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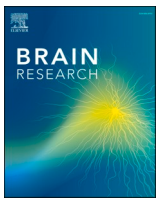

Research paper

Construction of brain age models based on structural and white matter information

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ABSTRACT

Brain aging is an inevitable process in adulthood, yet there is a lack of objective measures to accurately assess its extent. This study aims to develop brain age prediction model using magnetic resonance imaging (MRI), which includes structural information of gray matter and integrity information of white matter microstructure. Multiparameter MRI was performed on two population cohorts. We collected structural MRI data from T1- and T2-sequences, including gray matter volume, surface area, and thickness in different areas. For diffusion tensor imaging (DTI), we derived four white matter parameters: fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. To achieve reliable brain age prediction based on structure and white matter integrity, we employed LASSO regression. We successfully constructed a brain age prediction model based on multiparameter brain MRI (Mean absolute error of 3.87). Using structural and diffusion metrics, we identified and visualized which brain areas were notably involved in brain aging. Simultaneously, we discovered that lateralization during brain aging is a significant factor in brain aging models. We have successfully developed a brain age estimation model utilizing white matter and gray matter metrics, which exhibits minimal errors and is suitable for adults.

1. Introduction

Aging and its related degenerative diseases, particularly those affecting the central nervous system, pose significant challenges for individuals, regions, and countries globally. However, the lack of effective evaluation indices for overall or organ aging in the human body undoubtedly hinders the quantitative assessment of biological status and degenerative changes. The search for reliable indicators of biological age has been ongoing for nearly forty years, with the aim of objectively evaluating the degree of biological development or aging. Current multi-omics methods enable accurate age prediction based on various biological datasets (Jylhävä et al., 2017). When studying the biological age of the central nervous system, the concept of "brain age" (Mishra et al., 2023), based on magnetic resonance imaging, has been proposed to non-invasively evaluate the aging status of brain structure or function. The normal brain is utilized as a model to identify brain aging related modifications to evaluate premature or late aging. Therefore, using parameters derived from normal human brain images, a regression model is established, labeled with the actual age. The complex, multi-dimensional aging patterns of the brain are condensed into a single numerical value referred to as "brain age" for each distinctive brain image.

To prevent or postpone the onset and progression of neurodegenerative disorders, it is crucial to identify age-related health conditions as soon as possible using the genuine anatomical structure of the brain. In recent years, research on brain age has shown exponential growth (Baecker et al., 2021). When developing a brain age model with healthy individuals, the accuracy of the prediction model is evaluated using the mean absolute error (MAE), representing the average absolute difference in brain age between subjects. For the assessment of brain age, the

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primary outcome of brain age prediction is the difference between an individual's predicted age and their actual age, which is called the "brain age gap" (BAG). The fact that brain-age disparities strongly correlate with other age-related measures (Cole et al., 2018), such as a reduction in intellectual function and a weakened grip, supports the credibility of brain age as a predictive ageing biomarker. At the same time, research on brain age is increasingly incorporating multiple magnetic resonance imaging (MRI) modalities to depict brain health, which can help achieve smaller MAEs and accurately depict healthy brain morphology (Baecker et al., 2021; Rokicki et al., 2021).

Various age-related factors constantly affect the entire brain, with the most obvious being the discovery of a decrease in volume and cortical thickness (Weerasekera et al., 2023) in specific brain regions as age increases. Many studies use T1-weighted imaging (T1WI) (Soumya Kumari and Sundarrajan, 2024; Peng et al., 2021), which reflects brain structure, to construct brain age models, whether in machine learning or deep learning. However, a single mode could not fully describe the aging state of the brain, but in the face of clinical applications, it could not endlessly scan MRI. Study had suggested that the combination of T1WI and diffusion tensor imaging (DTI) holds promise as the optimal pairing (Cole, 2020), of which was because T1WI primarily reflected gray matter atrophy, while DTI mainly captured microstructural damage in white matter, offering complementary insights for a refined characterization of brain aging.

In summary, the purpose of this paper is to build a new brain age estimation framework based on brain structure and white matter information based on multimodal MRI data and two-centers data from healthy individuals. The goal is to comprehensively characterize the healthy brains of people and provide accurate assessment strategies for brain aging in populations. Based on the experimental purpose, we designed a data screening and experimental process within the database (Fig. 1).

