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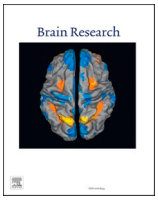

Review

A review on brain age prediction models

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ABSTRACT

Brain age in neuroimaging has emerged over the last decade and reflects the estimated age based on the brain MRI scan from a person. As a person ages, their brain structure will change, and these changes will be exclusive to males and females and will differ for each. White matter and grey matter density have a deeper relationship with brain aging. Hence, if the white matter and grey matter concentrations vary, the rate at which the brain ages will also vary. Neurodegenerative illnesses can be detected using the biomarker known as brain age. The development of deep learning has made it possible to analyze structural neuroimaging data in new ways, notably by predicting brain ages. We introduce the techniques and possible therapeutic uses of brain age prediction in this cutting-edge review. Creating a machine learning regression model to analyze age-related changes in brain structure among healthy individuals is a typical procedure in studies focused on brain aging. Subsequently, this model is employed to forecast the aging of brains in new individuals. The concept of the "brain-age gap" refers to the difference between an individual's predicted brain age and their actual chronological age. This score may serve as a gauge of the general state of the brain's health while also reflecting neuroanatomical disorders. It may help differential diagnosis, prognosis, and therapy decisions as well as early identification of brain-based illnesses. The following is a summary of the many forecasting techniques utilized over the past 11 years to estimate brain age. The study's conundrums and potential outcomes of the brain age predicted by current models will both be covered.

1. Introduction

The human brain, with its intricate network of neurons and synapses, remains one of the most enigmatic and captivating organs in the realm of biological sciences (Han and Ge, 2023). For generations, researchers have been captivated by the developmental and aging processes of the brain (Lin et al., 2019). The emergence of advanced neuroimaging methods has bestowed scientists with an unparalleled understanding of the brain's structural and functional transformations as time passes. Among these advancements, the emergence of machine learning (ML) and computational modeling has provided a new lens through which to study brain aging (Mwangi et al., 2013). A fundamental challenge in neuroscience has been to decipher the mechanisms underlying brain aging, with a particular focus on distinguishing normal aging from pathological conditions (Anatürk, 2021).

Nowadays, the idea of the brain age is widely accepted. Humans age chronologically, and as they get older, their brains likewise deteriorate at a rate of about 5 % every decade after the age of 40, with the real rate of decline potentially rising with age, especially beyond the age of 70. In the course of aging, the structure of the brain and its related functions will change accordingly (Walhovd et al., 2023). The frontal cortex will become smaller as you become older. As we age, our brains gradually lose their ability to do memory-related tasks. The brain aging process will have the biggest impact on episodic and semantic memory abilities. Moreover, there is a deeper connection between the progression of brain aging in terms of grey matter and white matter. According to a theoretical perspective, the use of MRI scans on the brains of individuals in good health allows for the estimation of their age. This brain age might slightly deviate from the person's chronological age. The variation between chronological age and calendar age is termed the brain age gap, more commonly referred to as the brain age difference (Sporns, 2013). When the brain-age gap is positive, it signifies that an individual's projected brain age surpasses their actual age, a condition referred to as "accelerated" or "premature" aging. Conversely, a negative brain-age gap suggests a lower projected brain age, also termed "delayed" aging.

The brain age is a popular indicator for assessing and predicting

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different neurodegenerative disorders. As a result, brain age can be employed as a key in a variety of neurological research (Shah, 2018). Neurodegenerative illnesses influence our body's functioning, resulting in severe circumstances for those who have been affected mentioned in Sajedi et al. (Sajedi and Pardakhti, 2019). Individuals who are affected by conditions like AD (Alzheimer's Disease) and PD (Parkinson's Disease) may experience significant distress and struggle to perform essential physiological activities such as communication, equilibrium, and mobility (Douaud et al., 2014; Persson, 2023). As a result, the above-mentioned diseases and other neurodegenerative disorders that require greater consideration can be recognized from brain age prediction models described in Lea Baecker et al. (Baecker et al., 2021).

According to the findings, multiple prediction methods may accurately predict brain age. M. Tanveer et al. (Tanveer et al., 2023) classified deep learning architectures based on slice/voxel-based input data and classified deep learning architectures based on brain age estimation models. They also investigated the modalities, data size, performance, and datasets used. The review by Mishra et al. (Mishra et al., 2023) presents findings that endorse the utilization of brain age estimation techniques for identifying different brain diseases or conditions. The research also accentuates the tools and strategies employed for predicting brain age and delves into possibilities for future investigations. In a separate publication, Sajedi et al. (Sajedi and Pardakhti, 2019) emphasize and analyze primary techniques for predicting age based on brain MRI scans. This encompasses preprocessing methodologies, pertinent tools employed in diverse research endeavors, and predictive algorithms. The authors categorize brain age estimation approaches into two groups: those related to MRI image processing (pixel-based, surface-based, or voxel-based methods) and the development of machine learning algorithms (conventional or Deep Learning methods) (Peng, 2021).

Lea Baecker et al. (Baecker et al., 2021) delivered a comprehensive overview of techniques for predicting brain age and their applications in clinical settings. Generally, investigations into brain aging commence by constructing a machine-learning model that employs regression to capture age-related neuroanatomical alterations in healthy adults. This model is subsequently harnessed to predict the brain age of new individuals. Taking advantage of deep learning, Sebastian G. Popescu and collaborators (Sone and Beheshti, 1850) proposed an innovative approach for determining "brain age" based on neuroimaging at a localized level within the brain. In contrast to prior global methodologies, this localized strategy imparts spatial insights into the anatomical patterns of brain aging. By employing brain MRI data from a cohort of 3,463 healthy participants spanning ages 18 to 90, they trained a U-Net model to construct personalized 3D brain age prediction maps. Notably, they achieved heightened accuracy (mean absolute error of approximately 7 years) within the prefrontal cortex and periventricular regions. Additionally, they introduced a novel voxel-wise technique to mitigate age-related biases when forecasting local brain age disparities.

In the review conducted by M. A. Ganaie and colleagues (Ganaie et al., 2023), a comprehensive summary of the diverse clinical applications of brain age estimation in neuropsychiatry and general populations is provided. The authors initiated by introducing common neuroimaging modalities, techniques for feature extraction, and ML models that have been instrumental in devising a framework for estimating brain age. Subsequently, the focus shifted to the noteworthy outcomes of brain age estimation within the realm of neuropsychiatry, alongside the utility of this method in addressing pertinent clinical inquiries within this field.

From the studies discussed earlier, it is evident that the dynamic realm of predicting brain age could lead to certain studies being overlooked or not thoroughly examined because of the review's termination date. Additionally, the process of selecting studies for incorporation into a review entails subjective assessment, which could potentially introduce bias. Different review papers may use varied criteria for evaluating and comparing brain age prediction models, leading to inconsistent assessments. As new studies and models emerge, review papers may become outdated relatively quickly, requiring frequent updates to remain current. Due to space limitations, review papers might not provide an exhaustive analysis of individual studies or methodologies, potentially missing important nuances. Some review papers may focus predominantly on technical aspects without providing a broader context of the implications and real-world applications of brain age prediction models.

In light of these limitations, we have discussed the Brain Age Prediction Using Several Models in section II. Sections III and IV contain a comparison study of different models used for brain age prediction and the corresponding datasets used for the same. Part V summarizes the problems discovered by the models. The efficacy of using brain age as a predictor and classifier for a variety of neurodegenerative disorders has been demonstrated. Part VI discusses the future potential of brain age prediction from MRI data.

2. Survey of models used in brain age prediction and current status

A person's health and sickness can be affected by their brain age in a variety of ways, the potential therapeutic uses for brain age at various patient lifecycle phases are depicted in Fig. 1. The prediction of brain age uncovers a variety of approaches used to gauge an individual's brain age through the analysis of neuroimaging information. These models leverage various machine-learning techniques and imaging modalities to achieve accurate predictions. Here we have utilized the research works of predicting the brain age from the past 11 years, this included various algorithms and methods like Ensemble Methods, Support Vector Regression (SVR), Convolutional Neural Networks (CNNs), and Recurrent Neural Networks (RNNs) for deep learning. Deep learning models have become more well-liked because of their capacity to identify intricate linkages and patterns in data from brain imaging. While SVR provides the ability to tackle nonlinear interactions, linear regression models give a straightforward and understandable methodology. To increase prediction precision, ensemble models mix several different models. Regarding performance, computing needs, and interpretability, each model has its advantages and disadvantages. The study emphasizes the need for thorough assessments and comparisons to determine the best models for brain age prediction, considering elements like dataset characteristics, needs for interpretability, and computing limitations. Such a survey contributes to the growth of this subject and its prospective applications in comprehending brain development and aging processes by offering insightful information on the changing landscape of models employed in brain age prediction. Fig. 2 displays a summary of the machine learning approach used in a simplified study for predicting brain age.

a. Training and cross-validation (CV):
b. Brain age studies often make use of k-fold cross-validation in their training process. This technique involves utilizing a fraction of (k-1)/k from the original dataset for each model iteration. Conversely, a portion of 1/k of the data is set aside as a validation set to evaluate the model's age prediction performance. In every fold of cross-validation, a distinct parameter is tested, which can be employed to fine-tune the hyperparameters of the ML model. The visual representation illustrates a 10-fold cross-validation methodology. b. Testing (optional): An independent dataset is used to test the trained model. An independent dataset enables more accurate model bias estimates.
c. Calculation of brain-age gap: Each subject's brain-age difference is computed as predicted age - chronological age. Reproduced with permission of Baecker et al. (2021) (Tanveer et al., 2023).

