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## Brain age prediction in schizophrenia: does the choice of machine learning algorithm matter?

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### Abstract

Brain-predicted age difference (brainPAD) has been used in schizophrenia to assess individual-level deviation in the biological age of the patients' brain (i.e., brain-age) from normative reference brain structural datasets. There is marked inter-study variation in brainPAD in schizophrenia which is commonly attributed to sample heterogeneity. However, the potential contribution of the different machine learning algorithms used for brain-age estimation has not been systematically evaluated. Here, we aimed to assess variation in brain-age estimated by six commonly used algorithms [ordinary least squares regression, ridge regression, least absolute shrinkage and selection operator regression, elastic-net regression, linear support vector regression, and relevance vector regression] when applied to the same brain structural features from the same sample. To assess reproducibility we used data from two publically available samples of healthy individuals (n=1092 and n=492) and two further samples, from the Icahn School of Medicine at Mount Sinai (ISMMS) and the Center of Biomedical Research Excellence (COBRE), comprising both patients with schizophrenia (n=90 and n=76) and healthy individuals (n=200 and n=87). Performance similarity across algorithms was compared within each sample using correlation analyses and hierarchical clustering. Across all samples ordinary least squares regression, the only algorithm without a penalty term, performed markedly worse. All other algorithms showed comparable performance but they still yielded variable brain-age estimates despite being applied to the same data. Although brainPAD was consistently higher in patients with schizophrenia, it varied by algorithm from 3.8 to 5.2 years in the ISMMS sample and from 4.5 to 11.7 years in the COBRE sample. Algorithm choice introduces variations in brain-age and may confound inter-study comparisons when assessing brainPAD in schizophrenia.

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## Keywords

brain age prediction; schizophrenia; structural MRI; machine learning; regression

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## 1. Introduction

Schizophrenia is a severe mental illness that presents with positive and negative symptoms [APA, 2013] and brain structural alterations [Haijma et al. 2013; Radua et al. 2012; Steen et al. 2006; van Erp et al. 2016, 2018; Vita et al. 2006]. Lower intracranial volume is a consistent finding that reflects early developmental vulnerability [Bois et al. 2015; Fusar-Poli et al. 2014]. Moreover, cortical thickness and subcortical volumes [Haijma et al. 2013; Radua et al. 2012; Steen et al. 2006; van Erp et al. 2016, 2018; Vita et al. 2006] generally show a steeper age-related decline in patients than that observed in healthy individuals [Haijma et al. 2013; van Haren et al. 2008, 2011, 2016; Olabi et al. 2011]. Collectively, these findings suggest that schizophrenia is associated with lifelong deviation from normative neuroanatomical trajectories.

Application of machine learning algorithms to neuroimaging data offers a new lens for the examination of brain structural deviation in schizophrenia. Using these algorithms, it is possible to generate estimates of the biological age of an individual's brain (i.e., brain-age) by comparing their neuroimaging data against a normative population dataset of the same neuroimaging features [Franke et al. 2010; Franke and Gaser, 2019]. In each individual, subtracting their chronological age from their brain-age generates a metric that quantifies the degree of deviation; this is referred to here as "brain-predicted age difference" (brainPAD) although the term brain-age-gap-estimation has also been used to denote the same metric; a positive brainPAD indicates that the biological age of an individual's brain is "older" than their actual age, and a negative brainPAD reflects the inverse.

A recent study using brain structural magnetic resonance imaging (sMRI) data from 35,474 healthy individuals and 1,110 patients with schizophrenia found a moderate increase in brainPAD (Cohen's  $d$  effect size = 0.51) in patients [Kaufmann et al. 2019]. Five further studies have estimated brainPAD in schizophrenia using various machine learning algorithms applied to sMRI data [Koutsouleris et al. 2014; Schnack et al. 2016; Nenadic et al. 2017; Hajek et al. 2019; Shahab et al. 2019], Koutsouleris and colleagues [2014] used a support vector regression (SVR) algorithm trained on data from 800 healthy individuals, and found that patients with schizophrenia ( $n=141$ ) had a mean brainPAD of 5.5 years. Schnack and colleagues [2016] using a SVR algorithm trained on healthy individuals ( $n=386$ ) reported that patients with schizophrenia from two independent samples ( $n=341$  and  $n=60$ ) had mean brainPAD of 3.8 years and 5.6 years. Using relevance vector regression (RVR), Nenadic and colleagues [2017] reported that patients with schizophrenia ( $n=45$ ) had a mean brainPAD of 2.6 years compared to 70 healthy individuals. A similar mean brainPAD of 2.6 years in patients with schizophrenia ( $n=43$ ) was reported by Hajek and colleagues [2019] using RVR trained on data from 504 healthy individuals. Shahab and colleagues [2019] used random forest regression trained on data from 50 healthy individuals, and showed that patients with schizophrenia ( $n=81$ ) had a mean brainPAD of 7.8 years. Inter-study variability