2. Materials and methods

2.1. Dataset

We followed the principles proposed by the reporting guideline of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). Neuroimaging data were acquired using 3.0 Tesla MRI scanner with the same model (General Electric 750 W, Milwaukee, WI, USA) in this multicenter study. Data from the study were acquired from 2020 to 2022. The data used for this analysis was derived from the following databases:

(1) Baseline and follow-up clinical data were collected from the KaiLuan study and the Multi-modality MEdical imaging sTudy bAsed on the KaiLuan Study (META-KLS) (Sun et al., 2023). KaiLuan Research and the META-KLS were approved by the Medical Ethics Committee of KaiLuan General Hospital (IRB numbers 2008 No.1 and 2021002). Written informed consent was obtained from each participant. We selected over 1200 healthy individuals without mental illness and ultimately included data from 900 healthy individuals based on image quality. The specific parameters for T1WI were as follows: a total of 170 slices were acquired with a slice thickness of 1 mm; repetition time (TR)/echo time (TE) = 6.7 ms/2.6 ms; flip angle = 15°; field of view (FOV) = 256 × 256 mm^2; and matrix = 256 × 256. For DTI, the specific parameters were as follows: data were acquired along 15 directions with b = 1000 mm^2/s; a total of 29 slices were scanned with a slice thickness of 5 mm; TR/TE = 8000 ms/97.9 ms; flip angle = 90°; FOV = 240 × 240 mm^2; and matrix = 128 × 130. For more detailed information on imaging acquisition parameters in the META-KLS cohort, please refer to the supplementary materials in the database (https://bmjopen.bmj.com/content/13/2/e067283.long#supplementary-materials).

(2) Complete three dimensional (3D)-T1 MRI and DTI scans were obtained from 105 healthy individuals (age from 30-60 years) recruited from the External Center in Beijing (Data Source: Beijing Friendship Hospital, Beijing, China). The specific parameters for T1WI were as follows: a total of 192 slices were acquired with a slice thickness of 1 mm; repetition time (TR)/echo time (TE) = 2530 ms/2.98 ms; flip angle = 7°; field of view (FOV) = 256 × 256 mm^2; and matrix = 256 × 256. For DTI, the parameters were as follows: data were acquired along 64 directions with b = 1000 mm^2/s; a total of 64 slices were scanned with a slice thickness of 2 mm; TR/TE = 8500 ms/63 ms; flip angle = 90°; FOV = 224 × 224 mm^2; and matrix = 128 × 128.

The inclusion criteria for this study were as follows: participants were selected from the aforementioned two cohorts with complete clinical baseline data; they underwent comprehensive MRI scans, including T1-weighted imaging (T1WI) and diffusion tensor imaging (DTI); and they had no history of major neurological or psychiatric