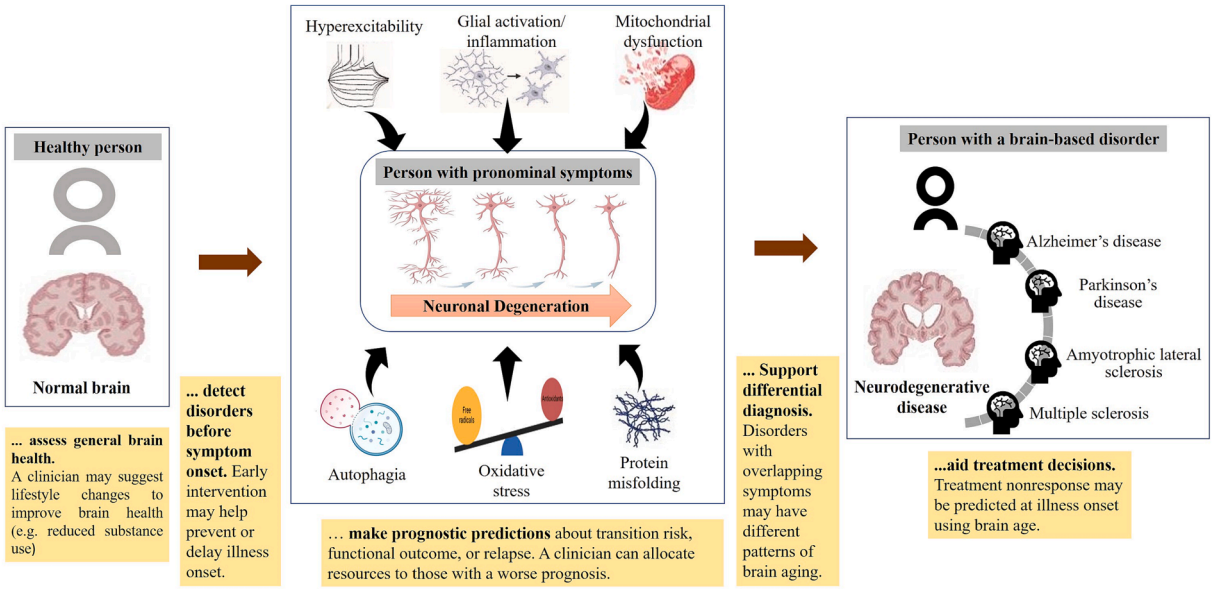

Fig. 1. Potential therapeutic uses for brain age at various patient lifecycle phases.

2.1. Convolutional neural network

With the aid of structural neuroimaging data, age predicted by Convolutional Neural Network (Cole, 2017) could be used to scrupulously arbitrate a human being's brain age. In terms of predicting brain ages, a light-weighted 3D CNN (Peng, 2021) will perform better than a deep CNN. To reckon the contingency of dementia, a deep learning model that incorporates MRI data, as well as the brain age gap or difference, can be employed (Wang, 2019). Most often, linear, and nonlinear models are utilized using a 3D CNN with a simpler model (Herent et al., 2018). Google Research brain team developed a family of Convolutional Neural networks' 2-dimensional models called Efficient Nets (Katia Maria Poloni, 2022) that have improved accuracy and efficiency over ImageNet CNNs. Built on the B0 foundation architecture is this series of networks. While exploring architectures aiming to enhance precision and floating-point operations per second, researchers came across this particular network. Its composition primarily comprises elements derived from the mobile inverted bottleneck convolution, supplemented by the incorporation of squeezing and scaling techniques. Applications for scaling the network simultaneously alter the layers, channels, and resolution using the underlying architecture. Moreover, Efficient Net's base architecture, B0, has fewer parameters and has demonstrated improved accuracy and efficiency. To save computation time and space, a deep 3D-CNN (Pardakhti and Sajedi, 2020) model based on Res Net can be trained with reduced-size data. Using regression techniques like SVR which Support Vector Regression and GPR which is Gaussian Process Regression in place of the Convolutional Neural Network's connected layers can increase system performance. Rather than using the entire 3D structure of the brain, it is feasible to use just a few smaller portions of it. The utilization of residual convolutional neural networks in a deep learning framework (Jonsson et al., 2019), trained on both shallow-based and voxel-based morphometry data along with relationship matrix features, demonstrates enhanced accuracy in predicting brain age compared to alternative machine learning methods. The deep learning approach (Murad and Kwon, 2018) performs better than other machine learning strategies like RVR which is relevance vector machines and another one is GPR which is gaussian process regression. Furthermore, if there is a facund contrariness amid the predicted age from MRI and chronological ages, this model may be utilized to identify subjects with cognitive impairment. The deep learning model had practical value for determining myelination delay (Kawaguchi et al., 2021). Except for one subject with delayed myelination, the model predicted that the age-predicted from MRI images of subjects were younger than the actual age which is based on chronological age. Clarifying a deep learning model's decision-making process is quite difficult. Despite the current shortage of data, an AI model can utilize age-related reduction in brain volume to approximate the age of adult brains. A sophisticated GAP layer, a lightweight full connect layer, and a 3D-CNN with a 1–1–1 kernel size (Rao et al., 2020) are used before output. These thoughtfully chosen combinations transform it into a general-purpose deep learning model that may be successfully applied to any other classification or regression problems. A useful tool for studying neurodevelopmental processes and problems would be this model. The Deep Neural Network (DNN) model we formulated exhibits notable distinctions in comparison to other Machine Learning (ML) algorithms. The reduction in ensemble variability implies that the DNN architecture can offer consistent age prediction even when datasets exhibit uneven age distributions across the age spectrum (Wang, 2023). Furthermore, the DNN models have the potential to yield unique insights into the mechanisms of morphological aging. This is achieved by identifying reliable imaging biomarkers that exhibit limited overlap with the key features selected by alternative methods. In cases where the dataset size is modest, transfer learning emerges as a promising avenue for the application of deep learning techniques, particularly the utilization of 3D Convolutional Neural Networks (3D-CNN), within the realm of medical practice. As a result, it might help with MRI-based assisted diagnosis of brain illnesses.

2.2. Sparse representation method

Substantial proof has been established to confirm the scattered arrangement of pattern representation within the brain. Notably, the activity levels of specific voxels exhibit significant correlations. Given the dispersed nature of aging spatial patterns in the brain, Multivariate Pattern Analysis (MVPA) becomes imperative. In the realm of MRI-based classification and prediction, the selection of voxels holds paramount importance. By reducing the dimensionality of GM concentration data, the classifier's performance can be substantially improved. When voxel correlations carry meaningful information, the traditional univariate voxel selection may not be optimal. This method is especially well-suited for choosing voxels from the GM concentration map, given the scattered nature of aging spatial patterns in the brain. A sparse representation-based multivariate voxel selection technique was developed to identify voxels undergoing age-related changes. Due to factors like noise and

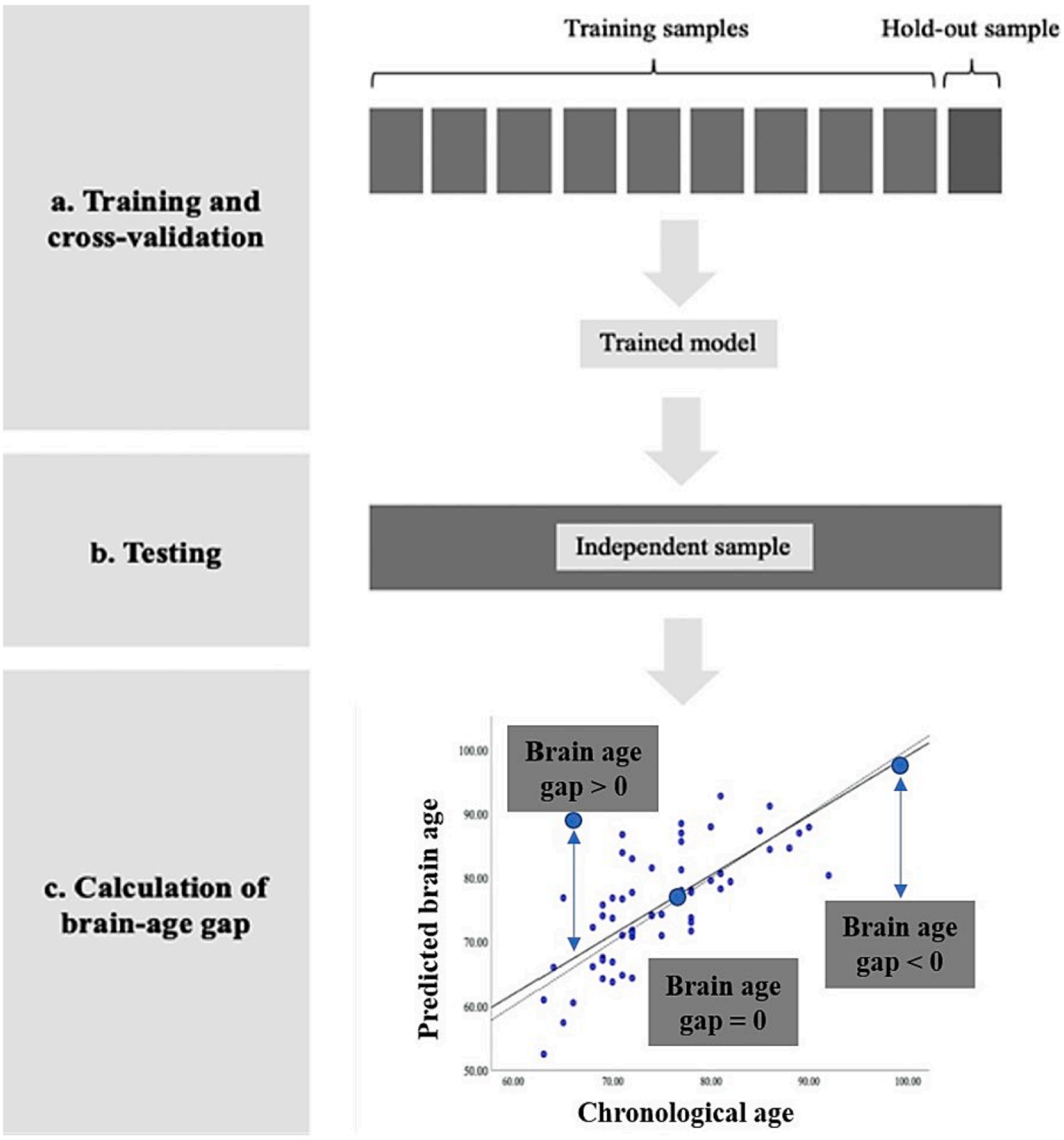

Fig. 2. Overview of the ML method of a simplified brain age prediction study.

inter-individual anatomical differences, only a small subset of voxels demonstrates high discriminative power. Consequently, voxel selection becomes necessary to streamline computational complexity and eliminate redundancy within this high-dimensional dataset. To identify diverse brain regions, one can utilize a sparse-based voxel selection approach (Su et al., 2011). The grey matter concentration map will serve as the basis for age prediction.

The utilization of the sparse representation technique enables the selective selection of voxels, as voxels undergo changes as they mature over time. The sparse representation of signals has garnered significant attention in recent times. An example of its practical application is in underdetermined blind source separation (BSS), a complex scenario that traditional independent component analysis (ICA) methods struggle to handle; here, sparse representation could prove beneficial. Another significant use of sparse representation is BP. It has recently been discovered that it can be used for tasks involving feature selection and detection. Only a small portion of the brain's enormous number of voxels can be used to describe a sensory function. The sparsity demonstrates this. Using sparse representation, we create a voxel combination. Due to its tiny number of voxels, this combination of voxels may efficiently reflect the stimuli. As a result, an effective/sparse representation emphasizes the connections between those voxels in the combination. Those voxels that are chosen via a sparse visualization may be divided into two groups: those whose time series are strongly correlated and those whose time series are weakly linked but contain crucial information. Using common statistical parametric techniques, the initial set of voxels may be located. These statistical parametric approaches, however, make it difficult to identify the second group of voxels. The model chooses which combinations of voxels to use based on the idea of task-sparse representation. Voxel being chosen may be better suited for decoding tasks than GLM models, which do not take task representation into account.

