Harnessing the brain-age methods for assessing brain health

Authors and affiliations:

Christian Gaser[1,2,3*], Polona Kalc[1*], James H. Cole[4,5]

[1] Structural Brain Mapping Group, Department of Neurology, Jena University Hospital, Germany

[2] Department of Psychiatry and Psychotherapy, Jena University Hospital, Germany

[3] German Centre for Mental Health (DZPG), Jena-Halle-Magdeburg, Germany

[4] Centre for Medical Image Computing, Department of Computer Science, University College London, London, UK

[5] Dementia Research Centre, Queen Square Institute of Neurology, University College London, London, UK

[*]contributed equally

Addresses:

Am Klinikum 1, 07747 Jena

90 High Holborn, London, WC1V6LJ, UK

Corresponding author: Christian Gaser

christian.gaser@uni-jena.de

Abstract

Brain-age estimation has gained increased attention in the neuroscientific community due to its potential use as a biomarker of brain health. The difference between estimated and chronological age based on neuroimaging data enables a unique perspective on brain development and ageing, with multiple open questions still remaining in the brain-age research field. This perspective article presents an overview of current advancements in the field and envisions the future evolution of the brain-age framework before its potential deployment in hospital settings.

Main

As chronological age does not comprehensively represent the complexity and heterogeneity of the process of ageing, the construct of biological age, encompassing various biophysiological measures, has been proposed to explore why ageing affects people differently and to better determine age-related risks of adverse outcomes[1,2]. Multiple ways of estimating biological age have been developed to improve the understanding of the diverse nature of the body's ageing course[3,4,5,6], with brain age estimation thought to reflect the brain's biological age[7].

Brain-age estimation has provided a novel framework centred on the general concept of ageing patterns, moving away from disease-specific comparisons in studies that are restricted by sample size, pattern specificity, and disease heterogeneity. The brain-age approach builds on the understanding that the ageing human brain undergoes characteristic changes and that various factors, including disease, can accelerate or slow down the natural ageing process of the brain[8,9].

The brain-age framework typically utilises machine learning (ML) in a prediction task where the machine is trained on brain features (i.e., structural and/or functional properties of the brain) of people without psychiatric or neurological diagnoses, and is later applied to new data, resulting in a predicted age. The algorithm estimates an individual's brain age by comparing their brain pattern to the one common for a brain at a given age (Fig. 1a). The difference between the estimated and the chronological age is used as a simplified measure of the brain's ageing progression. A positive value (i.e., older estimated brain age) indicates more prominent brain changes that commonly occur with ageing progression, whereas a negative difference (i.e., younger estimated brain age) signifies a more youthful-appearing brain pattern than expected for that individual's age[10].

Brain-age estimation has been applied in various studies investigating psychiatric and neurological conditions, cognitive and physiological markers, genetic factors, as well as environmental and lifestyle factors[11,12,13,14,15]. The implementation of the brain-age method is becoming more popular and accessible with the increasing availability of ML frameworks and large (open-access) MRI datasets[16]. This wealth of data facilitates and improves the overall process, ultimately leading to more accurate and reliable assessments of brain ageing. Multiple advances have been made in brain-age estimation over the past decade and novel challenges have arisen in the field, which we briefly discuss in this Perspective.

Benefits and applications of the brain-age estimation

Advances in brain-age estimation can enable the investigation of risk- or protective factors associated with brain health in development and ageing. Brain-age could be used as a tool to assess the effectiveness of interventions in clinical trials of age-associated neurodegenerative diseases or aimed at promoting healthy brain ageing. By monitoring changes in an individual's brain-age estimate over time, the impact of lifestyle changes, pharmacological treatments or

cognitive training programmes on brain ageing can be evaluated, leading to development of personalised strategies for healthy ageing[7,12].

The application of brain-age estimation extends beyond research settings, as it provides a straightforward and intuitive measure of a complex brain ageing pattern, potentially serving as a non-invasive biomarker of brain health[10]. It supports early clinical identification of individuals at higher risk of neurodegenerative disorders, as well as disease staging and further monitoring[17].

