

A perspective on brain-age estimation and its clinical promise

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Brain-age estimation has gained increased attention in the neuroscientific community owing 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 aging, with multiple open questions still remaining in the brain-age research field. This Perspective 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.

As chronological age does not comprehensively represent the complexity and heterogeneity of the process of aging, the construct of biological age, encompassing various biophysiological measures, has been proposed to explore the reason why aging 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 aging course^{3–6}, with brain-age estimation thought to reflect the brain's biological age⁷.

Brain-age estimation has provided a novel framework centered on the general concept of aging 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 aging human brain undergoes characteristic changes and that various factors, including disease, can accelerate or slow down the natural aging process of the brain^{8,9}.

The brain-age framework typically utilizes machine learning (ML) in a prediction task where the machine is trained on brain features (that is, structural and/or functional properties of the brain) of people without psychiatric or neurological diagnoses, and is later applied to new data, resulting in an estimated age. The algorithm estimates an individual's brain age by comparing their brain pattern to a sample brain pattern usually observed at their given age (Fig. 1a). The difference between the estimated and the chronological age is used as a simplified measure of the brain's aging progression. A positive value (that is, older estimated brain age) indicates more prominent brain changes that commonly occur with aging progression, whereas a negative difference (that is, younger

estimated brain age) signifies a more youthful brain pattern than expected for that individual's age¹⁰.

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^{11–15}. The implementation of the brain-age method is becoming more popular and accessible with the increasing availability of ML frameworks and large (open access) magnetic resonance imaging (MRI) datasets¹⁶. This wealth of data facilitates and improves the overall process, ultimately leading to more accurate and reliable assessments of brain aging. Multiple advances have been made in brain-age estimation over the past decade and multiple 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 aging. 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 aging. By monitoring changes in an individual's brain-age estimate over time, the impact of lifestyle changes, pharmacological treatments or cognitive training programs on brain aging can be evaluated, leading to development of personalized strategies for healthy aging^{7,12}.

The application of brain-age estimation extends beyond research settings, as it provides a straightforward and intuitive measure of a complex brain-aging pattern, potentially serving as a non-invasive

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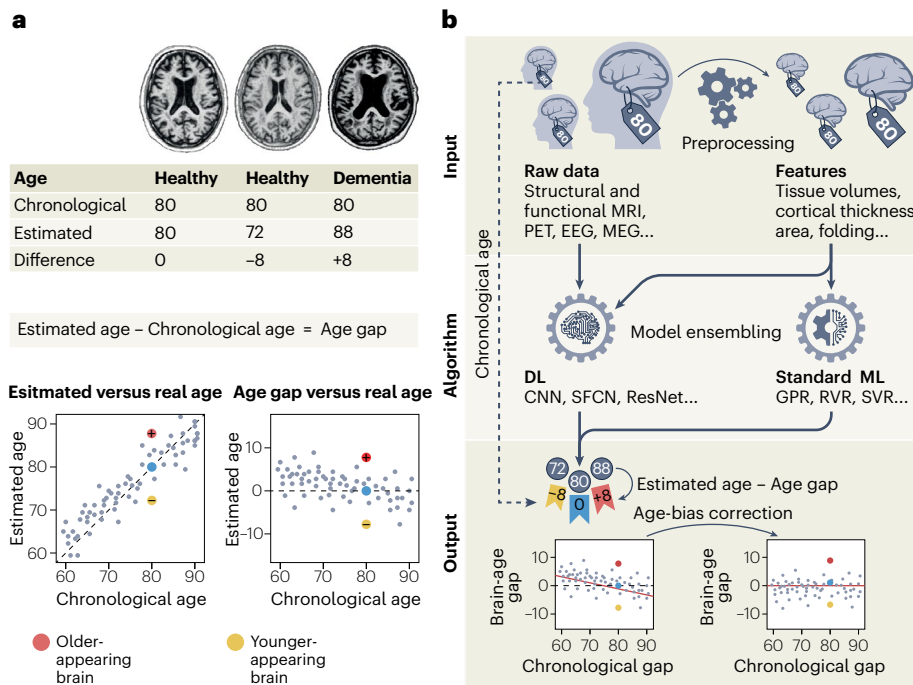


Fig. 1 | The brain-age estimation framework. **a**, The brain-age estimation framework stems from the idea of creating a model that fits well to the healthy aging brain, but shows greater errors in prediction in non-normative cases. **b**, There is at present no standard way of building a brain-age estimation model; however, here are depicted common steps of the workflow. The initial input (MRI, positron emission tomography (PET), electroencephalography (EEG),

magnetoencephalography (MEG)) can be (minimally) preprocessed and fed to the algorithm. 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 with the chronological age and can be debiased via statistical procedure.

biomarker of brain health¹⁰. It supports early clinical identification of individuals at higher risk of neurodegenerative disorders, as well as disease staging and further monitoring¹⁷.