2.3. Cortical structure

It is possible to predict brain age by examining cortical structure (Madan and Kensinger, 2018) utilizing a significant amount of structural MRI data. The three parameters that define cortical morphology are thickness, gyrification, and dimensionality. Using parcellation techniques, it may be determined which cortical structure best predicts a person's brain age. There are no metrics that can reliably identify which people are most likely to be on an accelerated aging pattern, and there is no way to easily distinguish between different age-associated trajectories without collecting multiple MRI scans from the same person.

The initial stage of this study was to determine which parcellation methods and cortical anatomy estimations would be most accurate at predicting a person's years of age. Importantly, rather than just measuring correlations with age, studied age predictions in this research since statistically significant connections are not always suggestive of validity as forecasts.

Another aspect to consider is that the changes in these measures due to age exhibit a nonlinear pattern, wherein the decline in age-related trajectories becomes steeper after specific 'critical ages,' which also differ across various structures. In response to this insight, they utilized an elaborate regression approach based on smoothing splines. These cortical coverings not only enhance the understanding of age-related alterations in gyrification and sulcal breadth, but they also make the extent of individual variations in cortical structure more apparent. Additionally, it can be shown that male brains are typically a little bit bigger than female brains and that as people age, their brains are likely to get smaller.

2.4. High-Resolution pattern recognition

Brain age can be automatically determined because of advanced dimensional pattern recognition (Luders et al., 2016). The brain age index is effectively changed by more complex aging patterns. If the brain age index shows a negative or positive sign, that is indicated by the sign. An artificial intelligence (AI) model is utilized to construct a healthy aging pattern for the brain using regression vector regression (RVR).

The approach efficiently converts the multivariate aging pattern throughout the whole brain into just one score. In this analysis, the valuable measure of projected brain age was employed as the dependent variable to compare different categories. Additionally, an investigation was conducted to determine if there were alterations in the connections between chronological age and estimated brain age over a period of time. These investigations revealed an intriguing discovery particular to the group of individuals who practiced meditation: with each passing year beyond the age of 50, the neurons of meditators exhibited a reduction in growth equivalent to one month and twenty-two days compared to their actual age on the calendar.

The fact that levels in tissues in particular brain areas were greater than what calendar age would suggest could have been one of the explanations for why the high-resolution pattern-based algorithm used to analyze the data indicated younger cognitive ages in meditation practitioners. One of the possible explanations for why the high-resolution pattern-based algorithm used to analyze the data suggested younger brain ages in practitioners of meditation is that the levels of tissue in particular brain areas may have been greater than would be expected based on chronological years.

2.5. Hidden Markov model

A mathematical method for recreating the brain's MRI-based structure is the Hidden Markov Model (Wang and Pham, 2011). To extract useful characteristics from brain MRI, the wavelet coefficient is utilized. The wavelet coefficient is encoded using a vector quantization approach. Intra-cortical tissues, CSF, and grey matter are a few aspects of the brain that might reveal an individual's brain age. By utilizing Kullback-Leibler divergence to assess the similarity between manually constructed Hidden Markov Models (HMMs) of individuals, researchers can ascertain the brain age of the specific individual. In the process of establishing an HMM for the MRI-derived cerebral anatomical model, several statistical considerations come into play. In this context, important features are extracted from brain MRI using wavelet transformation coefficients, which are then employed to construct the HMM for the brain model.

The concealed modes of the HMM are then modeled by coding the wavelet coefficients using a vector quantization approach. The study additionally covers various components of HMM and concludes by providing an overview of the computational approach employed in constructing the HMM for the brain's structural framework based on MRI data.

A common signal processing method used in multisolution analysis and picture reduction is the wavelet transform. It can record data characteristics based on several ranges of frequency. With this method, pictures are instinctively divided into a variety of scales, each of which corresponds to a different degree of brittleness in the data being examined. Discrete wavelet transforms (DWT) is often employed for signal analysis, breaking down initial wave patterns into approximate and oscillatory parts. When defining the distribution structure of brain tissue and cerebrospinal fluid (CSF) in brain MRI, essential characteristics of voxel intensity variation can be derived using DWT, while disregarding overly frequent fluctuations.

The detection and normalization processes may have injected distortion into the extremely high-frequency factors, which the human visual system cannot differentiate. The discrete wavelet transform may be used on several levels of the brain's MRI, such as every single segment of dispersed MRI section and each MRI portion, or the entire volume of the brain. We are interested in learning more about the CSF and brain tissues' regional structures. Additionally, we want to document the slow anatomical modifications to the brain that come with maturing. As a result, they applied DWT to each segment of dispersed MRI slices for each individual.

The DWT's assumption captures the relative position of various tissues in each block of the MR images. For instance, the location of several tissue metrics might change if GM withering occurred in a single block. Consequently, this attribute enables the detection of structural brain modifications that accompany the aging process, and the brain model under development will consistently encompass these alterations. To mitigate the influence of noise and registration errors on the accurate Fourier transform coefficients, we retained solely the wavelet approximation coefficients.

2.6. Multimodal imaging

Cortical structure and functional connections within the brain are harnessed alongside diverse sets of data to enhance the prediction of brain age. The most effective method for this prediction involves a stacked approach utilizing multiple modes. When this multifaceted strategy is utilized, individuals with Objective Cognitive Impairment (OCI) show accelerated brain aging. To assess the accuracy of brain age prediction, the relationship between actual age and projected brain age was scrutinized. The integration of multiple modes is imperative for investigating disorders impacting brain structure and function, as well as for characterizing the process of healthy aging. The potential for further improving age prediction through the utilization of varied brain imaging features is promising. The utility of incorporating multiple modes into age prediction is supported by empirical evidence. Notably, it has been demonstrated that combining imaging data from all 3 modalities—namely, T1- and T2-weighted MRI, along with Diffusion Tensor Imaging (DTI)—resulted in superior prediction accuracy compared to using a single modality. Furthermore, a higher predictive performance than that achieved by individual features was observed when combining T1-weighted features with resting-state functional connectivity features. To anticipate brain age, a combination of resting-state fMRI characteristics, T1-weighted MRI, and DTI data from multifaceted brain imaging approaches has been employed. Building a model from a multimodal perspective (Lin et al., 2019 Jun 25) allows for predictions based on additional data in images since different imaging modalities gather characteristic information related to brain aging from different angles. They can enhance our understanding of brain aging by the synthesis of data from many sources. A typical strategy features superposition for features derived from various modalities. It respects the features of various modes equally, however, when the feature dimensions of various modes are significantly varied, the small-dimension mode's contribution to the model is relatively minimal. There is also

feature fusion, which involves training various models independently before merging them.

The piled-multimodal paradigm outperforms all other models, with the stacked categories performing better than single-source analyses. This model also has the least forecast uncertainty. Moving from the inferior stacked anatomy to the best, stacked-multimodal increases the precision of forecasts by around half a year. The multimodal technique also exhibits reduced variation in prediction accuracy. It is assumed that the increase in prediction accuracy is due to both the reduction of measurement inaccuracies in brain data and the reduction of common variance among the various brain imaging modalities as well as the inclusion of fresh data. It has been demonstrated that using Random Forest methods to combine data from several neuroimaging resources works effectively. For instance, using RF models to aggregate data produces higher age prediction accuracy than just combining estimates from different sources.

In individuals experiencing cognitive disorders, the utilization of this comprehensive approach accelerated the estimation of brain age. Predictive algorithms have the capacity to apply their knowledge to novel datasets, particularly when trained on extensive and varied information sources. It's crucial to highlight that brain-based age prediction is not influenced by head mobility. With the use of cross-validating models with 10 folds and the characteristics retrieved using the technique of hierarchical clustering, it was possible to estimate each person's brain age in many ways and with different emphases on different modalities. A correlation study for predicted vs actual ages was conducted to look at the precision of the prognosis. Although the fMRI model exhibited limited prediction reliability, the modality-specific grey and white matter models demonstrated comparable performance. This indicates that metrics related to connectivity had a weaker correlation with actual age compared to structural metrics.

2.7. Resting-State functional connectivity pattern

By employing resting-state fMRI (rsFMRI) data, functional connectivity has the potential to accurately estimate brain age, as suggested in reference (Li et al., 2018). It enables research into how the brain develops as well as several illnesses that have an adverse impact on neuropsychiatry. To combine FC data into a prediction of brain age, subject-specific ICNs which are known as Intrinsic Connection Networks, and measurements based on the voxel of each Intrinsic Connection Network can be used.

The simplicity of rsFMRI data makes it possible to precisely determine the brain age of various subjects. Initially, they detect subject-specific sparse intrinsic connectivity networks (ICNs) from rsFMRI data, using a combination of positive matrix factorization techniques. These identified ICNs are both subject-specific and nonnegative, and they focus on maintaining sparsity. Subsequently, they calculate whole-brain voxel-wise functional connectivity (FC) measurements. While this method prioritizes specific positive ICNs, it does come at the expense of sacrificing inter-subject coherence. To compute the voxel-wise FC measurements, they determine Pearson correlation values between the respective time courses and voxel-wise rsFMRI signals across the entire brain for each ICN identified through subject-specific ICNs. These correlation values are then transformed into Fisher's z-scores. This procedure enables the derivation of both local and distant FC measures for every individual ICN.