Fig. 1: The brain-age estimation framework. a) The brain-age estimation framework stems from the idea of creating a model that fits well to the healthy ageing brain, but shows greater errors in prediction in non-normative cases. b) There is at present no standard way of building a brain-age estimation model, however, here are depicted common steps of the workflow. The initial input (MRI – magnetic resonance imaging, EEG – electroencephalography, MEG – magnetoencephalography) can be (minimally) preprocessed and fed to the algorithm. Abbreviations: CNN – convolutional neural networks, SFCN – simple fully convolutional network, ResNet – Residual Network CNN, GPR - Gaussian process regression, RVR – relevance vector regression, SVR – support vector regression. The estimated age can be compared to the chronological age and can be debiased via statistical procedure.

Computational aspects of brain age prediction

With the advancement of MRI technologies and the availability of large neuroimaging datasets, such as UK Biobank (https://www.ukbiobank.ac.uk/), OASIS (https://www.oasis-brains.org/), NKI (https://fcon_1000.projects.nitrc.org/indi/pro/nki.html), IXI (https://brain-development.org/ixi-dataset/), and many others, multiple brain-age algorithms have emerged, employing various terms to name the difference between the estimated and chronological age, such as brain age gap estimate (BrainAGE)[18], brain-predicted age difference (Brain-PAD)[19], brain age delta [20,21,22], and brain estimated age difference (Brain-EAD)[23]. Despite differences in nomenclature, general commonalities of the brain age estimation process can be identified (Fig. 1b). However, there is currently no standard way of estimating the brain age and changes in the common steps can lead to variation in brain-age estimation accuracy and subsequent sensitivity to disease effects.

Input

A brain-age model's performance depends heavily on the amount and type of input data, which can range from resampled raw data to fully preprocessed analysis-ready brain features. The first can be used in deep learning (DL) workflows, whereas standard ML algorithms typically require feature selection and/or feature reduction[24].

The most commonly utilised neuroimaging features to date have been from structural MRI, preprocessed in either region- or voxel/vertex-wise manner, resulting in measures such as brain tissue volumes[18,25,26], cortical thickness, area, and curvature[27,28]. In addition, features from

other imaging modalities have been employed to predict brain age, such as resting state functional connectivity MRI[29,30], diffusion MRI[31], positron emission tomography (PET)[32], and other data-acquisition techniques, e.g., EEG[33] or MEG[34].

Joining features from multiple modalities in an age-prediction model has been shown to improve the performance in comparison to single modality approaches[35,36,37,38]. The optimal methods for combining modalities are an open area of research, as part of wider efforts to optimise the 'fusion' of different data types. This can be 'early' fusion, such as simple concatenation of features or images[35], or 'late' fusion such as ensemble methods where brain-age predictions are generated separately for each modality and then combined using averaging or a more sophisticated ensemble approach[37]. Alternatively, 'mid' fusion techniques that define latent representations from different modalities, using auto encoders or similar methods, before combining these latent representations, can be considered[39]. Not only do brain-age prediction models stand to benefit from developments in data fusion research, but the brain-age paradigm serves as a useful 'sandpit' in which to develop such methods for neuroimaging, since abundant imaging data with age labels are readily available to the community.

Algorithm

The amount and type of available input can help determine the choice of the algorithm[40], which in turn affects the results of brain-age prediction[41,42] and the associations to cognitive measures[43]. Among the possible (non-)parametric, (non-)linear, Bayesian, tree-based, and kernel-based models that have been developed, brain-age studies utilising standard ML algorithms have predominantly employed relevance vector regression (RVR)[18], Gaussian process regression (GPR)[19], support vector regression (SVR)[23], or extreme gradient boosting (XGBoost)[22].

With the advances in data sharing and aggregation, the shortage of data is often a trivial problem, and in recent years DL models started gaining more attention in the field. Various models, such as convolutional neural networks (CNN)[44], ResNet[45], and simple fully convolutional network (SFCN)[46], have been developed to predict the brain age. These models utilise either slice-based (2D) or voxel-based (3D) input type and some of the pretrained brain-age models are openly available online[20,47,48,49].