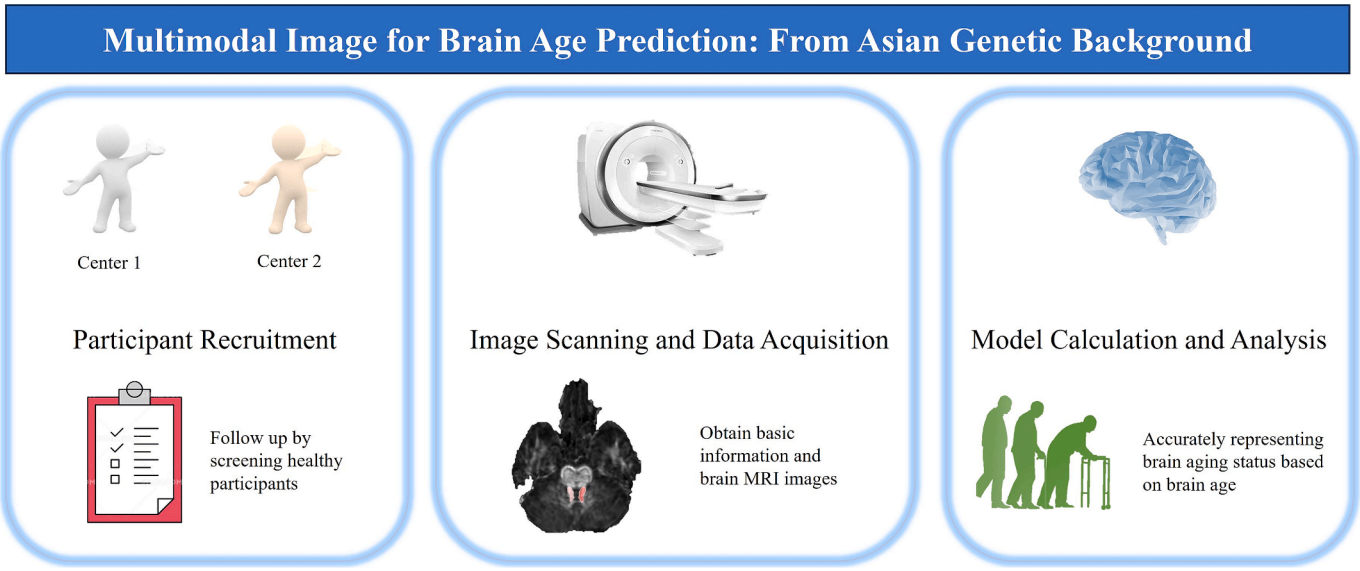

Fig. 1. Overall scheme design diagram. In this study, we mainly utilized data from different centers to jointly construct a brain age model and validated it.

disorders, such as stroke, dementia, or neuropsychiatric conditions. The exclusion criteria were as follows: participants with incomplete or missing images that could not be processed; those missing essential clinical data, such as gender or age; and those with conditions such as cancer, limb loss, or major trauma affecting the central nervous system.

2.2. Image processing

This study mainly used 3D-T1 and DTI sequences from healthy individuals. Regardless of the database type, we implemented a standardized image data processing procedure to minimize variations between sites. For image processing, we mainly used tools such as FSL and FreeSurfer. We cropped and registered T1 images to the Montreal Neurological Institute 152 (MNI152) "non-linear 6th generation" standard space T1 Template (https://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin6). The regions of interest (ROIs) were defined in the MNI152 space, combining parcellations from the HarvardOxford cortical and subcortical atlases. Cortical reconstruction, region of interest (ROI) segmentation, and metric calculation were conducted utilizing Freesuffer. The segmentation outcomes were then subjected to manual verification for accuracy. For DTI images, we used the eddy tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/EDDY). Eddy current and head motion artifacts were removed, and abnormal slices were corrected. The mean value of four DTI metrics—fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD)—were calculated on each white matter fiber to represent the fiber situation.

2.3. Model establishment

To constructed a brain age prediction model using 377 metrics extracted from T1 and DTI images. This included the volume of 45 subcortical regions, the area and thickness of 68 cortical regions (34 per brain hemisphere), and the mean FA, MD, axial diffusivity (AD), and radial diffusivity (RD) of 49 brain regions. The cerebral cortex was reconstructed and subcortical and cortical metrics were calculated using Freesurfer. The mean DTI metrics were calculated based on the brain regions delineated in the International Consortium for Brain Mapping DTI-81 white-matter labels atlas.

In this study, the relationship between the age and the metrics extracted from MRI images was assumed to be linear. Therefore, we employed multiple linear regression models to investigate the extent to which MRI metrics influence the brain aging process. Before establishing the regression model, all indicators were standardized by the Z-score, thus the importance of each metric in predicting brain age can be compared according to the magnitude of the regression coefficients.

Due to collinearity of metrics, brain age prediction models were built using Least Absolute Shrinkage and Selection Operator (LASSO) regression. The objective function of Lasso regression is based on ordinary least squares regression, augmented by an additional L1 regularization term:

$$min_{\beta_0,\beta_1,\cdots,\beta_p}\left(\sum_{i=1}^{n}\left(y_i-\beta_0-\sum_{j=1}^{p}\beta_j x_{ij}\right)^2+\alpha\sum_{j=1}^{n}\left(\beta_j\right)\right),$$ where α is the regularization parameter, which controls the intensity of regularization, and β_j is the regression coefficient. Due to the nature of L1 regularization, Lasso automatically filters out the most important variables and reduces the coefficients of other irrelevant or redundant variables to 0. Therefore, Lasso is particularly suitable for high-dimensional datasets, especially when the number of independent variables is larger than the sample size.

The full set of subjects was randomly divided into a training set and a validation set (8:2). In the training set, nine-tenths of the samples were used to build multiple models with varying alpha values in the range of 0.01 to 1, and the optimal alpha was determined by assessing the MAE of the model's predicted age on the remaining samples. After determining the model in the training set, we use the data from the testing set to test it.

To better visualize the impact of DTI metrics on the brain age model, we assigned the FA and MD values to each voxel of the image and performed linear regression of age at the voxel level. The distribution of MAE from the voxel-wise regression analysis was then used to further illustrate the association between DTI metrics and aging.