2.8. TSAN model.

Utilizing T1-MRI data, the two-stage-age network (TSAN) (Liu et al., 2020) has the capacity to precisely ascertain the brain age of individuals without medical conditions. This network has brought forth various innovative aspects in the realm of predicting brain age. It initiates by evaluating the overall brain age prior to making a more precise age prediction. As TSAN operates as a sequential network, it allows for an accurate estimation of brain age by building upon the initial approximation of the brain's age. The fact that gender labels are considered in addition to MRI for better prediction is unusual in this case. In a more comprehensive explanation, the initial model computes an estimated brain age, while the subsequent stage system refines this estimation into a more accurate brain age by utilizing the transformed approximation from the first stage. Given that gender is a piece of well-known screening information about them, the biological sex label is employed as a parameter for both of the systems. In all stages, visualizations of features of various sizes are combined utilizing sparsely linked routes in a new scaled dense network architecture. Two supplementary ranking losses are introduced to enhance the regularization of the learning process, alongside the commonly used mean square error loss. The initial disparity in ordering for each of the two sets arises from the mean square error across differentiation in chronological and estimated ages. The subsequent loss in ordering for a collection of samples is gauged by evaluating the spearman correlation coefficient between chronological and predicted ages. A linear regression model is employed to counteract bias and refine the estimation of brain age. We show that, despite bias adjustment, the estimated age via TSAN has a reduced MSE and an improved categorization result. In contrast to the more sophisticated Dense Net, they do not investigate feature maps of various sizes. Without employing any ranking loss for a collection of samples, they merely consider the MAE deficit associated with the projected and real ages of each person in the specimen. However, a decent approximation entails both a small ranking attrition for an entire set of samples as well a low MAE reduction between individual samples. Additionally, the rank correlation spearman's factor, which wasn't previously considered in instruction, was one of the assessment factors for PAC-2019.

Individuals frequently ignore biological gender designations on MRIs, even though men and women possess distinct brain architecture and experience aging in different ways. The suggested TSAN is a unique 3D convolutional neural network with a two-stage cascade structure for brain age estimate from MRIs, in comparison to existing brain age estimation techniques.

The first-stage system only requires a rough estimate because of the level of discretization in the first-stage net. The first-stage network then subtracts the discretized output brain age from the second-stage network's estimation of the remnant age. They discovered that doing so yields more favorable empirical outcomes than using the conventional cascade structure of networks without discrepancy and a remaining path. Following bias revision, the suggested ensemble TSAN often produces the highest possible categorization outcomes with respect to AUC, precision, sensitivity, and range. It demonstrates that cerebral age is a promising biomarker for the initial stages of risk for dementia testing or dementia categorization.

2.9. Deep learning with handcrafted data

The effectiveness of deep learning for the task of age prediction can be improved by including context data, such as volumetric estimates of significant anatomical structures (Bermudez et al., 2019). This is an age prediction method that is more precise. The approach of combining deep learning with anatomical, hand-crafted features generalizes to orbital CT and is not restricted to brain MRI. There is a novel age estimation biomarker, Orbit BAG, based on orbital CT.

Self-optimized CNN models produce more accurate brain age predictions in comparison to MLP models using morphological hand-crafted features (Mouches et al., 2022) After performing an extensive analysis of the value of including morphological hand-crafted features for the brain age prediction task as opposed to using imaging data. By doing this, it may be possible to enhance the brain age gap biomarker's quality and its capacity to detect biologically significant departures from typical brain aging patterns. The findings of the current investigation show the advantages of employing a variety of data sources to provide input for the brain's age-forecasting job. By doing this, it may be possible to enhance

the brain age gap biomarker's reliability and its capacity to detect physiologically significant departures from typical brain aging trends. Additionally, connections between the brain's age difference and variables influencing trends in typical brain aging should be carefully understood. The current results show that these relationships depend on the facts that the data include as well as the data pretreatment techniques. Therefore, combining clinical expertise with cutting-edge black-box deep learning techniques should aid in retrieving more diverse data and, as a result, construct superior brain aging simulations.

There are a few restrictions on this investigation that need to be made clear. In the beginning, cross-sectional data and cardiovascular risk variables that have been collected at a single moment in life were employed in the present investigation. Nevertheless, the length of exposure to risk variables may have a significant influence on the BAG. Therefore, considering historical information might potentially show if alterations in the brain brought on by exposures to risk factors are transitory. Additionally, the current research was restricted to a review of certain risk factors for cardiovascular disease. Prospective studies ought to take into consideration the BAG biomarker's associations with more varied elements, including genetics and medical records that have been demonstrated to be related to it. Next, there are still certain restrictions on how fairly the simulations were compared.

2.10. Sparse group Lasso (SGL) + Gaussian process regression (GPR)

Cortical thickness data can be used to predict brain age by first using Sparse Group Lasso (SGL) (Aycheh et al., 2018) to choose out the core aspects from each major cortical lobe, and then GPR to fit the age prediction model. Each cortex lobe may experience a different rate of cortical thickness loss. Healthy brain-change patterns within the corresponding cortical lobes are linked to human aging. The SGL method of regularized regression for grouped variables supports feature selection at both the group and intragroup levels. In terms of feature selection, SGL is strong and reliable. In order to choose explanatory features on and within the cortical lobes, SGL is a suitable method. Based on the chosen features, GPR, a non-parametric, non-linear regression technique, predicts the brain age of the target subject.

The impact of SGL is scarce both between and within groups. Sparseness is a characteristic of mechanisms of learning that arises when just a tiny portion of the model's parameters are non-zero. Because just a portion of the basic characteristics is necessary to create a model that fits the real-world situation the best and generalizes effectively to test examples, the vast majority of real-world issues may be sparsely represented. Regularization techniques are typically employed to keep the algorithm's sophistication at a manageable level in order to avoid the issue of excessive overfitting.

A small number of groups connected to the answer parameter are generated using the Group Lasso. In other words, if an assortment is chosen in the framework, then all of the unit's indices are non-zero. To choose those that are significant factors among and between sections, SGL integrates Group Lasso and Lasso techniques. Because just a tiny portion of the SGL's generating factors are non-zero, the most significant features exhibiting non-zero components can be routinely chosen. As a result, it provides just one structure that allows both picking features and regression factor computation simultaneously. In the suggested method, we classified the cortex's organization into major categories based on the frontal lobes. We may utilize GP in an inference scenario known as Gaussian Process Regression since it can be used to represent odds across any type of variable. An informal regression model based on the Bayesian method is called GPR.

Local patterns of covariance between specific locations can be seen in multivariate GP. Additionally, GP's use of numerous Gaussians makes it more adaptable than parametric simulations and can simulate non-stationary connections.

GPR has already shown that it can accurately identify age given T1-MRI scans obtained by voxel-based morphometry. The primary selling point of SGL is how well it can choose traits at both the on-group and within-group planes. The SGL advantage is achieved most effectively by arranging brain components following cerebral regions. The SGL and GPR composite model's conclusion as a whole indicated a little boost beyond GPR. Additionally, numerous crucial cortical areas can be determined using SGL. Resampling was utilized in the present investigation to confirm the coherence of the SGL feature selection. To test the predictability of the SGL model, we educated it using 10 distinct randomly chosen pairings from the data we had available.

When paired with GPR, the piled auto-encoders sophisticated automated feature-learning capabilities also produced equivalent results. Overall, the evaluation of this study demonstrates the value of methods for choosing features for developing generalizable surface-based cerebral age models for forecasting.

2.11. Heteroscedastic noise model

A Gaussian conditional likelihood was used to model heteroscedastic aleatoric uncertainty. To consider aleatoric uncertainty for global and regional age estimation, a heteroscedastic noise model (Hepp et al., 2021) was implemented. For the automatic estimation of global and regional age, a supervised DL-based strategy utilizing a 3D-CNN can be used: The entire brain can be trained on down-sampled images to estimate age globally. This model provides a high accuracy of the trained model with a mean absolute error of about 3 years, which is consistent with earlier work on DL-based brain age estimation on MR images. Young subjects' brain ages were found to be slightly overestimated.

The age descriptor is inevitably vulnerable to contamination because of physiological fluctuation since the age in years is not precisely stored in the picture (aleatoric ambiguity). This implies that even for extremely identical photographs, the chronological age might vary. Because the level of noise varies depending on the topic in question, it must be simulated using an eclectic approach. Due to endogenous fluctuation, strictly deterministic strategies do not permit relating the error in forecasting to aleatoric ambiguity. Due to the possibility that hidden noise contributes to the estimate's inaccuracy, this could end up resulting in significant misconceptions. Merely some studies have so far looked at the idea of uncertainty for an estimate of age.

In this paper, a DL model for MR-based age assessment using T1-weighted cerebral scans gathered from the GNC is being proposed. To consider aleatoric variability for universal and localized age estimates, a heteroscedastic noise model was constructed. Grad-CAM technology maps of saliency are used to display the importance of different brain areas.

2.12. Decentralized or federated algorithm

Decentralized (or federated) algorithms (Basodi and "Federation of Brain Age Estimation in Structural Neuroimaging Data,", , 2021) are those that don't require the data to be assembled in one location. Decentralized algorithms are especially vital when it comes to performing analysis on huge data sets involving various global datasets without having to worry about data transmission or violating privacy. Decentralized algorithms are a popular subject for studies because they have been successfully applied in numerous fields. Prediction models with decentralized processing perform similarly to centralized processing. Only the data required to train a model is shared, as opposed to the entire set of data; this keeps the data secure at the local sites while also enhancing the model's ability to predict the future. At the main site, data is gathered to create an aggregated model from data sent from local sites. Estimating brain age is a popular method for determining how different neurodegenerative or neuropsychiatric brain problems affect the progression underlying brain growth.

According to recent studies, data from neuroimaging may be used to estimate brain age since it records the changes in structure and function that the brain goes through as it develops and ages. A reliable model for

predicting brain aging can aid in not merely the early identification of neurological conditions but also in the tracking and assessment of therapeutic outcomes. Investigators frequently have restricted possession of information about the brain owing to its challenging and costly gathering method, although having accessibility to vast volumes of data helps construct better models and confirm their efficacy.

Due to laws regarding privacy, this sort of information is not usually accessible to others. Decentralized approaches offer a solution that eliminates the need for data sharing across many relevant entities. Throughout this study, they suggest a decentralized method for estimating brain age and then validate the hypotheses using structural magnetic resonance imaging data characteristics. Results show that when juxtaposed with systems developed from all of this information in one place, our decentralized brain age prediction performs similarly.

2.13. Extreme learning Machine (ELM) framework

A classifier using a single hidden layer feedforward neural network is the ELM framework. Since all weights are set at random in ELM (Kassani et al., 2020), there is no need to learn weights from the input layer to the hidden layer. To predict brain ages, this framework learns informative features from functional connectivity measurements derived from fMRI scans of adolescent brains. Important features can be distinguished, and multimodal data can be integrated, using ELM. According to recent research, using combinations of FCs from various fMRI modalities enhances the performance of brain age prediction. Since every weight in ELM is assigned at random, there can be no requirement to transfer proportions from the layer that supplies input for the layer that is concealed. Three successive phases make up the suggested RES-ELM. To minimize the number of dimensions of the data, the first stage uses a total of three sets of fMRI paradigms to perform group-level component analysis independently. Based on the ICA temporal instruction, each individual's FC is then calculated. The neural network's structure is sacrificed in the following stage to prioritize remaining errors. The remaining error of neurons that are concealed rankings are calculated to do this. We may rank neurons that are concealed using the individual neuron's remaining error rates in this method.