has been typically considered in terms of sample characteristics while brainPAD estimation can also be influenced by the algorithm used and the choice of neuroimaging features entered into the model. At present, the influence of these various algorithms on brain-age estimation remains unclear as their comparative performance has not been systematically evaluated.

In response, the current study evaluated six algorithms, namely ordinary least squares (OLS) regression [Rudolph et al. 2017], least absolute shrinkage and selection operator (Lasso) regression [Bagarinao et al. 2018; Cole, 2020], ridge regression [Guggenmos et al. 2017; Zhao et al. 2019], elastic-net regression [Khundrakpam et al. 2015], SVR, and RVR, which are commonly used because they are interpretable and resilient to over-fitting. The six algorithms were applied to the same morphological features from each of four independent samples. Two samples comprised healthy individuals participating either in the Human Connectome Project (HCP) [van Essen et al. 2013] or the Cambridge Centre for Ageing and Neuroscience project (Cam-CAN) [Shafto et al. 2014]. Two further samples, from the Icahn School of Medicine at Mount Sinai (ISMMS) and the Center of Biomedical Research Excellence (COBRE) [Aine et al. 2017], comprised both patients with schizophrenia and healthy individuals. Using four datasets enabled testing the robustness of the results to sample composition. The sMRI data of all samples were processed using identical pipelines to extract FreeSurfer-derived regional morphometric measures. We chose these measures as they are amongst the most widely used features in brain imaging studies of schizophrenia [van Erp et al. 2016, 2018], are cost-efficient alternatives to using more fine-grained parcellations for brain-age estimation [Valizadeh et al. 2017] and have been employed to study brain-age in recent large scale studies in neuropsychiatric disorders [Han et al. 2000; Kaufmann et al. 2019].

## 2. Materials and Methods

### 2.1 Samples

**Human Connectome Project:** The HCP ([www.humanconnectome.org](http://www.humanconnectome.org)) acquired sMRI data from 1113 adults living in the USA. Following exclusion of participants with medical problems, we used data from 1092 individuals aged 22–37 years [mean age=28.8 years, standard deviation (SD)=3.7 years; 507 males] (details in Supplementary Methods).

**Cambridge Centre for Ageing and Neuroscience Project.**—The Cam-CAN Project ([www.mrc-cbu.cam.ac.uk](http://www.mrc-cbu.cam.ac.uk)) acquired sMRI data from 652 adults living in the UK. Following exclusion of participants with medical morbidity and/or poor image quality, we used data from 492 individuals aged 18–87 years (mean age=54.4 years, SD=18.3 years; 248 males) (details in Supplementary Methods).

Ethical approval enabling sharing de-identified data from the HCP and Cam-CAN was obtained by the respective coordinating study centres.

**ISMMS Sample:** This sample was recruited and assessed at the Icahn School of Medicine at Mount Sinai (ISMMS) (details in Supplementary Methods). It comprised 90 outpatients (mean age=27.4 years, SD=7.5 years; 69 males) fulfilling diagnostic criteria of

schizophrenia according to the Diagnostic and Statistical Manual of Mental disorders, 5th Edition (DSM-5) [APA, 2013] and 200 healthy individuals without a personal or family history of major psychiatric disorders (mean age=37 years, SD=12.4 years; 110 males). The study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai and all participants gave written informed consent.

**COBRE Sample:** This sample was recruited by Center of Biomedical Research Excellence (COBRE) (<http://cobre.mrn.org> & <http://coins.mrn.org>) (details in Supplementary Methods). It comprised 76 outpatients (mean age=37.9 years, SD=14.2 years; 62 males) fulfilling DSM-IV criteria for schizophrenia [APA, 2000] and 87 healthy individuals (mean age=38.2 years, SD=11.8 years; 62 males) without a personal or family history of major psychiatric disorders. The study was approved by the Institutional Review Board of the University of New Mexico and all participants gave written informed consent.

All participants in the ISMMS and in the COBRE samples were screened to exclude those with IQ<70, a history of neurological disorders, severe head trauma, substance abuse or dependence within the last 12 months and MRI contra-indications.