3. Results

After screening, we ultimately selected 1005 healthy individuals (Supplementary 1) for modelling, by randomization, comprising a training set with 804 subjects and a test set with 201 subjects (Supplementary 2). The brain volume and white matter related features of each individual were calculated from complete T1-w MRI and DTI.

One-tenth of the training set sample is selected for validation, and the rest is used to train the model. By adjusting the parameters of LASSO regression, we ultimately chose the model with the smallest MAE in validation set (Fig. 2) to represent the final result. In the training set, the MAE consistently decreased as the alpha reduced, while in the validation set, the MAE reached its minimum at an alpha value of 0.06. At this point, the lasso regression yielded 27 non-zero coefficients, resulting in a MAE of 3.87 and R^2 of 0.84 ($p < 0.05$) in the training set and 4.94 and R^2 of 0.60 ($p < 0.05$) in the validation set. Six subcortical regions influenced the prediction of brain age (Table 1). The volume of the left thalamus, left putamen, left cerebellum cortex, right thalamus, and mid-anterior corpus callosum were negatively correlated with brain age, and the volume of the left thalamus exhibited the greatest effect on the prediction of age in all metrics. The optic chiasm volume was positively correlated with brain age, but the magnitude of its regression coefficient was small. Cortical and regional volumes exhibited a negative correlation between brain age and the degree of correlation (Fig. 3). Meanwhile, the damage to the white matter fiber transport tract is also reflected in the contribution to brain age regression, with specific fiber bundles highlighted in Fig. 4.

In this subsection, models for brain age prediction were built at the voxel level. Subcutaneous volume, as well as cortical thickness and area, were excluded from the modelling process, as discussing them as the single voxel level is not meaningful. The FA and MD were available for each voxel of each subject, and a linear regression model aiming at assessing physiological age was built. The average MAE of all voxels was 9.76 ± 0.08, which is significantly higher than the result based on measures extracted from brain structures. Fig. 5 illustrates the spatial

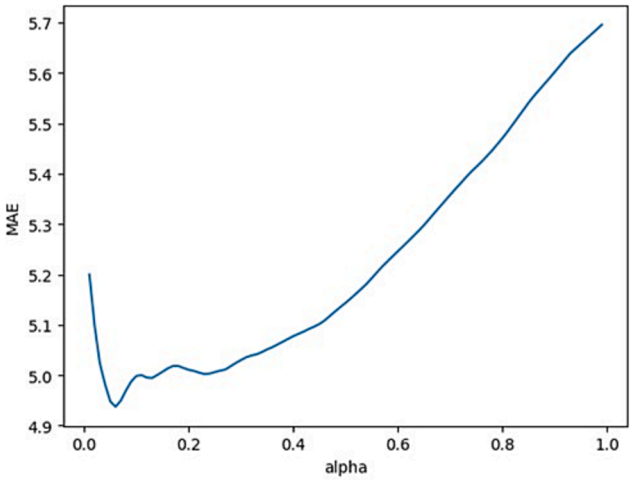

Fig. 2. Illustrates the curves of mae with alpha for the training sets. in the training set, the data is randomly divided equally, with one portion used to construct the model and the other portion used to form a direct relationship between the regularization parameter alpha and mae.

Table 1
Demonstrates the non-zero regression coefficients obtained from lasso regression using the optimal alpha.

	Metrics	Coef.
1	Volume of thalamus (left)	−2.4032
2	Average FA of genu of corpus callosum	−1.7080
3	Average RD of unclassified region	1.3655
4	Average AD of fornix	1.1223
5	Average AD of cingulum gyrus (right)	1.1217
6	Average AD of posterior thalamic radiation (right)	0.9176
7	Average FA of superior cerebellar peduncle (left)	0.8367
8	Thickness of superior frontal (left)	−0.6633
9	Volume of putamen (left)	−0.6626
10	Thickness of superior temporal (left)	−0.4951
11	Average AD of cingulum hippocampus (left)	0.4293
12	Average FA of unclassified region	−0.3983
13	Thickness of medial orbitofrontal (left)	−0.3197
14	Average FA of superior cerebellar peduncle (right)	0.2462
15	Thickness of rostral anterior cingulate (left)	−0.1522
16	Thickness of insula (left)	−0.1439
17	Average AD of superior longitudinal fasciculus (left)	0.1301
18	Area of middle temporal (right)	−0.1251
19	Volume of Cerebellum-Cortex (left)	−0.1128
20	Volume of Thalamus (right)	−0.0929
21	Average AD of sagittal stratum	0.0813
22	Volume of optic-chiasm	0.0621
23	Average AD of external capsule (right)	0.0580
24	Average AD of anterior limb of internal capsule (left)	0.0567
25	Thickness of insula (right)	−0.0472
26	Volume of CC_mid_anterior	−0.0389
27	Thickness middle temporal (left)	−0.0120

distribution of MAE at the voxel level. The lower MAE observed in the corpus callosum, caudate, and hippocampus suggests a stronger association of these regions with the aging process of the brain, aligning with previous findings.