A network's secret neurons as well as information dimensionality are pruned in the third stage. To predict brain ages, ELM is suggested to learn instructive characteristics from network connectivity measurements acquired from fMRI images of teenage brains. A novel method of learning features is offered as a result of the suggested RES-ELM, which makes use of the minor mistakes ignored during RSS reduction. Additionally, there are many characteristics in the categorizing tasks examined in this paper, but barely any of those characteristics are helpful for gaining knowledge.

The practical and scientific results demonstrate the capability of RES-ELM to distinguish critical characteristics and integrate multimodal data. According to recent research, using multiple FCs across several fMRI paradigms enhances the accuracy of cerebral age forecasting. The findings show that using many modalities increases the accuracy of neural age categorization. The findings indicate that only SBELM can compete against RES-ELM in terms of testing precision, which has greater advantages than any of its peers. RES-ELM achieves an outstanding overall mean reliability across all single-modal contexts and multimodalities.

2.14. Brain functional networks (BFNs)

Assuring the non-negativity of connections between brain functions, the BFNs (Han and Ge, 2023) created using the NBDR (Nonnegative Block Diagonal Representation) method were sparse, modular, and adjacent. A node's association with every other node is considered simultaneously by the BFNs method that was adopted. In addition to sparsity and modularity, the BFNs estimated by the NBDR method also take adjacency into account. It is easier to interpret functional connections because the BFNs that were generated were nonnegative. Community structure along with other graph-based metrics work together to extract features that fully describe the characteristics of BFNs. The thorough features produced encouraging outcomes in brain age prediction at various scale levels. The prediction did well even when the strength of each community was used as a feature.

Brain functional networks (BFNs) and machine learning have been shown through research to be effective approaches for estimating cognitive age. Many research investigations, nevertheless, fail to consider the crucial BFN neurological features and social structure changes in normal aging brains. Due to this problem, researchers created a unique method using resting-state functional magnetic resonance imaging to forecast brain age. Initially, developed a unique BFNs framework employing the non-negative block diagonally representation (NBDR) with blocks longitudinal matrix-induced regularization, which was driven by the fact that the brain is organized with sparsity, modularity, and various other features. Furthermore, a micro-scale network organizational layout together with modest and massive topologies of networks was employed as characteristics to determine the level of individual community assets using collectively compact asymmetric positive matrix factorizing. Lastly, a system for machine learning built around the retrieved information was used to estimate brain age employing 6 distinct algorithms.

The unique BFNs technique outperformed previous comparison techniques in connection, according to findings from experiments on both generated and actual data, and the parameter collection strategy suggested did well in forecasting brain age. The process of typical brain aging may be understood with the use of the aforementioned investigation's fresh insights regarding the creation of BFNs and the identification of features of neurological signals.

2.15. Machine learning models

The majority of research on brain age prediction employs supervised machine learning techniques (Baecker et al., 2021), which means that the models are first trained on labeled data (i.e., the subject's MRI scan is associated with their chronological age) and then applied to a test dataset without labels to see how well they predict the brain ages of unseen subjects. Most of these models employ regression analysis, where the dependent variable is chronological age, and the independent variables are anatomical brain characteristics. Generally, the complexity and computational capabilities of machine learning models for brain age prediction vary. To predict brain age, a variety of Machine Learning (ML) methods (Niu et al., 2020) have been employed, including support vector regression (SVR), Gaussian process regression (GPR), relevance vector regression (RVR), ridge regression, and elastic net. Overall, the performance of these ML models for age prediction was comparable. With regards to the prediction of the motor and cognitive scores using aspects of resting-state functional connectivity, it has been demonstrated that SVR, RVR, ridge regression, and elastic net performed equally. While many machine-learning algorithms can provide precise age, estimates based on brain features, there is a large amount of heterogeneity in model performance reported between research. Recent research has demonstrated that ML systems are highly accurate at predicting age from MRI data. The size and age range of the training and test sets, along with variations in feature sets, can cause a great deal of variation in model performance measures between studies. The gradient tree boosting-based XGBoost regression approach can be used to determine the global brain age. Several recent brain age studies (de Lange et al., 2022) have employed XGB and found it to perform exceptionally well.

A popular technique for building forecasting models is Support vector regression (SVR) (Lin et al., 2019 Jun 25), which can produce high-precision forecasting even with a small training sample size. SVR (Da Costa Pedro et al., 2020) is a supervised learning model that minimizes the sampled points' distance to a tolerance margin around the

fitted hyperplane to fit a regression to the training data. This technique is sparse, which means it can predict data that hasn't yet been observed by using information from only a few data points (support vectors). This makes handling datasets with a lot of data points easier. In order to represent the relationship between the independent variables and the target variable, one simple parametric modeling strategy is called linear regression (LR) (Da Costa Pedro et al., 2020). By changing the weights to fit a linear equation to the observed data, it achieves this. An issue with this model is that LR expects a linear relationship between the independent factors and the target variable, even though the input brain data for this model is very nonlinear regarding the dependent variable, age. The simplicity, clarity, and analytical solution of this modeling approach are its key benefits.

GPR (Da Costa Pedro et al., 2020) is a non-parametric modeling strategy that resolves regression issues through the use of Bayesian inference. This is accomplished by learning a Gaussian process (GP) prior-based probability distribution of potential target values that utilizes prior space information. A mean function and a covariance function, often known as a kernel, are used to specify the GP. Brain Age Gap, which is determined after analyzing brain age, can be utilized as a biomarker to compare people with Parkinson's disease and Alzheimer's disease. The gap between chronological age and age inferred from brain MRI can be determined using T1 weighted MRI data and advanced machine learning methods. According to studies (Beheshti et al., 2020), people with Parkinson's disease (PD) may have a larger age difference between the white and grey matter of their brains. When compared to PD participants, the white matter and grey matter age gap in AD subjects is significant. The brain ages of healthy people might be automatically examined using T1-MRI and RVM-based regression (Franke et al., 2010).

2.16. SFCN model

The architecture (Peng, 2021; Wang and Pham, 2011; Holm et al., 2022), which is based on VGG Net and uses a completely convolutional structure, to reduce the number of parameters to about 3 million, keeps the number of layers as low as feasible, which in turn lowers computational complexity and memory cost. This simple design beyond an utterly connected layer produces less constitutive and superior outcomes to elaborating models. The impetus behind the lightweight model performing better than the elaborate ones is an intriguing question. One realization is that classification tasks in medical imaging applications only involve a small number of echelons, negating the necessity for a broad utterly connected layer. Regarding neurological information, deep learning offers enormous promise for precise illness prognosis; however, the effectiveness of the forecast is frequently constrained by the quantity of its training collection and the storage needs of the computing device. To solve this, research suggested utilizing T1-weighted structural scans to accurately estimate brain age using a deep convolutional neural network architecture called the Simple Fully Convolutional Network. Since SFCN has a smaller number of parameters than other well-known deep network designs, it is better suited to smaller file sizes and 3D volumetric data.

In order to improve effectiveness, the creation of networks was integrated with several approaches, involving data supplementation, preliminary training modeling regularization, model outfit, which consisted of and forecast bias reduction. A complex structure made up of a series of basic elements is provided by the popular CNN framework VGG net and its variation with Batch Norm stacks. Before any Max Pool layer, the network layer SFCN only stores one conv-layer to conserve capacity. Additionally, we get rid of every entirely linked layer, which drastically cuts down on the total number of parameters but also creates a completely functional framework that can handle a range of data quantities.

The highest possible MAE is obtained by the SFCN system after training with a dropout layer and information augmentation. The constructed models use one of the three normalization strategies—dropout, pixel transferring, or mirroring in an attempt to explore the effects of these approaches.

2.17. Deep learning and multiplex networks

A multiplex network (Amoroso et al., 2019 May) has multiple layers. The nodes in a multiplex are different anatomical regions of the brain, and the connections between them are determined by how similar the regions are to one another. In terms of intrinsic information, multiplex networks offer an advantage over single networks, as evidenced by recent studies. In actuality, a multiplex's instruction innards are not only the total of the instruction contained in each of its layers. Multiplex networks can be distinguished from regular networks by appropriate metrics; thoroughly, we leverage nodal attributes to build a feature depiction of a brain and then use this scheme to input a deep learning model to forecast the age. Standard machine learning techniques like Random Forest Algorithm, Lasso regression, Ridge Regression, and SVM cannot accurately simulate the intricate interactions involved in this brain description; in leu, a deep neural network could be employed. Latest research has shown that concerning inherent knowledge, multiplex networks are preferable over individual systems because the knowledge capacity of the multiplex is not merely a compilation of the material quality of its segments. They leverage topological attributes to generate a characteristic depiction of a brain and subsequently use that structure to input a deep learning algorithm to estimate the neural network's age. As for standard networks, multiplex networks may be characterized by pertinent measurements in specific. Utilizing a deep learning simulation efficiently and considerably maximizes the informative potential of multiplex features. The left hemisphere of the cerebral cortex is where the suggested technique places the brain areas most responsible for aging. The outcomes reported are encouraging, but more information would significantly enhance the research's numerical resilience and would be crucial for an equitable comparison alongside comparable investigations when it comes to prediction preciseness. Therefore, additional research involving more respondents needs to be conducted.

Subsequently found that the degree of heteroses has a significant impact on cerebral aging, and research studies looking into life expectancy interprets must adequately take into consideration this effect. Specifically, the greatest decline in the accuracy of forecasting was discovered in the chronological range of 30 to 70, which would indicate the significant degree of specificity and fluctuations that characterize brain decline during this period.

Still, to support this idea, more research that goes beyond the scope of the current study will be required. A complicated network is made up of two separate sets: a set of vertices and a collection of interconnections. The components of the network that are being modeled are called the nodes, and their interactions are called the connections. The physical component of the connections is not taken into consideration by the aforementioned basic architecture; balanced connections are established to account for this feature. To identify an ordered system, an additional collection of components is allocated to it. These elements are referred to as loads and often take the form of either actual or integer quantities. Loads indicate the intensities of every relationship amongst nodes in the network.

2.18. Bias-adjustment scheme

The proposed strategy to address bias involves using a linear regression model's slope and intercept, derived from brain age delta and chronological age data in the training set, with chronological age acting as a control. This relationship is explored within a 10-fold cross-validated training set, showing that the model's predictions can either overestimate (false positive) or underestimate (false negative) actual brain age by around + 16 to 17 years, as indicated by the linear regression line connecting the two variables. To counteract this bias in

samples with a known age Ω, an adjustment is calculated: Adjustment Ω $= +\alpha\beta$, where α and β are the slope and intercept of a linear regression model linking brain age delta and chronological age from the training set. By subtracting this adjustment from the estimated brain age, a more accurate and unbiased brain age value is obtained for each analyzed sample (Beheshti et al., 2019).