Moreover, the development of transformers and diffusion models for natural language processing or computer vision respectively, have recently made pronounced societal impacts. This has led to a new wave of mainstream interest in AI, through technologies such as ChatGPT[50] or Stable Diffusion[51]. These approaches have already been adopted to estimate brain age, including the vision transformer (ViT[52]) and graph transformer[53], and the latent diffusion model[54]. However, no benchmark study comparing the brain-age prediction performance of these emerging DL models, or DL more generally, with 'classic' ML methods has yet been published[55], so the extent to which these methods improve performance remains an open question. For an in-depth overview of the ML and DL algorithms in the field, we direct the reader to recent review papers[13,55], respectively.

Output

The output of the brain-age algorithm is the individual's predicted age, which is typically a single whole-brain measure or a set of values if trained on separate brain regions[56,57]. By subtracting the chronological age from the predicted age, we obtain the measure of interest, which is not independent from age and shows an underestimation in older- and overestimation in younger subjects[21,58,59]. To remove the age-dependency, a so-called age-bias correction can be applied (i.e., regressing out the effects of age)[60]. Several propositions of statistical age-bias corrections have been made, some of which either use chronological age in the correction [21,22,59] or not[25]. The choice of age-bias correction method can influence the final performance accuracies[61], while the source and amount of data used to estimate the regression parameters for the correction strongly affect the results[62]. The resulting gap, either age-bias corrected or uncorrected (with age added as a covariate in further statistical models), can be used in further (brain-behaviour) analyses. Potentially, the most transparent method is to avoid explicit age-bias correction and rely on using age as a covariate, since the subsequent statistical analyses should provide the same results[58].

Theoretically, an accurate brain-age model has a low mean absolute error (MAE) on a test set of healthy individuals and results in high correlation between estimated and chronological age. Furthermore, it enables reliable and consistent estimations in a short-term test-retest or longitudinal scenario, and is generalisable to different datasets[62]. It makes valid predictions in healthy and clinical groups, and demonstrates construct validity by meaningful associations with other physiological and cognitive measures. However, due to various factors contributing to differences in model accuracy, it is often impossible to directly compare the brain-age models' performance[61,63].

Challenges and advancements of brain-age estimation

Recent breakthroughs in brain-age research have brought to light new challenges in the field. We here envision the prospects of further research topics as well as the challenges needed to address to make the brain-age a useful biomarker in the hospital settings (Fig. 2).

Fig 2. Advancements and challenges in the brain-age field. For a brain-age measure to be applied in clinics as a biomarker, it must be accurate, reliable, and valid. Further scientific endeavours in standardising the data, models, measures, and routines are necessary before the potential approval by national agencies. In addition to improving the accuracy of the models, the validity of the measure will have to be investigated along with reducing the black box factor. Reliable longitudinal predictions are essential for monitoring the progression of brain changes, and uncertainty-aware approaches can increase the clinicians' trust in predictions. After the spillover into the hospital settings, the initial efforts are expected in the areas of technical implementations as well as improving quality of medical imaging data (by computational advancements in DL preprocessing or within the brain-age model itself). The ethical use of this measure is crucial, particularly given the growing availability of imaging data and portable low-field scanners.

Brain-age research

The field lacks consensus regarding the construction and evaluation of developed brain-age models. Several initiatives have sought to establish a platform for standardisation and benchmarking of both new and extant brain-age models[63,64], and a recent study conducted a benchmark analysis on various publicly available brain-age models[65], underscoring the importance of further work in this area. Although these recent attempts at standardisation have provided a welcome framework to compare the accuracy and reliability of different models, they lack the inspection of validity of brain-age as a biomarker. In fact, it is not clear if the most accurate models really provide the most useful biomarkers[66,67], as they may overlook the meaningful biological information necessary to discriminate between the healthy and clinical population[20].

The brain-age method provides an estimate of the brain's biological age, capturing relevant biological variance (of ageing), but also modelling- and data-related noise[7,17]. Further research is needed to disentangle this variance and to uncover the underlying biological mechanisms of brain ageing within the brain-age paradigm. As has been pointed out, brain age does not necessarily show only the patterns of brain ageing but could reflect the congenital and/or early-life brain variability that continues through the lifespan (e.g., a person might have larger ventricles since their childhood)[68].