4. Discussion

In this study, we established a multimodal imaging brain age model based on brain MRI, which can effectively predict the true brain age of individuals. The parameters of this model are all obtained based on brain structure or white matter fiber link parameters, which means that this model can accurately describe the biological age of the brain based on information from the cortex and white matter. At the same time, we also used multi-center data for validation to demonstrate the generalizability of the model.

Brain age (Soumya Kumari and Sundarrajan, 2024; Wilms et al., 2022; Wen et al., 2024) is more than a simple mathematical model based on brain MRI, it serves as a comprehensive assessment of brain health. It is increasingly recognized as a widely applied imaging-based biomarker for neural aging and a potential proxy for brain integrity. Research has shown that MRI can reflect aging at the level of both functional and structural brain connectivity (Damoiseaux, 2017). Meanwhile, a study based on the United Kingdom Biobank showed that in multimodal imaging, T1 based cortical imaging parameters and DTI derived related imaging parameters contribute the most to the brain aging model (Cole, 2020), undoubtedly demonstrating the enormous potential of 3D-T1-w MRI combined with DTI to accurately predict brain age. Meanwhile, multimodal imaging studies have shown a small correlation between functional connectivity features and brain age (de Lange et al., 2020). Recently, researchers have analyzed the brain age formula from the perspective of genetic association (Satizabal et al., 2019; Brouwer et al., 2022), and unsupervised methods have also been applied to explore brain aging (Yang et al., 2024). It is well known that MRI is time-consuming and costly, and therefore cannot be included as a scanning modality for brain assessments without limitations. Therefore, the best modality combination for predicting brain age using MRI may be T1-w and DTI, given their ability to reflect indicators with high age correlation and sensitivity.

According to previous studies, multiple prediction methods can accurately predict brain age. For instance, M. Tanveer and colleagues (Ganaie et al., 2023) categorized deep learning architectures according to input data based on slices and voxels as well as according to models for estimating brain age. Then, they conducted comparisons across the datasets utilized, simultaneously assessing performance, data volumes, and patterns. Meanwhile, a novel approach (Sone and Beheshti, 2022) has been developed to calculate “brain age” based on neuroimaging at the local level within the brain. This targeted approach offers more comprehensive spatial insights into the structural patterns of brain aging

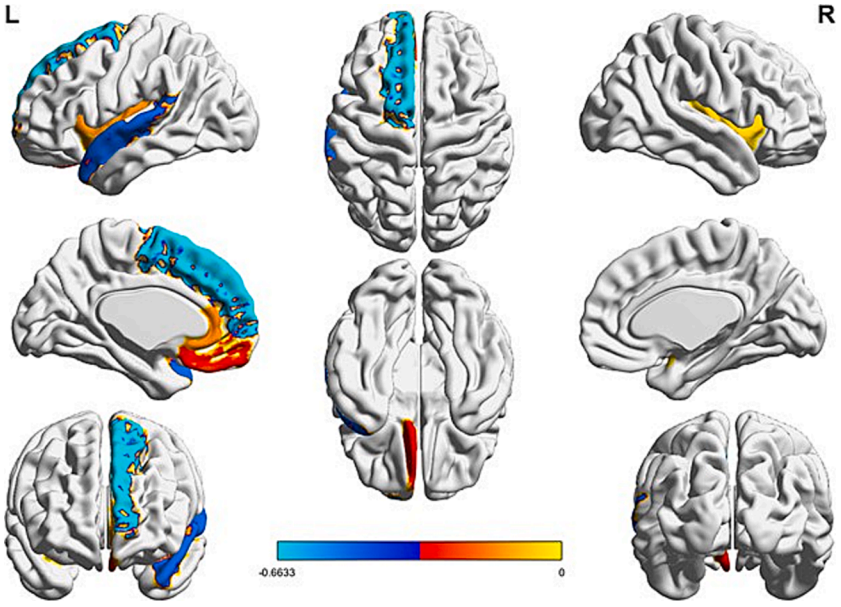

Fig. 3. Illustrate the effect of thickness and area of each region of the cerebral cortex on predicted age. after screening by lasso regression, the thickness of seven cortical regions was retained as a predictor variable, and except for the right insula, the remaining six regions were in the left hemisphere. as can be seen from the regression coefficients, cortical thickness and predicted age were always negatively correlated. the area of only one cortical region, the right middle temporal, was retained and had little effect on predicting brain age.