Iman Beheshti and colleagues (Beheshti et al., 2019) highlighted the connection between the accuracy of forecasting brain age in estimation frameworks and the dependability of statistical inference via regression models. Their study introduces a straightforward yet impactful method for mitigating prediction bias in Brain-age estimation frameworks. This method involves incorporating chronological age during training to counteract bias. Integrated into a machine learning-based brain age framework, this bias-mitigation technique utilized a comprehensive dataset of metabolic brain features from 675 cognitively healthy adults. The resulting Brain-age estimation framework demonstrated notable robustness. Testing across distinct groups—75 cognitively normal adults, 561 mild cognitive impairment patients, and 362 individuals with Alzheimer's disease—revealed that the proposed technique achieved a strong correlation (R2) of 0.81 between chronological age and predicted brain age. Applying the method to an independent group of 75 cognitively healthy adults resulted in an impressive mean absolute error of 2.66 years. Without bias adjustment, the R2 decreased to 0.24, and the mean absolute error increased to 4.71 years. Simulations further underscored the approach's effectiveness in reducing prediction errors, particularly in clinical contexts.

2.19. 3D patch technique

Recent years have seen considerable breakthroughs in the field of brain age estimate and neuroimaging, and researchers are always looking for new ways to improve accuracy and resilience, especially when working with small sample numbers. While conventional methods have offered useful insights into predicting brain aging, the introduction of newer methodologies has opened up fresh research directions. The 3D patch approach is one such method that has attracted interest and shows promise in resolving issues brought on by small sample numbers. In an effort to improve brain age estimate, researchers have explored patch-based techniques. These methods, which deviate from traditional approaches, are exemplified by significant studies like (Beheshti et al., 2019 Aug); (Beheshti et al., 2020). These approaches make use of regional patterns and variances by segmenting brain pictures into smaller, more manageable regions, providing more precise and nuanced age forecasts. The use of patches not only makes it easier to handle small sample numbers, but it also improves the models' capacity to adapt to individual variances and particular brain areas.

It is essential to thoroughly analyze and contrast these new patch-based techniques with established ones in the context of the examined literature. Each approach has its own set of benefits and drawbacks, necessitating a thorough analysis. Although the 3D patch approach shows promise for addressing the problems associated with the scarcity of data, its computing requirements and possible sensitivity to patch selection highlight the need for careful thought. The patch-based tactics, on the other hand, excel at capturing fine-grained local fluctuations, whereas established approaches may give stability and generalizability. Furthermore, the inclusion of longitudinal reliability evaluation, as noted in "Patch-wise brain age longitudinal reliability," is a significant advancement in improving the validity of brain age forecasts across time. This dimension gives the evaluation of these strategies a time component and sheds information on their consistency and effectiveness during various stages of maturity.

In this survey paper, we aim to provide an inclusive overview of the diverse landscape of brain age estimation methodologies, encompassing both traditional and emerging patch-based approaches. By critically examining the strengths and limitations of each technique, we endeavor to guide future research directions and inspire the development of innovative strategies that harness the power of patch-based procedures while addressing their inherent challenges. As the field continues to evolve, the insights gained from this comprehensive survey will undoubtedly contribute to advancing the accuracy, reliability, and applicability of brain age estimation across various contexts and populations.

3. Comparative study

Predicting brain age using various models has been a topic of interest in neuroimaging research. Several models have been employed, each with its advantages and limitations. The availability and caliber of the data, the computing capabilities, and the particular research goals all play a role in the model selection process. Deep learning models, such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs), have demonstrated remarkable proficiency in extracting detailed patterns from brain imaging data. RNNs can capture temporal relationships in sequential data, whereas CNNs are excellent at automatically extracting hierarchical features from pictures. These models have the ability to handle complicated interactions in the data, but they could need a lot of annotated data and a lot of computing power to be trained. Linear regression-based models provide a simpler and more interpretable approach. A linear combination of chosen characteristics is used to estimate brain age. The contribution of certain attributes may be understood using linear regression models, which are computationally efficient. The nonlinear linkages and intricate exchanges that the data contains, however, may be difficult for them to grasp. SVR, or support vector regression, is another prominent method for estimating brain age. Finding the best-fitting hyperplane while minimizing errors is the goal of SVR. It uses kernel functions to handle nonlinear interactions. SVR can efficiently describe complicated data variations and is resilient to outliers. It can be computationally significant for large datasets and may be sensitive to parameter adjustment. The predictions of various models are combined in ensemble models, such as random forests or gradient boosting, to enhance overall performance. These models can lessen the chance of overfitting by utilizing the advantages of various methods. Although ensemble models are reliable and adaptable, their implementation may be more difficult and need careful optimization. The quantity and quality of the dataset, the available computing resources, and the specific study objectives all have a role in the model for estimating the brain age that is chosen. Deep learning models have great performance, but they also need a lot of data and processing power. Although they offer interpretability and computational efficiency, linear regression, and SVR models may have trouble understanding complicated interactions. By integrating several techniques, ensemble models can provide increased accuracy.

Furthermore, ensemble models, which incorporate the predictions of many models, have demonstrated promise in enhancing prediction precision. When choosing the best strategy for forecasting brain age, it is crucial to consider the interpretability, generalizability, and computational viability of various models. To progress the area of brain age prediction and its possible medicinal purposes, future studies should concentrate on overcoming issues with data heterogeneity, model interpretability, and transferability across populations. Table 1 presents a thorough analysis of previous brain age prediction methods, along with their respective MAEs (Mean Absolute Errors) and correlations between anticipated and actual ages.

Table 1 presents a thorough analysis of previous brain age prediction methods, along with their respective MAEs (Mean Absolute Errors) and correlations between anticipated and actual ages.

4. Datasets

The typical benchmark dataset for the brain age detection approach is a specific subset of publicly available datasets. The most common datasets are ADNI, PNC, PAC 2019, IXI, ICBM, OASIS, BANC, NKI-RS, DLBS, ABIDE, CoRR, UK Biobank, and PPMI. These datasets were

Table 1
Comparison of different models used for predicting brain age.

Sl. No.	Reference Paper	Published Year	Models Used	Mean Absolute Error	Correlation (*represented as "r")
1	Ziegler S et. al. (Franke et al., 2010)	2010	Support Vector Regression and Relevance Vector Regression (RVR)	5 years	r = 0.92
2	S. Wu et al. (Lin et al., 2016)	2016	Back Propagation Artificial Neural Network improved by Hybrid Genetic Algorithm (GA) and Levenberg-Marquardt (LM) Algorithm.	4–29 years	r = 0.8
3	Cole et. Al. (Cole, 2017)	2017	CNN	Grey Matter data: 4–16 years, raw data: 4–56 years	Grey Matter data: r = 0.96, raw data: r = 0.9
			GPR (Gaussian processes regression)	Grey Matter data: 4–66 years	Grey Matter data: r = 0.95
4	Y. Fan et al. (Li et al., 2018)	2018	Deep Convolutional Neural Network.	2–15 years	r = 0.614
5	Seong J-K, et.al. (Aycheh et al., 2018)	2018	SGL + GPR	4–05 years	_
6	Shikha Chaganti, et.al (Bermudez et al., 2019)	2019	Deep convolutional networks	Volumetric features:8–23 years Raw images:5–00 years Combined features:4–08 years	Volumetric features: r = 0.84 Raw images: r = 0.95 Combined features: r = 0.97
7	Bjornsdottir et.al (Jonsson et al., 2019)	2019	3D CNN	IXIdataset: 4–14 9 years UK Biobank:3.631 years	IXI dataset: r = 0.907 UK Biobank: r = 0.614
8	Sheng Ge et.al (Han and Ge, 2023)	2019	OLR (Ordinary Linear Regression) SVR (Support Vector Regression) Lasso Regression	14.2 years 0.753 years 0.817 years	0.668 11.4 9.2
9	La Rocca M et.al. (Amoroso et al., 2019)	2019	Deep Neural Network	3.7 ± 0.2	0.43 ± 0.02
10	J. Wang et al. (Wang, 2019)	2019	Convolutional Neural Network, Logistic Regression	4.45 years	r = 0.85
11	Qiang Luo et.al. (Ren et al., 2019)	2019	3D CNN SVR RVR	4.20 years 3.32 years 3.48 years	_ _ _
12	Pardakhti et.al. (Pardakhti and Sajedi, 2020)	2020	3D CNN	5 years	_
13	A. Li et.al. (Rao et al., 2020)	2020	CNN	1.89 years	_
14	Dafflon Jessica et.al. (Da Costa Pedro et al., 2020)	2020	shallow machine learning methods	3.7597 years	_
15	Lange et.al. (de Lange, 2020)	2020	XG Boost regressor.	Multimodal = 3.37 GM = 3.60 WM = 3.51 Functional Connectivity (FC) = 4.18 External GM = 10.69	r = 0.55 r = 0.46 r = 0.49 r = 0.04 r = 0.45
16	H. Matsuda et.al. (Beheshti et al., 2020)	2020	Multivariate Machine Learning Methods	GM = 3.60 WM = 4.85	r = 0.92 r = 0.91
17	J.Zhang et. al. (Liu et al., 2020)	2020	Convolutional Neural Network	2.428 years	r = 0.985
18	W. Gong et.al. (Peng, 2021)	2021	SFCN	2.14 years	r= <0.1
19	Hepp T et.al (Hepp et al., 2021)	2021	Regression model based on 3D CNN	3.2 years	r=<0.001
20	Hiroyuki Kidokoro et.al. (Kawaguchi et al., 2021)	2021	Convolutional Neural Network	1.4 months	r = 0.97
21	Luca Marzano et.al. (Bellantuono et al., 2021,117458)	2021	Structural connectivity using AI	2.19 years	r = 0.89
22	Monaco A et.al. (Lombardi et al., 2021 Jan)	2021	Deep neural networks	4.6 years	r = 0.98
23	Mouches Pauline et.al. (Mouches et al., 2022)	2022	CNN MLP	T1 w MRI:4.20 years TOF MRA:9.52 years	_ _
24	Ricardo José Ferrari et.al. (Katia Maria Poloni, 2022)	2022	CNN	3.31 years	r = 0.95
25	Rokicki et.al. (de Lange et al., 2022)	2022	XG Boost regression algorithm	UK Biobank dataset: 2.933 ± 0.011 Cam-CAN dataset: 5.924 ± 0.171	UK Biobank dataset: 0.900 ± 0.001 Cam-CAN dataset: 0.927 ± 0.005
26	Esten & Becket (Holm et al., 2022)	2023	CNN	1.4 years	_
27	M. A. Ganaie et al. (Ganaie et al.,April, 2023)	2022	Improved least squares twin support vector regression (ILSTSVR)	2.1 years	r = 0.97
28	Iman Beheshti et al. (Beheshti et al., 2022 Feb)	2022	T1-weighted voxel-wise and region-wise metrics	4–63 years	–
29	Iman Beheshti et al. (Beheshti et al., 2022 Apr)	2022	Quadratic Support Vector Regression algorithm (QSVRA) & Binary Decision Tree algorithm (BDTA)	QSVRA: 4–63 years BDTA: 7.14 yrs	QSVRA: 0.88 BDTA: 0.76