### Neuroimaging Acquisition, Processing and Feature Extraction

T1-weighted images for all samples were acquired on 3T Siemens scanners (Siemens Medical Systems, Erlangen, Germany). The acquisition parameters are described in the Supplementary Material. The initial studies on sMRI-based brain-age prediction used voxel-based analyses [Franke et al. 2010; Franker and Gaser, 2019]. The T1-weighted MRI images of the four study samples were processed using identical pipelines to extract morphometric measures using FreeSurfer 6.0 (<http://surfer.nmr.mgh.harvard.edu>) (Supplementary Material). Cortical reconstruction was based on the Desikan-Killiany atlas [Desikan et al. 2006] and subcortical segmentation was performed using the probabilistic atlas in FreeSurfer [Fischl et al. 2002]. In each participant's dataset, this procedure generated measures of total intracranial volume and regional measures of cortical thickness (n=68), cortical surface area (n=68) and subcortical volumes (n=16) (Supplementary Table S2).

### Machine learning algorithms for brain-age prediction

The linear models examined can be generally formalized as follows:

$$y_i = \sum_{j=1}^p \beta_j x_{i,j} + \beta_0$$

where  $y_i$  is the age of the  $i^{th}$  individual,  $p$  is the number of features,  $x_{i,j}$  is the value of  $j^{th}$  feature of the  $i^{th}$  subject, and  $\beta_j$  is the regression coefficient.

We evaluated the following six algorithms:

**(1) Ordinary least squares (OLS) regression:** OLS regression algorithm fits a linear model by minimizing the residual sum of squares between the observed  $y_i$  in the training dataset ( $i=1, \dots, N$ , the sample size) and the values  $f(x_i)$  predicted by the linear model. The object function is as follows:

$$\min_{\beta} \sum_{i=1}^N (f(x_i) - y_i)^2$$

where  $y_i$  is the actual value of the chronological age. The least squares solution was computed using the singular value decomposition (SVD).

**(2) Ridge regression:** Ridge regression is a regularized linear model that minimizes the sum of the squared prediction error in the training data and a L2-norm regularization, i.e., the sum of the squares of regression coefficients [Hoerl and Kennard, 1970]. The object function is as follows:

$$\min_{\beta} \sum_{i=1}^N (f(x_i) - y_i)^2 + \lambda \sum_{j=1}^p \beta_j^2$$

The tuning parameter  $\lambda$  controls the model's complexity. If  $\lambda = 0$ , ridge regression becomes a traditional linear regression model. The optimal choice of  $\lambda$  parameter in this study was based on 10-fold cross-validation (see below).

**(3) Least absolute shrinkage and selection operator (Lasso)**

**regression:** Lasso is another form of regularized linear regression using an L1-norm penalty, aiming to minimize the sum of the absolute value of the regression coefficients [Tibshirani, 1996]. The objective function is as follows:

$$\min_{\beta} \sum_{i=1}^N (f(x_i) - y_i)^2 + \lambda \sum_{j=1}^p |\beta_j|$$

The L1-norm regularization tends to set most coefficients to zero and retains one random feature among the correlated ones, thus resulting in a sparse predictive model that facilitates optimization of the predictors and reduces the model complexity.

**(4) Elastic-net regression:** This linear regression model combines both L1-norm (i.e., Lasso regression) and L2-norm (i.e., ridge regression) regularizations in the OLS loss function [Zhou and Hastie, 2005]. The object function is as follows:

$$\min_{\beta} \sum_{i=1}^N (f(x_i) - y_i)^2 + \lambda \sum_{j=1}^p (\alpha |\beta_j| + \frac{1}{2}(1 - \alpha)\|\beta_j\|^2)$$

This allows the number of selected features to be larger than the sample size while achieving a sparse model. A hyperparameter  $\alpha$  (between 0 and 1) is used to control the relative weighting of the L1-norm and L2-norm contributions. The optimal choice of the  $\alpha$  parameter in this study was based on 10-fold cross-validation (see below).