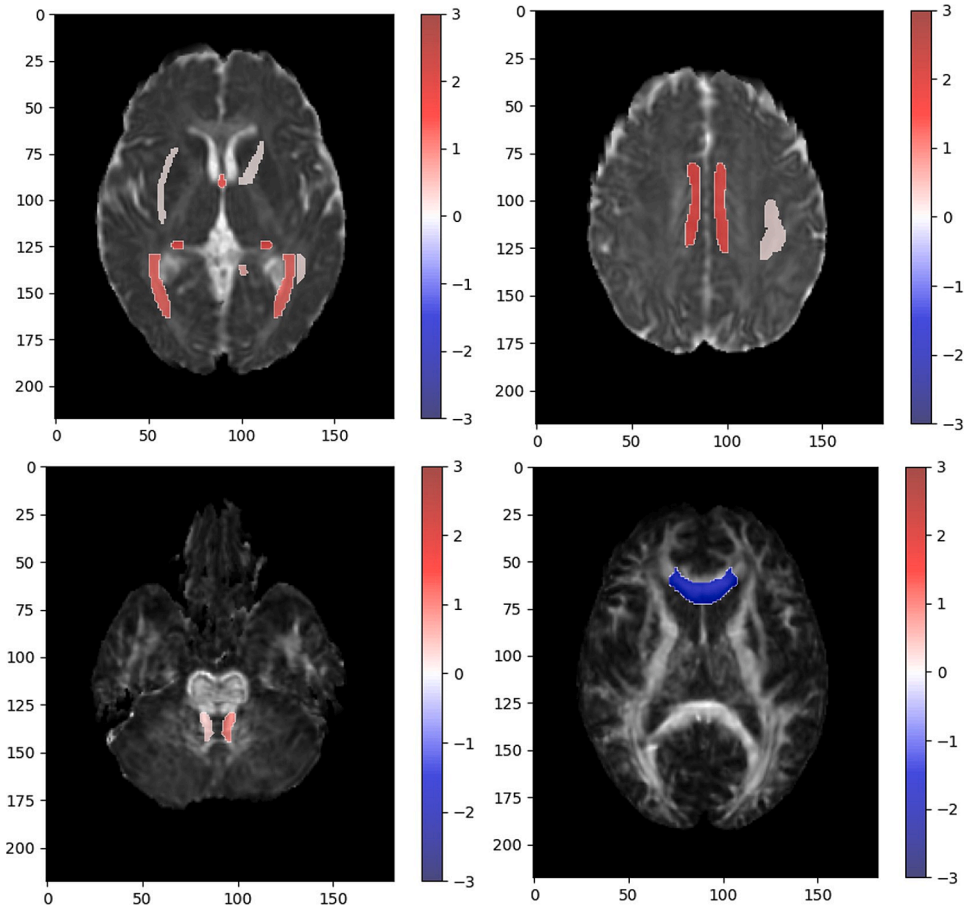

Fig. 4. Shows the effect of the average dti metrics for the white matter regions. in critical white matter regions (except unclassified region), all md and rd metrics were discarded in the lasso regression, and ad in 8 regions and fa in 4 regions were retained. among them, the average ad of fornix, cingulum and posterior thalamic radiation and the average fa of genu of corpus callosum and left superior cerebellar peduncle were more influential in predicting brain age. notably, both average rd and fa for unclassified region were retained in the lasso regression, especially mean rd, which ranked fourth in importance among all indicators.