(*continued on next page*)

Table 1 (*continued*)

Sl. No.	Reference Paper	Published Year	Models Used	Mean Absolute Error	Correlation (*represented as "r")
30	Xia Liu et al. (Liu et al., 2022)	2022	Multi-feature-based network (MFN)	3–73 years	–
31.	Leonardsen et al. (Leonardsen, 2022)	2022	CNN transfer learning SFCN	T1-weighted MRI scan dataset (total N = 53542) 3–95 yrs.	r = 0.976
32.	Kaufmann et al. (Kaufmann, 2019)	2019	Centralized and harmonized processing protocol	Structural MRI dataset (N = 35474 3–96 yrs	r = 0.29 P = $2*10^{-29}$

provided in the form of zip files. Some of the datasets are only accessible after requesting login authorization and can be used for free. Table 2 compares several datasets used in prior models and lists the number of participants and their age range as well as the number of subjects utilized for the prediction. Additionally, it shows if the subject participants are healthy or not, whether they are meditation practitioners or not, and whether they have Parkinson's or Alzheimer's disease.

A comparison of the various datasets utilized in prior models is shown in Table 2. The many datasets that have been compared in prior brain age prediction models are shown in Table 2. Research on brain age prediction seeks to determine an individual's age from their brain imaging data. Researchers can learn more about brain development, aging, and any variations from the typical aging process by comparing this estimated brain age to the subject's chronological age. Researchers have gathered details on several datasets that have been used in prior research on brain age prediction in Table 2. These datasets often include brain imaging information from people of various ages, such as magnetic resonance imaging (MRI) data. Key details of each dataset, such as the number of individuals, age range, imaging modalities employed, and any other pertinent information, are highlighted in the table. Researchers and readers can better comprehend the variety and variability among the datasets used in brain age prediction studies by looking at this table. Assessing the generalizability and dependability of the prediction models created using these datasets requires careful consideration of this information. It also enables comparisons between research and the discovery of patterns or discrepancies in the results across datasets.

Table 2 summarizes and presents the features of datasets used in prior investigations, making it a significant resource in the field of brain age prediction. It helps evaluate and enhance brain age prediction models and gives researchers insightful information about the data sources that are accessible.

5. Advantages and disadvantages

Advantages of brain age prediction model

- **Early Detection of Cognitive Decline and Disorders:** Brain age prediction models can help identify early signs of cognitive decline, such as Alzheimer's disease and other neurodegenerative disorders. By comparing an individual's predicted brain age to their chronological age, researchers and clinicians can detect anomalies that might indicate the presence of neurological conditions before clinical symptoms manifest.
- **Personalized Medicine and Treatment:** Brain age prediction models can aid in developing personalized treatment plans for individuals. By understanding the deviation between predicted brain age and chronological age, healthcare professionals can tailor interventions and therapies to target specific aspects of brain health and aging.
- **Objective Biomarker:** Brain age prediction serves as an objective biomarker of brain health and aging, unlike subjective measures like cognitive assessments or self-reported symptoms. This provides a quantitative and measurable metric to track changes in brain structure and function over time.
- **Research Insights:** Brain age prediction models contribute to our understanding of brain aging and associated factors. Researchers can analyze the features that contribute most to predicted brain age deviations, shedding light on the biological and environmental factors influencing brain health.
- **Individualized Risk Assessment:** These models can assess an individual's risk of developing certain neurological conditions based on their brain age. This information can guide targeted preventive measures and lifestyle interventions to mitigate potential risks.
- **Non-Invasive and Cost-Effective:** Brain age prediction models are often based on non-invasive neuroimaging techniques like MRI scans, making them relatively safe and cost-effective tools for assessing brain health compared to invasive procedures.
- **Longitudinal Monitoring:** Brain age predictions can be tracked longitudinally over time, enabling researchers and clinicians to monitor changes and progression in brain aging or disease. This longitudinal data can enhance our understanding of the trajectories of brain health and disease.
- **Population Studies and Public Health:** Brain age prediction models can be applied to large-scale population studies to gain insights into regional or demographic variations in brain aging. This information can inform public health strategies and resource allocation.
- **Validation and Model Improvement:** The development of brain age prediction models encourages the integration of different neuroimaging modalities, machine learning algorithms, and statistical techniques. This iterative process contributes to advancements in neuroimaging analysis and predictive modeling.
- **Early Intervention and Lifestyle Modifications:** If an individual's predicted brain age is significantly higher than their chronological age, it can motivate them to adopt healthier lifestyle choices, such as regular exercise, a balanced diet, stress reduction, and cognitive training, to promote brain health and potentially slow down the aging process.

Disadvantages of the brain age prediction model

- **Limited Generalizability:** Brain age prediction models often rely on specific datasets that might not represent diverse populations. This can lead to biases and reduced generalizability to different demographics, ethnicities, and socioeconomic backgrounds.
- **Data Quality and Quantity:** The accuracy of brain age prediction models is heavily dependent on the quality and quantity of the training data. Insufficient or noisy data can lead to suboptimal model performance and unreliable predictions.
- **Ethical and Privacy Concerns:** The use of brain age prediction models raises ethical concerns, especially when dealing with sensitive medical data. Privacy issues and the potential misuse of predictive information can be significant drawbacks.
- **Interpretability:** Many brain age prediction models, particularly deep learning approaches, lack interpretability. It can be challenging to understand the exact features or biomarkers that contribute to the predicted brain age, making it difficult for clinicians and researchers to trust or validate the model's results.

Table 2
Comparison of Various Datasets used in Brain Age Prediction Models.

Sl. No.	Reference Paper	Datasets Used in Brain Age Prediction Models	Age Range of subjects (in years)	No of Subjects used for prediction
1	(Franke et al., Apr. 2010)	T1 w MRI from Information extraction from Images Database	19 to 86	Healthy 550 subjects
2	(Su et al., Jan. 2011)	T1 w Structural MRI from International Consortium of Brain Mapping dataset.	19 to 79	Healthy 84 volunteers
3	(Wang and Pham, Jul. 2011)	T1 w MRI from ABSIS database	50 to 86	Healthy 20 subjects
4	(Luders et al., Jul. 2016)	T1 MRI of meditators from Los Angeles	4 to 46	50 Meditation practitioners
		T1 MRI from the International Consortium of Brain Mapping dataset database	24 to 77	50 Control Subjects
5	(Lin et al., Mar. 2016)	T1weighted MRI	50 to79	112 normal old age subjects
6	(Cole, 2017)	T1 weighted MRI from Brain-Age Normative Control.	18–90 years	2001 healthy subjects
		Individuals selected from UK Adult Twin Register.	Mean age: 61.86 ± 8.36	27 monozygotic twins, 4 dizygotic twins
7	(Liem, Mar. 2017)	MRI from LIFE and Nathan Kline Institute-Rockland Sample.	19 to 82	2354 subjects
8	(Madan and Kensinger, Mar. 2018)	T1 MRI from Information extraction from Images dataset.	20 to 86	427 healthy adults
		T1 MRI from Open Access Series of Imaging Studies dataset.	18 to 94	314 healthy adults
		T1 MRI from Dallas Lifespan Brain Study dataset.	20 to 89	315 healthy adults
9	(Li et al., 2018)	rsfMRI scans from the Philadelphia Neurodevelopmental Cohort dataset.	8 to 22	983 subjects
10	(Wang, Oct. 2019)	T1 w MRI from Rotterdam Study	Mean Age: 66 ± 11	3688 dementia-free participants
11	(Liang et al., Aug. 2019)	T1 weighted MRI, DTI, rs-fMRI from Autism Brain Imaging Data Exchange, Consortium for Reliability and Reproducibility, Dallas Lifespan Brain Study, Nathan Kline Institute-Rockland Sample.	6 to 89	2026 healthy subjects
12	(de Lange, 2020)	T1w, FLAIR images, Diffusion-weighted, rs-fMRI MRI selected from White Hall II imaging subsets.	60.34 to 84.58	610 participants
13	(Beheshti et al., 2020)	T1 weighted MRI from Information extraction from Images, Open Access Series of Imaging Studies), Alzheimer's Disease Neuroimaging Initiative, Parkinson's Progression Markers Initiative.	35 to 90	839 healthy controls
		T1 weighted MRI from Parkinson's Progression Markers Initiative.	Mean Age: 71.64 ± 5.81	160 PD patients
		T1 weighted MRI from Alzheimer's Disease Neuroimaging Initiative	Mean Age: 64.53 ± 6.98	129 CE patients
14	(Liu et al., 2020)	T1 weighted Structural MRI from Alzheimer's Disease Neuroimaging Initiative, Open Access Series of Imaging Studies, Predictive Analytics Competition 2019.	17 to 98	2001 subjects
15	(Peng, 2021)	T1 w MRI from UK biobank	44 to 80	12,949 subjects
		T1 Structural MRI from Predictive Analytics Competition 2019.	17 to 90	2638 subjects
16	(Bermudez et al., 2019)	9 datasets	4 to 96	5121 Healthy Controls
17	(Pardakhti and Sajedi, 2020)	T1 weighted MRI from Information extraction from Images.	20 to 86	600 Healthy samples
		T1 weighted MRI from Alzheimer's Disease Neuroimaging Initiative.	65	47 Healthy Samples
18	(Mouches et al., 2022)	T1 weighted MRI and TOF MRA datasets from SHIP	21 to 81	1,658 healthy adults
19	(Aycheh et al., 2018)	T1 weighted MRI from Health Promotion Center SMC	45	2,911 cognitively normal subjects
20	(Hepp et al., 2021)	T1w brain MRI selected from German National Cohort Study	20 to 72	10,691 participants
21	(Basodi et al., 2021)	UPENN- Philadelphia Neurodevelopmental Cohort sMRI dataset	8 to 21	1591 healthy subjects
22	(Jonsson et al., 2019)	Information extraction from Images and UK Biobank	20 to 86	1264 healthy subjects
23	(Han and Ge, 2023)	Nathan Kline Institute-Rockland Sample.	6 to 85	496 individuals
24	(Niu et al., 2020)	T1 weighted MRI, Diffusion Tensor Imaging, and rs-fMRI from the Philadelphia Neurodevelopmental Cohort study.	8 to 21	839 subjects
25	(Katia Maria Poloni, 2022)	T1 weighted MRI images from NAC.	20–70	149 healthy old male
		T1-w, T2-w, PD MR images from Information extraction from Images.	70 above	600 MR images
26	(Amoroso et al., 2019)	Autism Brain Imaging Data Exchange 1	7 to 80	484 subjects
		Alzheimer's Disease Neuroimaging Initiative 2	7to 20	133 subjects
		Beijing Normal University3	20 to 40	120 subjects
		International Consortium of Brain Mapping Dataset 4	40 to 60	127 subjects
		Information extraction from Images 5	above 60	104 subjects
27	(Rao et al., 2020)	T1 w MRI of native Chinese	12 to 30	1721 healthy subjects
28	(de Lange et al., 2022)	UK Biobank	45 to 82	622 subjects
		Cam-CAN dataset.	18 to 87	622 subjects