**(5) Linear support vector regression (SVR):** Linear SVR aims to find a function  $f(x_i)$  whose predictive value deviates by no more than a required accuracy  $\epsilon$  from the actual  $y_i$  for all the training data while maximizing the flatness of the function [Smola and

Scholkopf, 2004]. Flatness maximization is implemented using the L2-norm regularization by minimizing the squared sum of the regression coefficients. The object function is as follows:

$$\min_{\beta} \frac{1}{2} \sum_{j=1}^p \|\beta_j\|^2 + C \sum_{i=1}^l (\xi_i + \xi_i^*)$$

$$\text{subject to} \begin{cases} y_i - f(x_i) \leq \varepsilon + \xi_i \\ f(x_i) - y_i \leq \varepsilon + \xi_i^* \\ \xi_i, \xi_i^* \geq 0 \end{cases}$$

where  $l$  is the quantity of ‘support vectors’, which are the samples that deviate by more than  $\varepsilon$  from the actual  $y_i$  used to fit the model. A parameter  $C$  regulates the smoothness of function  $f(x_j)$ . The optimal choice of  $C$  parameter in this study was based on 10-fold cross-validation (see below).

**(6) Relevance vector regression (RVR):** RVR is a Bayesian sparse learning model and has an identical functional form to SVR [Tipping, 2001]. The function is as follows:

$$f(x_i) = \sum_{i=1}^p \beta_i \Phi_i(x) + \beta_0$$

where  $\beta = (\beta_0, \dots, \beta_p)$  is a vector of weights and  $\Phi_i(x) = K(x, x_i)$  is a linear kernel function defining the basis function. The sparsity of RVR is induced by the hyper-priors on model parameters in a Bayesian framework with the maximum a posteriori (MAP) principle. RVR determines the relationship between the target output and the covariates by enforcing sparsity. The L1-norm-like regularization used in RVR encourages the sum of absolute values to be small, which often drives many parameters to zero and provides significantly few basic functions. Notably, RVR has no algorithm-specific parameter.

The scikit-learn library (version 0.23.1) was used to implement OLS regression, ridge regression, Lasso regression, and elastic-net regression (<http://scikit-learn.org/>) [Pedregosa et al. 2011], the LIBSVM function in MATLAB (Mathworks, Natick, MA) was used to implement SVR (<https://www.csie.ntu.edu.tw/~cjlin/libsvm/>) [Chang and Lin, 2011], and the PRoNTTo toolbox (<http://www.mlnl.cs.ucl.ac.uk/pronto/>) was used to implement RVR [Schrouff et al. 2013].

### Brain-age prediction framework

The six algorithms were applied separately to each sample (HCP, Cam-CAN, ISMMS and COBRE) using identical procedures involving the following steps: (i) prior to modeling, each neuroimaging measure was linearly scaled so that all values in the feature set ranged between 0 and 1; (ii) a nested 10-fold cross-validation (10F-CV) was applied to the dataset of healthy individuals which was randomly split into 10 equal-sized subsets. For each cross-validation, one subset was left out as the test subset while the remaining nine subsets were

used together as the training set for estimating the model parameters. These parameters were then applied to the left-out subset. Specifically, for ridge regression, Lasso regression, elastic-net regression, and SVR, cross-validation procedure was applied with an outer 10F-CV to evaluate model generalizability and an inner 10F-CV to determine the optimal parameters ( $\lambda$ ,  $\alpha$ , or  $C$ ) for these algorithms; (iii) the performance of each algorithm was quantified by the mean absolute error (MAE), averaged across all cross-validation folds; (iv) for each algorithm, the regression weights for each brain region were used for the comparative evaluation of the algorithms; the absolute value of these weights represents the importance of the corresponding features in the brain-age prediction of the model [Haufe et al. 2014].

For the ISMMS and COBRE samples, each of the 6 models was estimated in the healthy participants of each sample and then the regional regression weights were applied to the brain structural data of the respective patient group; brainPAD was then calculated for each algorithm by subtracting the chronological age of each individual from their brain-age as predicted from that algorithm.

### Statistical analysis

Comparative evaluation of the algorithms was conducted within each dataset separately (i.e., HCP, Cam-CAN, ISMMS, COBRE) based on the within-sample similarity in predicted brain-age and brain regional regression weights as assessed using correlation analyses and hierarchical clustering with Ward's minimum variance method for Euclidian distances implemented in MATLAB (Mathworks, Natick, MA) (Supplementary Material). In the ISMMS and COBRE samples only, case-control differences in brainPAD were examined using the t-statistic and effect sizes were expressed in terms of Cohen's *d*. Significance was set at  $P_{FDR} < 0.05$  with the false-discovery-rate (FDR) correction [Benjamini and Hochberg, 1995].