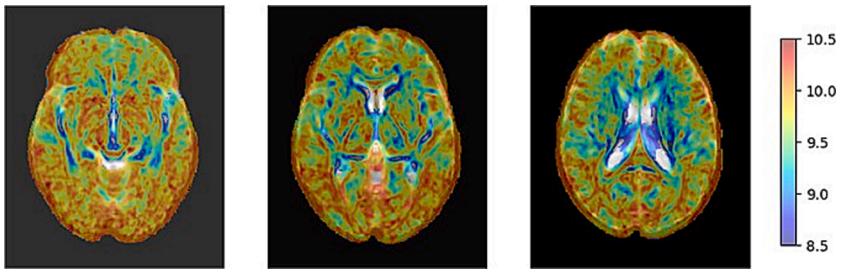

Fig. 5. Distribution of MAE in regression analysis at the voxel level.

than earlier techniques. Using brain MRI data from more than 3000 healthy subjects, a U-Net model was built, progressively creating a customized 3D brain age prediction map. It is interesting to note that they achieved a higher accuracy, with a MAE of 7 years, in the periventricular and prefrontal cortical areas. Furthermore, they implemented an image voxel analysis-based phase to address age-related biases and local brain age disparities. A simple fully convolutional network (SFCN) (Peng et al., 2021; Gong et al., 2021), based on the VGG (Visual Geometry Group) Net and featuring a fully convolutional structure, has gained prominence in brain age analysis and challenge competitions. This model reduces the number of parameters to about 3 million whilst retaining a smaller number of layers. Lastly, one of the most promising models is the completely linked model, which significantly reduces the amount of space and processing resources needed. This model employs a deep convolutional neural network architecture to successfully utilize T1-w structural scans and reliably estimate brain age.

Compared to other well-known deep network designs, SFCN has fewer parameters, making it more suited for smaller file sizes and 3D volume data. Network development is integrated with many techniques, such as data augmentation, regularization of early training models, model assembly, and prediction error reduction, to increase efficiency. Simultaneously, the model generates a fully operational framework capable of managing diverse data quantities. The SFCN system can use dropout layers and information gain to accomplish the maximum MAE training under specific conditions. The constructed model employs one of three normalization techniques. The work of Iman Beheshti (Beheshti et al., 2019) presents a straightforward and efficient technique to reduce

prediction bias in frameworks for estimating brain age. This approach highlights the connection between the reliability of statistical reasoning and the accuracy of forecasting brain age estimate frameworks though regression models. It achieves this by combining real age during training to counteract bias. The integration of this bias mitigation strategy into a machine learning-based brain age framework produced a notably robust framework for estimating brain age, with a remarkable correlation (R^2) of 0.81 between the anticipated and real brain ages. When the technique was used on a separate group of seventy-five individuals with good cognitive health, the average absolute error was a remarkable 2.66 years. Without deviation correction, the R^2 will drop to 0.24. The simulation further demonstrates the efficacy of this approach in reducing prediction errors, particularly within the framework's control environment. In healthy individuals, reviews (Baecker et al., 2021; Soumya Kumari and Sundarrajan, 2024; More et al., 2023; Cole and Franke, 2017; Beheshti et al., 2022) utilizing voxel-based morphometry to determine brain age claimed prediction errors of 5–8 years. Even though the prediction error of the test set was less than five years, we were still able to drop the average MAE to 3.87 years in this work by utilizing cortical structural information and DTI data, which is the lowest MAE that can be achieved based on neuroimaging parameters at present. Our model combined data from two centers, with an 80/20 random split for training and validation. Training and parameter tuning were restricted to the training set, ensuring that the validation set was exclusively used for unbiased performance assessment (Varoquaux and Cheplygina, 2022). While this approach demonstrates robust internal validation, we acknowledge the lack of external multi-centres' validation as a limitation. External validation on independent multi-centres' datasets would provide a stronger demonstration of the model's generalizability and clinical applicability (Luo et al., 2016). Future studies will prioritize external validation to further establish the robustness of our findings.