(continued on next page)

Table 2 (*continued*)

Sl. No.	Reference Paper	Datasets Used in Brain Age Prediction Models	Age Range of subjects (in years)	No of Subjects used for prediction
29	(Holm et al., 2022)	T1w MRI from 21 publicly available datasets	5 to 93	53,542 subjects
30	(Da Costa Pedro et al., 2020)	T1 w 17 different sites	17 to 90	2, 640 healthy individuals
31	(Kawaguchi et al., 2021)	T1 w MRI from the Department of Pediatrics.	0 to 2	441 subjects
32	(Bellantuono et al., 2021,117458)	T1 w MRI from Autism Brain Imaging Data Exchange.	7 to 64 years	1112 individuals
33	(Lombardi et al., 2021 Jan)	T1 w MRI from 17 sites	20 to 96	2638 healthy individuals
34	(Ren et al., 2019)	T1 weighted MRI from UK Biobank	45 to 79	9850 subjects
		T1 weighted MRI from Nathan Kline Institute-Rockland Sample.	9 to 85	395 subjects
		T1 weighted MRI from Cambridge	18 to 86	652 subjects
		T1 weighted MRI from Information extraction from Images	35 o 84	293 subjects

- **Complexity and Computational Demands:** Some brain age prediction models, especially deep neural networks, are computationally intensive and require significant resources in terms of processing power, memory, and time. This can limit their accessibility and practicality in certain settings.
- **Vulnerability to Overfitting:** Complex models may be prone to overfitting, where they memorize the training data instead of learning meaningful patterns. This can lead to poor generalization and inaccurate predictions on new, unseen data.
- **Temporal Variability:** Brain age prediction models might not account for natural changes in brain structure and function that occur over time. Factors such as cognitive development, aging, and neuroplasticity can introduce variability that challenges the accuracy of predictions.
- **Limited Clinical Utility:** Despite their potential, the clinical utility of brain age prediction models in real-world healthcare settings is still being explored. The models may not always provide actionable insights or improve diagnostic accuracy beyond existing methods.
- **Lack of Causation:** Brain age prediction models typically focus on correlation rather than causation. While they can identify associations between certain features and brain age, they might not reveal the underlying mechanisms driving these relationships.
- **Validation and Reproducibility:** Ensuring the reproducibility and validity of brain age prediction models across different datasets and research settings is a challenge. Lack of standardized evaluation protocols and benchmarks can hinder the comparison of different models.
- **Dynamic Nature of the Brain:** The brain is a highly complex and dynamic organ, and its age-related changes can be influenced by a variety of factors, including genetics, environment, lifestyle, and disease. Brain age prediction models may struggle to capture all these nuances accurately.

6. Challenges and future scope

Due to a paucity of samples (Wang and Pham, 2011) related to the maximum and lowest age of respondents, a comparison analysis is not practical. Therefore, there is a need for more accurate prediction models. As the performance is assessed, it becomes clear that the sample size and subject age range have a significant impact (de Lange, 2020). Large numbers of T1-weighted samples are required for voxel-wise brain age to make an accurate prediction (Beheshti et al., 2020). In some cases, CNN models (Wang, 2019) are unable to handle unusual data samples when attempting to predict brain age. The bias correction method (Liang et al., 2019) cannot be used to estimate the brain ages of subjects who fall within tethered age ranges. When the distribution of the data sample is uneven, the prediction will have a large error (Liu et al., 2020). Compared to the functional interconnectivity pattern during repose, using multimodal data will improve brain age prediction (Li et al., 2018). A significant limitation of CNN's response is the lack of common sense (Herent et al., 2018). A significant obstacle to the study is that older people's ages are underreported, while younger people's ages are overreported (Lin et al., 2016). In medical facilities or clinics, gathering MRI instances is not an easy task (Wang and Pham, 2011), and doing so in large quantities makes it more difficult.

Another point is that individuals who have been referred to a clinic for MRI imaging typically have a brain disease; healthy individuals are much less likely to be referred for the same; Nonetheless, a model for brain age Assessment is created using scans of each individual's healthy brain. As a result, it is more difficult to collect MRI images from healthy individuals. Deep Learning techniques typically requires extensive training. It is necessary to use hardware that has high processing power and lots of memory when working with large amounts of data, especially when using DL methods. In general, parallel computation on GPU systems significantly reduces the time required for BAE modeling and prediction. The drawback of SVM (Lin et al., 2019 Jun 25) is that it necessitates extensive parameter adjustment and optimization. Due to their remarkable performance in brain age prediction models and their outstanding success in natural image categorization, convolutional neural networks are regarded as a model with high potential. As a result, the convolutional network's architectural design must meet stricter standards.

The field of estimating brain age is still developing yet has potential. It is possible to predict neurodegenerative diseases using standards based on brain age. A biomarker for assessing the impact of therapeutically relevant medicines can be used by using kernel methods (Franke et al., 2010) in addition to forecasting neurodegenerative diseases. It is possible to examine the connection between brain age and cognitive aging (Cole, 2017). It is feasible to investigate the effects of clinical conditions for assessing brain age using image-derived (de Lange, 2020) biomarkers, and the same procedure might well be refined to deliver a finer biomarker. Developing tools for therapeutic usage that can deliver unbiased, trustworthy information to doctors to aid in the treatment of brain illnesses is a primary objective of neuroimaging research (Cole, 2017). A novel future development in patients with PD and AD is the ability to evaluate how anxiety, depression, and hallucinations relate to brain age (Beheshti et al., 2020).

The field of brain age prediction research continues to evolve, offering exciting avenues for future investigations and advancements. Here are some potential areas of future scope in brain age prediction research:

1. **Longitudinal Modeling:** Incorporating longitudinal data to track individual brain age trajectories over time could provide deeper insights into the dynamics of aging and help differentiate normal aging from pathological processes. This may require addressing challenges related to data collection, alignment, and modeling of temporal changes.
2. **Multi-Modal Integration:** Integrating data from multiple neuroimaging modalities (e.g., structural MRI, functional MRI, diffusion tensor imaging) along with other biomarkers (e.g., genetic, proteomic) could enhance the accuracy and interpretability of brain age prediction models by capturing different facets of brain aging.

3. **Interpretability and Explain ability:** Developing methods to interpret and explain the predictions of brain age models can help bridge the gap between machine learning and neurobiology. This could lead to the identification of meaningful biomarkers and provide insights into the underlying biological mechanisms of aging.
4. **Personalized Medicine:** Exploring the potential of brain age prediction models for personalized medicine, such as predicting individual responses to interventions, therapies, or lifestyle changes, could have significant clinical implications for preventing or mitigating cognitive decline and neurodegenerative diseases.
5. **Cognitive and Clinical Correlations:** Investigating the relationships between predicted brain age and cognitive performance or clinical outcomes can provide a deeper understanding of the functional implications of brain age deviations and their relevance to cognitive health.
6. **Neurodevelopmental Studies:** Extending brain age prediction research to include developmental stages beyond adulthood can shed light on the trajectory of brain maturation, helping to differentiate age-related changes from lifelong developmental processes.
7. **Cross-Cultural and Ethnic Variability:** Research exploring how brain age prediction models generalize across diverse populations and ethnicities can improve the robustness and applicability of these models in different demographic groups.
8. **Neuroplasticity and Intervention Studies:** Investigating the potential for neural plasticity and its impact on brain age predictions could reveal how interventions, such as cognitive training or lifestyle modifications, might influence brain aging trajectories.
9. **Validation in Clinical Contexts:** Validating the utility of brain age prediction models in clinical settings for early detection, prognosis, and monitoring of neurodegenerative disorders can bridge the gap between research and clinical practice.
10. **Ethical and Privacy Considerations:** As brain age prediction models gain prominence, addressing ethical and privacy concerns related to data usage, informed consent, and potential biases becomes paramount to ensure responsible and transparent deployment.
11. **Meta-Analyses and Reproducibility:** Conducting *meta*-analyses across multiple brain age prediction studies can provide a more comprehensive understanding of the field's findings while enhancing the reproducibility and reliability of the results.
12. **Integration with Other Biomarkers:** Integrating brain age predictions with other established biomarkers of aging, such as epigenetic clocks, could yield a more comprehensive assessment of biological age and its implications.

These potential directions highlight the rich landscape of opportunities for brain age prediction research. As technology, methodologies, and interdisciplinary collaborations continue to advance, the insights gained from brain age prediction models hold the promise of transforming our understanding of brain aging and its implications for human health.

7. Conclusion

This study discusses several brain age prediction models that have been utilized during the last 11 years. Models for predicting brain aging and a comparison of the datasets utilized are also tabulated. The main shortcomings of the existing brain age models were the unfamiliar datasets and the scarcity of data samples. Brain aging is a biomarker that can be used to predict the ontogeny of Parkinson's, AD, and other neurodegenerative diseases. Models for predicting brain age show great potential for comprehending aging and how it affects brain health. More precise and individualized models are being created as a result of improvements in imaging methods, machine learning, and data integration. These models can assess the efficacy of therapies, identify risk factors for neurodegenerative disorders, and offer insights into the health of each individual's brain. The complexity and depth of these models are further increased by longitudinal research, as well as by the incorporation of lifestyle and environmental elements. Although the area is still developing, brain age prediction models provide a look into the future of personalized medicine and brain health management, opening the door for enhanced therapeutic and diagnostic approaches to support cognitive well-being and healthy aging. The development and widespread use of brain age prediction models in clinical and research environments will need ongoing investigation and multidisciplinary cooperation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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