axial slices covering the cortex but not the cerebellum, slice thickness = 4 mm, 138 volumes; each run lasting ~5 min 30 s.

Rs-fMRI processing. In order to limit site effects, all functional images were processed in our laboratory by APB applying the exact same pipeline and processing steps. The Neuroimaging Analysis Kit version 0.12.4 (NIAK, http://niak.simexp-lab.org/) was used for rs-fMRI preprocessing, following the procedure applied in the previous publications. Briefly, images underwent slice timing correction, and rigid-body motion parameters were estimated. T1-weighted images were linearly and non-linearly normalized to the MNI space. After coregistration to structural scans, functional images were normalized to the MNI space by applying parameters from the T1-weighted images and resampled to 2 mm isotropic. Slow time drifts, average white matter and cerebrospinal parameters from the T1-weighted images and resampled to 2 mm isotropic. The NeuroImaging Analysis Kit version 0.12.4 (NIAK; http://niak.simexp-lab.org/) was used for rs-fMRI preprocessing, following the procedure applied in the previous publications. Brie

Brain age model. The general procedure for iterating through different models included a 5-fold cross-validation within the training data, and a second validation with an independent, external-site dataset. Models with the lowest error in predicting age on this validation set then served as candidates for the final model. Once the final model was determined, our hypotheses were then tested on the test set. Of importance, the test set was composed of unseen data that were not used to create, optimize, or validate the model. Neither the model nor the hypotheses were modified after the model was considered final and ready for hypothesis testing.

In a second step, we aimed at creating an accurate model requiring the fewest number of features possible. We used training data to generate a neural net model and assessed its accuracy using the validation set. More specifically, the neural network was optimized by (i) generating different models using the training set, each model varying in number of features used as input and network complexity, and (ii) applying each model to the validation set (independent dataset/site) to evaluate which one provided the better generalizability (i.e., avoid overfitting and achieving higher accuracy). Because neural network units are initialized randomly, the training and validation sets were standardized by subtracting the training group mean and dividing by the training group standard deviation. Network models had 5–25 input features in increments of 5, entered according to their importance, as determined previously (see above). A null model was also tested by applying the same feature importance procedure but excluding any graph metrics in the training and validation sets. Models with the most brain nodes. The average rank from both models was then used to determine the overall importance of each feature.

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The presence or absence of ADAD mutation was assessed using PCR-based amplification of the appropriate exon followed by Sanger sequencing. APOE genotype was determined using an ABI predesigned real-time PCR Taqman assay (C_3084793_20 and C_990473_10 for rs429358 and number of units in the hidden layers (1, 2 or 3) Age was modeled on the training data using the fitnet function with Bayesian regularization backpropagation. Model accuracy was ultimately determined by the root mean squared error (rmse) between actual and predicted age on the validation data, with lower rmse reflecting higher accuracy. Because neural network units are initialized with random values, the rmse changed slightly each time model error was measured. Thus, the best model was determined by the lowest rmse, averaged over three iterations. Once the most accurate model was determined, it was applied on unseen data (test set).

Additional measures in DIAN and PREVENT-AD samples (test set) Genetics. DIAN genotyping was performed by the DIAN Genetics Core at Washington University. The presence or absence of ADAD mutation was determined using PCR-based amplification of the appropriate exon followed by Sanger sequencing. APOE genotype was determined using an ABI predesigned real-time PCR Taqman assay (C_3084793_20 and C_990473_10 for rs429358 and number of units in the hidden layers (1, 2 or 3) Age was modeled on the training data using the fitnet function with Bayesian regularization backpropagation. Model accuracy was ultimately determined by the root mean squared error (rmse) between actual and predicted age on the validation data, with lower rmse reflecting higher accuracy. Because neural network units are initialized with random values, the rmse changed slightly each time model error was measured. Thus, the best model was determined by the lowest rmse, averaged over three iterations. Once the most accurate model was determined, it was applied on unseen data (test set).
rs7412_amplification_reverse_biotinylated_5′-CCCGGGCCCTGGTACAGTG-3′ and rs7412 sequencing 5′-CGATGACCCGAGAGAAG-3′.

The full list of primers is provided in Supplementary Tables 3 and 4.