Moreover, brain-age estimation can be subjected to confounding factors related to input characteristics deriving from scanner differences, image acquisition protocols, image quality, preprocessing pipelines, etc.[67,69,70]. For models to generalise better to other datasets, harmonisation of data can improve the results of brain age estimation[71,72], while transfer learning[45,73] can provide another possible solution. To establish the brain-age as a clinical biomarker, future research endeavours are therefore expected in the fields of neurobiological underpinnings of brain age as well as modelling and data-acquisition related factors that contribute to the observed age differences.

In addition, if the brain-age is to be a valuable monitoring measure in the hospital setups, it should provide reliable and consistent longitudinal predictions. Since the method builds upon cross-sectional variability it has a limited validity from a longitudinal perspective[68]. The dependance on cross-sectional data for training potentially renders the method insensitive to cohort effects and can limit the possibility to detect longitudinal changes due to individual development[74]. Nevertheless, a recent application to a longitudinal birth cohort study has demonstrated that brain-age measure reflects both congenital and ageing differences[74], show longitudinal increase over time in early onset Alzheimer's disease (AD)[75], and corresponds with the presence of brain pathologies and prospective conversion to AD[32,76].

The longitudinal perspective of the brain-age method has to be further investigated. One of the significant bottlenecks both computationally and in terms of application is the availability of longitudinal data. The continuation of establishing collaborative frameworks for data sharing

and aggregation, as well as building open-source tools and frameworks, will help overcome these and similar problems in the future. In addition, future development of the brain-age field will rely on the advancements in artificial intelligence and the computational outputs of image processing.

An initial critique of brain-age estimation pertained to its inherently black box methodology, a factor contributing to its limited integration into clinical practice[10]. The advances in interpretable ML/explainable AI have made the brain-age estimation much less black box type of measure and various approaches have been utilised to gain understanding of the models' prediction. Different model-agnostic[77] and specific methods, such as saliency maps [32,49,78], as well as explainable prototype learning methods[79] have been implemented. However, the lack of ground-truth for the deviations from healthy brain ageing make validation challenging, so the explainability of the models should be further investigated.

Not commonly in use in the field of brain-age estimation but in line with current DL practices, the uncertainty of the estimation has also been recognised as an important step in brain-age modelling. Providing confidence intervals or similar around individual point predictions should increase end-user (e.g., clinician) trust in the predictions, increasing the likelihood that brain-age could be widely adopted. Recent studies implemented uncertainty aware approaches to brain-age estimation[47,80,81] and more advances are expected from this area of research. Further contributions from the computational perspective are also possible in the areas of ensemble (DL) architectures, automated machine learning (autoML[82]), reduction of computational complexity and others.

Moreover, a recent concern has been raised with regard to statistical age-bias correction, which can in certain cases artificially inflate the model's prediction accuracy or, under specific circumstances, may cause circularity in the procedure[83]. The authors question the interpretation of statistically modified brain age and request for a better measure to describe deviation from the norm. Nevertheless, brain-age research in narrow age cohorts, where the confounding effect of chronological age is removed, have validated the sensitivity of brain age to other ageing biomarkers or clinical outcomes[25,84]. These findings refute the circularity argument, but alternative concepts of deviation from the norm are still important to consider. Analogous to growth charts in paediatric care, normative modelling may present a possible alternative[85,86,87].

Application in the clinics

The initial conceptualization of brain age as a biomarker for brain health envisioned its application in hospital settings. However, despite over a decade of development, the brain-age framework has yet to mature before the implementation in clinical practice. Some of the fundamental challenges essential for enhancing the method were briefly presented before. Here we envision further (computational) advancements that could facilitate the method's transition into healthcare.

Most brain-age models are trained and tested on high resolution data from curated databases that do not represent current practices in clinical imaging, which typically provides low

resolution '2D' data[11,49]. However, a step in direction of clinical application has recently been made by training a DL model on raw clinical data of various MRI modalities, resulting in a potentially applicable screening tool for routine hospital examinations[49]. Computational advances that could prove beneficial in the context of clinical application further include models that are agnostic to the image resolution and MRI contrast type[88], facilitated by using synthetic images for learning[89], MRI-aware data augmentation methods to reduce the impact of, for example, bias field inhomogeneities[90], or image enhancement methods that are designed to improve the poorer-quality images[91,92]. This is important as the majority of clinical neuroimaging sites do not have access to the higher-quality MRI scanners available in research settings, and often have much higher throughput and less capacity for quality assurance and rescanning patients. Portable low-field MRI scanners may become more common in clinical situations[93]. Therefore, quality-agnostic models or image enhancement methods could be highly beneficial in enabling brain-age estimation in people who cannot normally undergo higher-field MRI (i.e., ≥1.5T).