## Results

### Comparative Performance of the algorithms in the HCP and Cam-CAN samples

The MAE and R values for each algorithm in the HCP and Cam-CAN samples are shown in Supplementary Table S3 and Supplementary Figure S1. In the HCP sample, MAE values for all algorithms ranged between 2.6-2.7 and pairwise correlations in individual predicted brain-ages between-algorithms ranged from 0.17-0.97 (Figure 1A). Hierarchical clustering of the individual predicted brain-ages identified three clusters; elastic-net regression and Lasso formed one cluster, SVR and RVR formed another and OLS and ridge regressions formed a third cluster (Figure 1B). In the Cam-CAN sample, MAE values for all algorithms ranged between 7.2-7.7 and correlations in individual predicted brain-ages between-algorithms ranged from 0.76-0.99 (Figure 1C). Hierarchical clustering of the individual predicted brain-ages in the Cam-CAN sample showed that elastic-net regression, Lasso and ridge regression together formed one cluster, SVR and RVR formed another cluster while OLS regression showed the lowest similarity with all the other algorithms (Figure 1D).

## Comparative Performance of the algorithms in the healthy individuals from the ISMMS and COBRE samples

The MAE and R values for each algorithm in the ISMMS and COBRE samples are shown in Supplementary Table S4 and Supplementary Figure S2. In the ISMMS sample, correlations in individual predicted brain-ages between-algorithm ranged from 0.61-0.99 (Figure 2A). Hierarchical clustering of the individual predicted brain-ages in the ISMMS sample identified three clusters; the OLS regression model showed a very low degree of similarity with all the other algorithms while the elastic-net regression, Lasso and ridge regression clustered together as did the SVR and RVR (Figure 2B). The regional regression weights of each algorithm are shown in Supplementary Table S5 and Supplementary Figures S3-S5. In the COBRE sample, individual predicted brain-ages showed moderate to high between-algorithm correlations (R range=0.55-0.99) (Figure 2C). Hierarchical clustering of the individual predicted brain-ages showed that elastic-net and ridge regression together formed one cluster, and SVR and RVR formed another cluster; and OLS and Lasso regression formed a third (Figure 2D).

## BrainPAD in Schizophrenia

In the ISMMS sample, with the exception of OLS regression, the mean brainPAD values obtained by all algorithms were statistically higher in patients with schizophrenia compared to healthy individuals (all  $P_{FDR}<0.001$ ), with a range of 3.8 to 5.2 years (Supplementary Table S6; Figure 3A). The effect size of case-control differences was moderate ( $d$  range: 0.23-0.66) (Supplementary Table S6). No sex differences in brainPAD were observed in patients with schizophrenia ( $P_{FDR}>0.05$ ). Similarly in the COBRE sample, the mean brainPAD values obtained by all algorithms were higher in patients with schizophrenia compared to healthy individuals ( $P_{FDR}<0.001$ ), with a range of 4.5 to 11.7 years (Supplementary Table S7; Figure 3). The effect size of case-control differences was large ( $d$  range=0.69-1.14) (Supplementary Table S7). No sex differences in brainPAD were observed in patients with schizophrenia ( $P_{FDR}>0.05$ ).

## Discussion

In this study, we compared the performance of six commonly used linear machine learning algorithms in brain-age prediction in healthy individuals and patients with schizophrenia. Regardless of algorithm, brainPAD was consistently higher in patients with schizophrenia than in healthy individuals although the mean brainPAD values differed by algorithm.

Evaluation of the six algorithms in two sizable samples of healthy individuals from the HCP and Cam-CAN yielded reproducible results with regards to the similarity between Lasso regression and elastic-net regression, and between the SVR and RVR that consistently clustered together. This pattern was also repeated in the smaller case-control samples suggesting that it is largely independent of sample size or composition. OLS regression underperformed in all samples. OLS regression is widely used in the neuroscience research as it is relatively easy to implement even when the number of predictor variables is large. However, the presence of collinearity among the predictor variables may be a particular vulnerability of OLS regression when applied to brain structural data due to the lack of



regularization (or penalty) term in the OLS model. By contrast, ridge regression and SVR apply L2-norm regularization, Lasso regression includes L1-norm regularization, elastic-net regression includes both L1-norm and L2-norm regularization, and RVR applies regularization through a Gaussian prior. Regularized algorithms tended to shrink many regional weights to zero, so the brain-age prediction was based on relatively few brain regions. It is worth noting that, across models, these regional feature weights are selected based on statistical properties and, they do not necessarily convey information about neurobiological processes [Haufe et al. 2014].