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/>), Open Access Series of Imaging Studies (OASIS; <https://www.oasis-brains.org/>), Nathan Kline Institute/Rockland Sample (NKI; https://fcon_1000.projects.nitrc.org/indi/pro/nki.html), Information eXtraction from Images (IXI; <https://brain-development.org/ixi-dataset/>) and many others, multiple brain-age algorithms have emerged, using 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^{20–22} 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 reduction²⁴.

The most commonly utilized neuroimaging features so far 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 used

to predict brain age, such as resting-state functional connectivity MRI^{29,30}, diffusion MRI³¹, positron emission tomography³² and other data-acquisition techniques, for example, electroencephalography³³ or magnetoencephalography³⁴.

Joining features from multiple modalities in an age-prediction model has been shown to improve the performance compared with single-modality approaches^{35–38}. The optimal methods for combining modalities are an open area of research, as part of wider efforts to optimize the 'fusion' of different data types. This can be 'early' fusion, such as simple concatenation of features or images (see, for example, ref. 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 (see, for example, ref. 37). Alternatively, 'mid' fusion techniques that define latent representations from different modalities, using autoencoders or similar methods, before combining these latent representations, can be considered³⁹. Not only do brain-age prediction models stand to benefit from developments in data fusion research but also the brain-age paradigm serves as a useful 'sandpit' in which to develop such methods for neuroimaging, as 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 algorithm⁴⁰, which in turn affects the results of brain-age prediction^{41,42} and the associations with cognitive measures⁴³. Among the possible (non-)parametric, (non-)linear, Bayesian, tree-based and kernel-based models that have been developed, brain-age studies utilizing standard ML algorithms have predominantly employed relevance vector regression¹⁸, Gaussian process regression¹⁹, support vector regression²³ 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

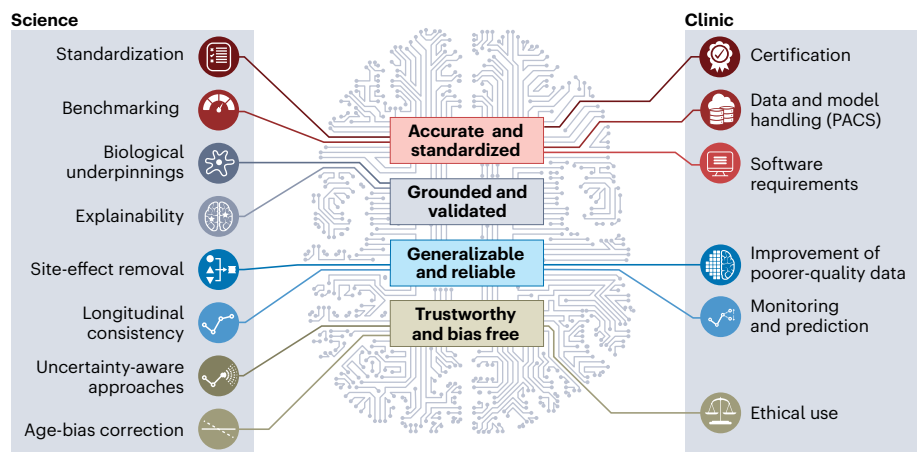


Fig. 2 | Advancements and challenges in the brain-age field. For a brain-age measure to be applied in clinic as a biomarker, it must be accurate, reliable and valid. Further scientific endeavors in standardizing the data, models, measures and routines are necessary before the potential approval by national 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. PACS, Picture Archiving and Communication System.

gaining more attention in the field. Various models, such as convolutional neural networks⁴⁴, ResNet⁴⁵ and simple fully convolutional network⁴⁶, have been developed to predict the brain age. These models utilize either slice-based (two-dimensional) or voxel-based (three-dimensional) input types and some of the pretrained brain-age models are openly available online^{20,47–49}.