Before the implementation in the hospital settings, the approval of national agencies will be necessary. Ensuring that brain-age models can be deployed on hospital computer systems (e.g., Picture Archiving and Communication System - PACS) will be essential for clinical access to brain-age results, and already commercial vendors are marketing their own versions of brain-age, to be used in hospital settings (e.g., BrainKey: https://www.brainkey.ai/). With clinical deployment comes the requirements of software consistency and back-compatibility, so that results can be reliably generated in different locations and at different times, even if computational advances render older models obsolete. Software 'containerisation' will be a key part of this, providing a standalone virtual environment including the relevant dependencies, so that brain-age models can be run on different operating systems and legacy versions maintained.

Another important computational development relevant to clinical deployment is federated learning, which has emerged as a promising way to overcome issues around privacy and data security for biomedical research, including neuroimaging[94]. With federated learning approaches, individual-level data do not need to be shared between sites, only the locally-learned model parameters are centralised or 'federated'. This potentially opens up access to much larger datasets for training brain-age models, and has already shown some promise[95]. The algorithms used for the federated aggregation of local parameters are a key component of the federated learning process, and are an active area of research[96]. As an alternative to federated learning, the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium, has been established to facilitate the pooling of anonymised neuroimaging data (e.g., FreeSurfer volumes and cortical thickness values) for either meta- or mega-analysis. The ENIGMA Brain Age working group (https://enigma.ini.usc.edu/ongoing/enigma-brainage/) is leading efforts to optimise models and harmonise procedures for the purpose of brain-age prediction from such datasets, including in major depressive disorder and schizophrenia[97,98,99].

Despite numerous potential improvements, further development of the brain-age method is similarly ambiguous as the progress in other measures of biological ageing, and could raise ethical concerns associated with employment, legal matters, insurance, and healthcare provision[100,101]. Although the costs of the MRI scanning are currently too high to be considered by the state authorities, life insurance companies or other actors, the potential of lowering these costs and the subsequent availability of brain-age estimation as a non-invasive Alzheimer's disease biomarker before the onset of the symptoms could be of relevance to these stakeholders. Furthermore, additional questions about stigma, discrimination, and stress inducement could arise in situations of revealing the higher brain-age estimation, especially for the working population without ongoing memory impairments[101].

Therefore, we caution against using brain-age estimation as a general screening tool. As it had been demonstrated in the Nun study[102], obvious pathological changes in the structure of post mortem brains of the participants had not been reflected in their cognition before death. A large difference between the estimated and chronological age of the subjects does not provide sufficient proof to determine diagnoses. The brain has a remarkable capacity for plasticity, adaptation and compensation, which can help maintain normal cognitive abilities even in the presence of significant brain atrophy[103,104]. It is therefore important to consider other factors such as cognitive performance, functional ability and the presence or absence of neurological symptoms to gain a full understanding of an individual's brain health. Brain-age estimation can rather serve as a supportive biomarker in helping physicians identify potential deviations from the normal ageing and monitoring the progression of brain changes.

Conclusion

The method of brain age estimation represents a departure from traditional approaches in analysing brain imaging data, providing a comprehensive understanding of health- and age-related brain changes. By utilising the advantages of ML while focusing on deviations from normal ageing patterns, brain-age estimation provides a simple quantification of a complex pattern of structural brain changes associated with ageing and disease. The approach minimises confounding factors and allows for a more accurate assessment of brain ageing within individuals, regardless of their specific clinical condition or disease stage. Many advances have been made in the field over the past years, however, further research supported by computational science is warranted to unravel method's potential in progressing our understanding of the brain and to apply it in clinical practice.

Data and Code Availability Statement

No data/code were generated for this article.

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Contributions

All authors discussed the content, reviewed and edited the entire manuscript.

Competing interests

J.H.C. is an advisor to and shareholder in BrainKey and ClaritasHealthPTE.

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