BrainPAD in patients with schizophrenia was higher than those of healthy individuals across all six algorithms. The mean brainPAD in patients ranged from 3.4 to 5.2 years in the ISMMS sample and from 4.3 to 9.4 years in the COBRE sample. In general, these findings are aligned with the range of the brainPAD values reported in previous studies in schizophrenia (range=2.6-8 years) [Koutsouleris et al. 2014; Schnack et al. 2016; Nenadic et al. 2017; Hajek et al. 2019; Shahab et al. 2019]. The current study demonstrates that the choice of algorithm has significant implications for brainPAD estimation given the variation observed when different algorithms were applied to the same dataset.

We acknowledge several limitations that could be addressed in future studies. The focus of this study was on the methodological aspects of computing brain-age in schizophrenia and not on the biological meaning of increased brainPAD in patients. The mechanisms underlying increased brainPAD in schizophrenia remain unclear. Schnack et al. [2016] have previously shown that the greater deviance in brainPAD is likely to occur within the first five years from disease onset thus implicating mechanisms that may be relevant or more active at the early stages of schizophrenia. All models used FreeSurfer-derived morphometric features and it is possible that the results may differ if finer morphometric parcellations are used. Schizophrenia is associated with abnormalities in other structural phenotypes, such as gyrification [Palaniyappan and Liddle, 2012] as well as in patterns of brain activation and functional connectivity [Karbasforoushan and Woodward, 2012] which were not examined here. Only linear regression models were evaluated while future work could assess nonlinear regression models such as Gaussian process regression [Jiang et al. 2019], random forest regression, and deep learning models [Bashyam et al. 2020; Cole et al. 2017; Jiang et al. 2019] but at the cost of interpretability and model complexity.

In summary, we provide evidence that linear machine learning algorithms, with the exception of OLS regression, provided similar performance for brain-age prediction on the basis of a combination of cortical and subcortical structural measures. There was variation in the mean brainPAD across algorithms even through they were applied to the same datasets. Therefore algorithm choice could be an important source of inter-study variability. Further studies are needed to address variations in brain-age prediction in schizophrenia attributable to other parameters and in other neuroimaging phenotypes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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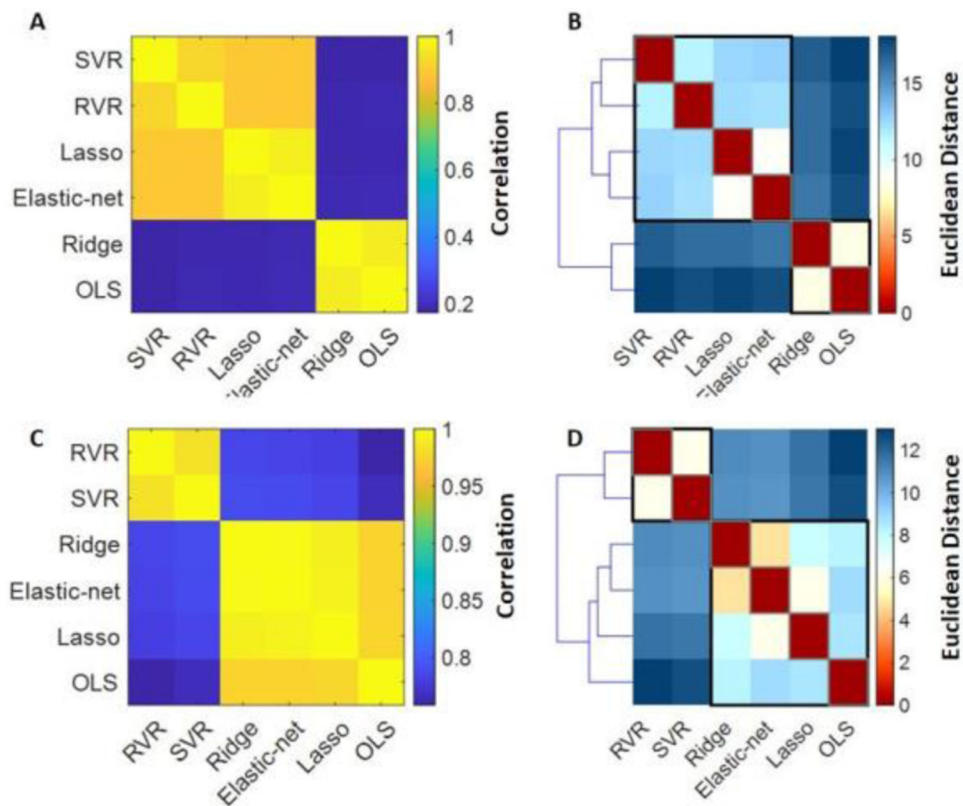
### Highlights