PET acquisition and processing. In DIAN, 28 mutation non-carriers and 117 mutation carriers from the test set had an Aβ-PET scans available at baseline. Aβ-PET scans were acquired in different centers, following ADNI protocol. Briefly, participants were injected intravenously with 8 mCi to 18 mCi of 11C-PIB. Part of the participants underwent a dynamic acquisition of 70 min, starting at the time of injection. The remaining part of the sample underwent a 30-min scan after a rest period of 40 min. A standard brain transmission scan (or computed tomography [CT] transmission scan for PET/CT scanners) was obtained for attenuation correction. Aβ-PET data was motion corrected and registered to their MRI. Standardized uptake value ratio (SUVR) were calculated using the cerebellum gray matter as a reference and a global measure of Aβ burden was calculated by averaging SUVs from the prefrontal cortex, temporal lobe, gyrus rectus, and precuneus of the Desikan-Killian atlas. A threshold of 1.31 was used to determine Aβ positivity.

In the PREVENT-AD cohort, Aβ-PET scans were performed at the MNI (Montreal, Canada) on a Siemens HRRT. Sixty-four individuals from the test set underwent this examination, at a mean of 10.30 ± 5.63 months from their closest MRI session and 43.10 ± 17.95 months after their baseline session. A 30-min Aβ-PET scan started 40 min after intravenous injection of ~5.4 mCi of 11C-NAV4494. Transmission scans were acquired for attenuation correction. Data were processed using a standard pipeline (see ref. 38 and https://github.com/villeneuval/lppf for details). A global index of neocortical Aβ burden was derived by extracting, in native space, the mean standardized uptake value ratio (SUVR) of the frontal, temporal, parietal, and posterior cingulate cortex of the Desikan-Killian atlas, using the cerebellum gray matter as reference region. A threshold for positivity was determined using Gaussian Mixture modeling and scans with global neocortical Aβ burden ≥1.39 were considered positive.

Estimated years to onset. Estimated years from expected symptom onset (EYO) was calculated in each cohort taking the parental age at onset as a reference (see Supplementary Methods for details).

Statistical analyses on the predicted age difference (test set). To analyze the specificities of brain aging in the context of pre-clinical AD, we calculated the predicted age difference for DIAN and PREVENT-AD participants in the test set, as previously detailed, by subtracting the actual chronological age from the predicted brain age (output from the model). We were particularly interested in the influence of the genes involved in AD, which are either responsible for ADAP or increase the risk of sAD. We compared, in the test set, the predicted age difference (i.e., PAD) between 1) mutation non-carriers and mutation carriers from DIAN, and 2) APOE4 carriers vs non-carriers in the PREVENT-AD. We were also interested to further understand the influence of Aβ accumulation on functional brain aging in asymptomatic individuals. To do so, we assessed the effect of Aβ deposition, measured by PET, on the PAD in both the DIAN and PREVENT-AD cohorts, both by comparing Aβ-positive and Aβ-negative individuals (dichotomous variable) and by assessing the correlation between PAD and Aβ load (continuous variable). All analyses were controlled for chronological age.

Exploratory analyses were conducted to assess the correlation between the PAD and estimated years to onset (EYO). Finally, we validated that our model was replicated using nonparametric test (Mann-Whitney) across the human lifespan using diffusion tensor imaging: a machine learning approach. NeuroImage 75, 58–67 (2018).


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Author contributions

Julie Gonenneau: study concept and design, data acquisition and processing, statistical analysis, interpretation of the results, writing the manuscript. Alex T. Baria: study concept and design, data acquisition and processing, neuro net development, interpretation of the results, revising the manuscript for intellectual content. Alexandre Pichet Binette: data acquisition, data processing, revising the manuscript for intellectual content. Brian A. Gordon: study concept and design, revising the manuscript for intellectual content.

Jasmeet P. Chhatwal: study concept and design, revising the manuscript for intellectual content. Carlos Cruchaga: study concept and design, revising the manuscript for intellectual content. Mathias Jucker: study concept and design, revising the manuscript for intellectual content. Johannes Levin: study concept and design, revising the manuscript for intellectual content. Stephen Salloway: study concept and design, revising the manuscript for intellectual content. Martin Farlow: study concept and design, revising the manuscript for intellectual content. Serge Gauthier: study concept and design, revising the manuscript for intellectual content. Tammie L. Benzinger: study concept and design, revising the manuscript for intellectual content. John C. Morris: study concept and design, revising the manuscript for intellectual content. Randall J. Bateman: study concept and design, revising the manuscript for intellectual content. John C. Morris: study concept and design, revising the manuscript for intellectual content. Jude Poitier: study concept and design, revising the manuscript for intellectual content. Elisabeth A. Laurin-Pouliot: study concept and design, revising the manuscript for intellectual content. Anna Maria Elvira: study concept and design, revising the manuscript for intellectual content.

Competing interests

The authors declare no competing interests.

Additional information

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Alzheimer’s Disease Neuroimaging Initiative (ADNI)

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Dominantly Inherited Alzheimer Network (DIAN) Study Group

Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer’s Disease (PREVENT-AD) Research Group

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