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 artificial intelligence, through technologies such as ChatGPT⁵⁰ or Stable Diffusion⁵¹. These approaches have already been adopted to estimate brain age, including the vision transformer (ViT)⁵² and graph transformer⁵³, and the latent diffusion model⁵⁴. 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 published⁵⁵, 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 individuals and overestimation in younger individuals^{21,58,59}. To remove the age dependency, a so-called age-bias correction can be applied (that is, 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 not²⁵. The choice of age-bias correction method can influence the final performance accuracies⁶¹, while the source and amount of data used to estimate the regression parameters for the correction strongly affect the results⁶². 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–behavior) analyses. Potentially, the most transparent method is to avoid explicit age-bias correction and rely on using age as a covariate, as the subsequent statistical analyses should provide the same results⁵⁸.

Theoretically, an accurate brain-age model has a low mean absolute error 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 generalizable to different datasets⁶². It makes valid predictions in healthy and clinical groups, and demonstrates construct validity by meaningful associations with other physiological and cognitive measures. However, owing 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 that need to be addressed to make the brain age a useful biomarker in the hospital settings (Fig. 2).

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 standardization 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 models⁶⁵, underscoring the importance of further work in this area. Although these recent attempts at standardization 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 whether 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 population²⁰.

The brain-age method provides an estimate of the brain's biological age, capturing not only relevant biological variance (of aging) but also modeling- and data-related noise^{7,17}. Further research is needed to disentangle this variance and to uncover the underlying biological mechanisms of brain aging within the brain-age paradigm. As has been pointed out, brain age does not only necessarily show the patterns of brain aging but also could reflect the congenital and/or early-life brain

variability that continues through the lifespan (for example, 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 and so on^{67,69,70}. For models to generalize better to other datasets, harmonization 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 endeavors are therefore expected in the fields of neurobiological underpinnings of brain age as well as modeling 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 hospital set-ups, it should provide reliable and consistent longitudinal predictions. As the method builds on cross-sectional variability, it has a limited validity from a longitudinal perspective⁶⁸. The dependence 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 development⁷⁴. Nevertheless, a recent application to a longitudinal birth cohort study has demonstrated that brain-age measure reflects both congenital and aging differences⁷⁴, shows a longitudinal increase over time in early onset Alzheimer's disease⁷⁵, and corresponds to the presence of brain pathologies and prospective conversion to Alzheimer's disease^{32,76}.

The longitudinal perspective of the brain-age method has to be further investigated. One of the substantial 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 practice¹⁰. The advances in interpretable ML/explainable AI have made the brain-age estimation a much less black-box type of measure and various approaches have been utilized to gain understanding of the models' prediction. Different model-agnostic⁷⁷ and specific methods, such as saliency maps^{32,49,78}, as well as explainable prototype learning methods⁷⁹ have been implemented. However, the lack of ground truth for the deviations from healthy brain aging 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 recognized as an important step in brain-age modeling. Providing confidence intervals or similar around individual point predictions should increase end-user (for example, 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 (autoML⁸²), 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 procedure⁸³. 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 aging 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 pediatric care, normative modeling may present a possible alternative⁸⁵⁻⁸⁷.

Application in the clinic

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 'two-dimensional' 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 examinations⁴⁹. 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 type⁸⁸, facilitated by using synthetic images for learning⁸⁹, MRI-aware data augmentation methods to reduce the impact of, for example, bias field inhomogeneities⁹⁰, 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 situations⁹³. 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 (that is, ≥ 1.5 T).

Before implementation in hospital settings, the approval of national agencies will be necessary. Ensuring that brain-age models can be deployed on hospital computer systems (for example, Picture Archiving and Communication System) 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 (for example, 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 'containerization' 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 neuroimaging⁹⁴. With federated learning approaches, individual-level data do not need to be shared between sites, only the locally learned model parameters are centralized or 'federated'. This potentially opens up access to much larger datasets for training brain-age models, and has already shown some promise⁹⁵. 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 research⁹⁶. As an alternative to federated learning, the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium, has been established to facilitate the pooling of anonymized neuroimaging data (for example, 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 optimize models and harmonize procedures for the purpose of brain-age prediction from such datasets, including in major depressive disorder and schizophrenia^{97–99}.

Despite numerous potential improvements, further development of the brain-age method is similarly ambiguous as the progress in other measures of biological aging, and could raise ethical concerns associated with employment, legal matters, insurance and healthcare provision^{100,101}. Although the costs of 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 impairments¹⁰¹.

Therefore, we caution against using brain-age estimation as a general screening tool. As demonstrated in the Nun study¹⁰², obvious pathological changes in the structure of post mortem brains of the participants was not reflected in their cognition before death. A large difference between the estimated and chronological age of the individuals 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 substantial 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 aging and monitoring the progression of brain changes.

Conclusion

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

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Author contributions

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

Competing interests

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

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