Different machine learning algorithms have been used to compute brain-predicted-age-difference (brainPAD) in schizophrenia

Inter-study BrainPAD variability is typically attributed to schizophrenia-related heterogeneity rather than the algorithms used

Comparison of 6 different algorithms in 4 independent samples yielded consistent differences in their performance

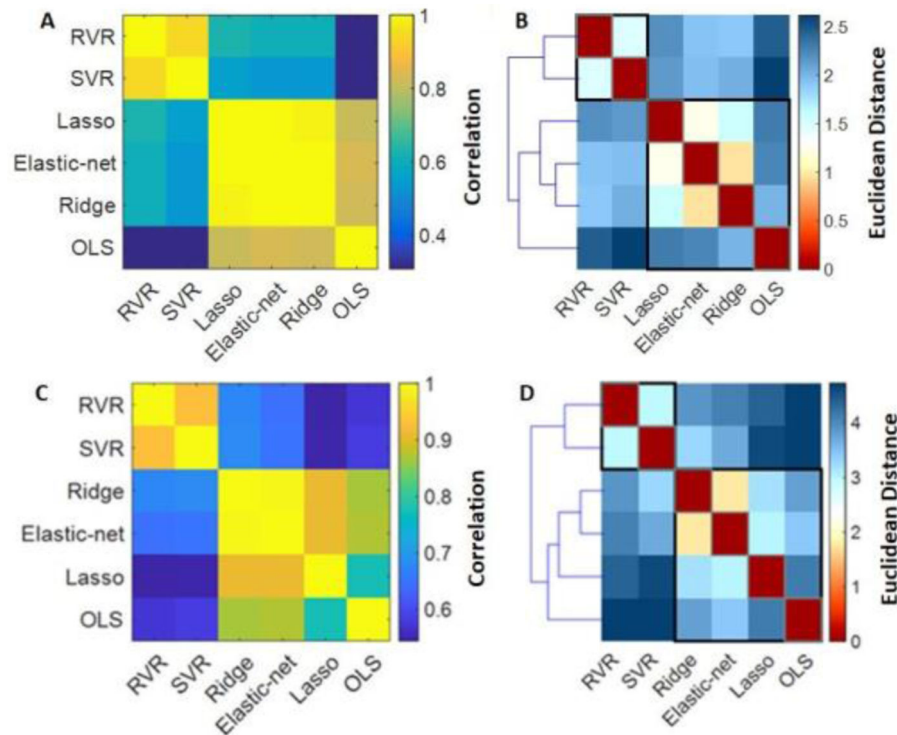
BrainPAD estimates in the same sample of patients with schizophrenia differed by up to 10 years depending on the algorithm used



**Figure 1. Similarity in predicted brain age in healthy individuals in the HCP and Cam-CAN samples across algorithms.**

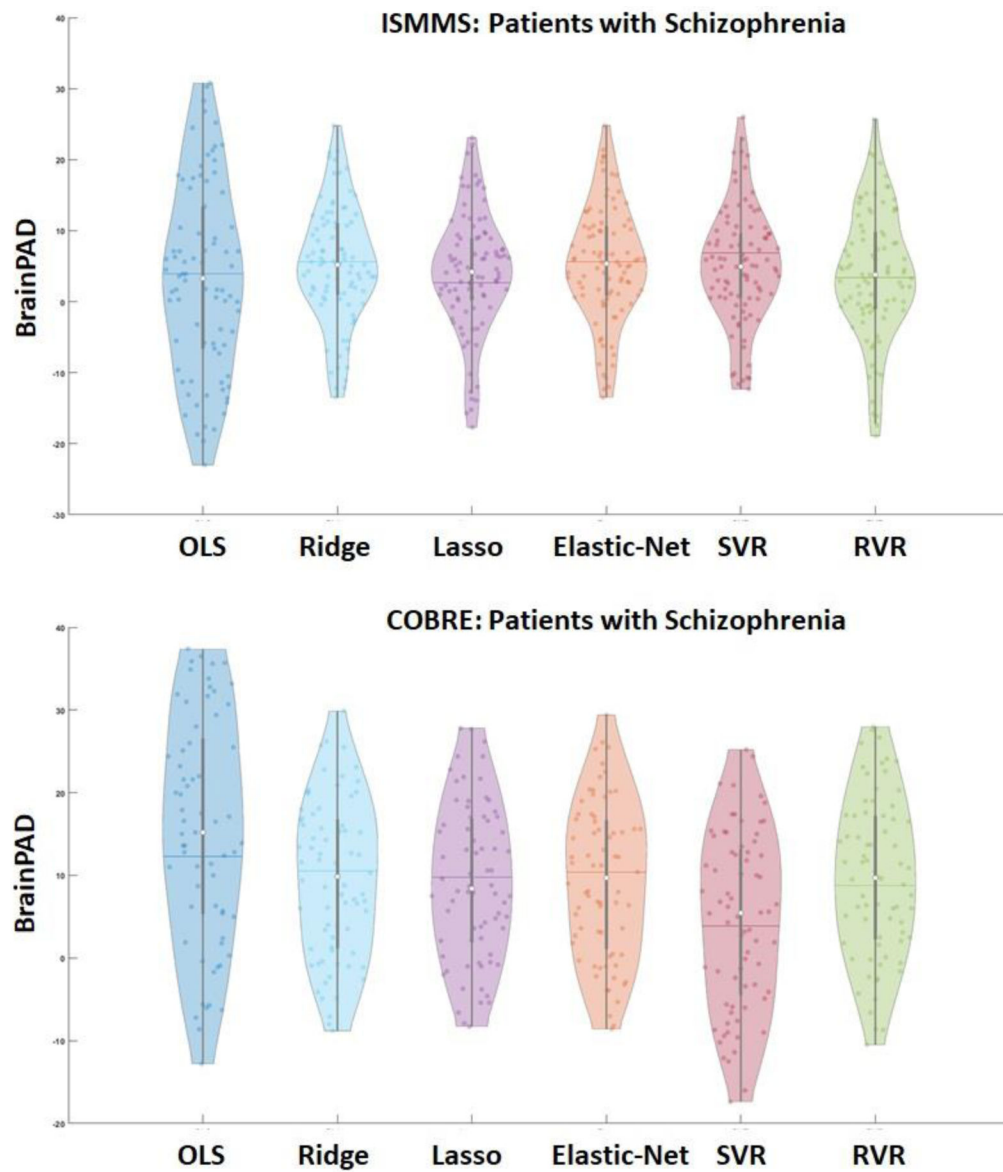
(A) HCP: Similarity matrix representing between-algorithm correlations of individual predicted brain-ages in healthy individuals; (B) HCP: Distance matrix and dendrogram resulting from hierarchical clustering of the individual brain-age results of the six algorithms; (C) Cam-CAN: Similarity matrix representing between-algorithm correlations of individual predicted brain-ages in healthy individuals; (D) Cam-CAN: Distance matrix and dendrogram resulting from hierarchical clustering of the individual brain-age results of the six algorithms. OLS: Ordinary least squares regression; Lasso: Least absolute shrinkage and selection operator; SVR: Support vector regression; RVR: Relevance vector regression; HCP: Human Connectome Project; Cam-CAN: Cambridge Centre for Ageing and Neuroscience Project.





**Figure 2. Similarity in predicted brain age in healthy individuals in the ISMMS and COBRE samples across algorithms.**

(A) ISMMS: Similarity matrix representing between-algorithm correlations of individual predicted brain-ages in healthy individuals; (B) ISMMS: Distance matrix and dendrogram resulting from hierarchical clustering of the individual brain-age results of the six algorithms in healthy individuals; (C) COBRE: Similarity matrix representing between-algorithm correlations of individual predicted brain-ages in healthy individuals; (D) COBRE: Distance matrix and dendrogram resulting from hierarchical clustering of the individual brain-age results of the six algorithms in healthy individuals; OLS: Ordinary least squares regression; Lasso: Least absolute shrinkage and selection operator; SVR: Support vector regression; RVR: Relevance vector regression. COBRE: Center of Biomedical Research Excellence; ISMMS: Icahn School of Medicine at Mount Sinai.



**Figure 3. Brain-predicted age difference the ISMMS and COBRE samples**

Violin plots showing the distribution of individual brain-predicted age difference (brainPAD) scores in patients with schizophrenia in the ISMMS sample (top panel) and the COBRE sample (lower panel). Horizontal line within each violin plot represents the mean and the white circle the median values. OLS: Ordinary least squares regression; Lasso: Least absolute shrinkage and selection operator; SVR: Support vector regression; RVR: Relevance vector regression. COBRE: Center of Biomedical Research Excellence; ISMMS: Icahn School of Medicine at Mount Sinai.