As shown in the results of this article, the prominent features in structural imaging are the reduction of volume and thinning of the cortex, which is in line with mainstream academic views (MacDonald and Pike, 2021). It is important to note that the left hemisphere of the brain experiences the majority of the effects of cortical thinning. Additionally, previous research could indicate that the left hemisphere, which is often the hemisphere predominately used for language and motor functions, may be more susceptible to neurodegenerative alterations associated with aging and illness (Minkova et al., 2017; Michaelis et al., 2020; Shan et al., 2005). The left thalamus volume demonstrated the most significant effect on brain age prediction, consistent with its established role in aging-related sensorimotor integration, cognitive functions, and global brain connectivity (Fama and Sullivan, 2015). As a critical information relay hub, the thalamus is particularly vulnerable to age-related structural changes (Tullo et al., 2019), explaining its prominent predictive power in our model. However, the substantial effect of the thalamus does not diminish the contributions of other regions, such as the prefrontal cortex and temporal lobe (Filippi et al., 2023). These areas are well-known to undergo significant age-related atrophy and play crucial roles in higher-order cognitive processes (Naya et al., 2017), including executive functions, memory, and emotion regulation. While their impact on age prediction may appear less pronounced in our analysis, this could be attributed to the distributed and interconnected nature of these regions, resulting in their contributions being captured more diffusely across multiple features. Additionally, methodological factors, such as feature aggregation and regularization (Vinga, 2021) in the model, may have influenced the relative importance of these regions. The incorporation of DTI metrics, particularly FA and MD, aimed to capture microstructural brain changes associated with aging, complementing the macroscopic insights provided by structural MRI. Our findings revealed that the most pronounced DTI changes occurred in the white matter surrounding the hippocampus, a region critical for memory and cognitive functions. These results align with prior research highlighting hippocampal vulnerability to age-related degeneration. Meanwhile, damage to white matter connections mainly occurs around the hippocampus, for example in the cingulate gyrus. This is also consistent with earlier scholarly opinions that show significant and early aging-related alterations, underscoring the importance of studying their role in aging for potential therapeutic implications (Fan et al., 2019; Archer et al., 2023; Bubb et al., 2018). White matter integrity (Tian et al., 2017; Li et al., 2022), as another aspect of white matter, undergoes fluctuations as we age, particularly in regions like the genu of the corpus callosum and postmolar thalamic radiation. By identifying region-specific microstructural alterations, our study underscores the value of DTI in enhancing brain age prediction models and offers a nuanced perspective compared to approaches that focus on global metrics (Hsieh and Yang, 2022; Beck et al., 2021). Future studies could further explore the interplay between hippocampal microstructure and brain aging using multimodal imaging integration (Metzler-Baddeley et al., 2019). In summary, the regions with significant structural and connectivity changes associated with aging are essentially covered by our brain age model.

The structural brain changes observed in this study, such as reductions in cortical thickness and alterations in white matter integrity, are consistent with known neurobiological mechanisms of aging. A major hallmark of neuroaging is the atrophy of brain tissue, particularly in the reduction of gray and white matter volumes. As people age, cortical thickness decreases, especially in regions linked to cognitive functions, such as the prefrontal cortex and temporal lobe (Proskovec et al., 2020). These structural changes reflect neuronal and synaptic loss, as well as myelin degradation and increased neuroinflammation (Andronie-Cioara et al., 2023). This atrophy is often accompanied by a decline in cognitive functions, particularly executive functions, memory, and attention (Price and Duman, 2020; Du et al., 2023). Brain age prediction models quantify these structural changes to estimate an individual's biological brain age, providing a direct indicator of brain aging.

White matter plays a crucial role in transmitting neural signals, and as individuals age, the integrity of white matter fiber tracts significantly declines. DTI studies show that white matter integrity decreases with age (Elmers et al., 2023; Molloy et al., 2021; Groechel et al., 2023), particularly in areas related to cognitive functions, such as the corpus callosum, hippocampus, and cingulate gyrus. And brain age prediction models that incorporate the diffusion characteristics of white matter can detect these microstructural degradations, thereby serving as markers of neuroaging. As the aging process progresses, neuroinflammation becomes one of the core driving factors of brain degenerative changes (Voet et al., 2019). Activation of microglial cells and chronic inflammatory responses could damage neurons and accelerate brain aging. Neuroinflammation not only affects synaptic function (Lecca et al., 2022) but also compromises the integrity of the blood–brain barrier (Candelario-Jalil et al., 2022), allowing more harmful substances to enter the brain (Mowry et al., 2021; Parsi et al., 2024), which further exacerbates inflammation and neuronal damage, leading to various neurodegenerative diseases. The information extracted from magnetic resonance signals (Wang et al., 2017) reflects, to a certain extent, the correlation with neuroimmune activities in the brain, which represents a potential biological link for the brain age model. While most brain age research have employed MRI data, DTI has been overlooked despite its capacity to detect microstructural changes that are important in aging and age-related illnesses. Recent research had shown that DTI has the ability to estimate brain age (Wen et al., 2024). Advanced reconstruction approaches, such as multishell free-water correction, have greatly improved age prediction accuracy by separating white matter signals from extracellular fluid (Nemmi et al., 2022). Furthermore, methodologies like 3D convolutional neural networks (3D-CNN) have shown the capability to predict brain age using DTI features alone (Wang et al., 2023), while low-rank tensor fusion approaches have successfully integrated DTI into multimodal frameworks, improving both predictive accuracy and interpretability (Liu et al., 2024). Clinically, DTI-based

brain age estimation (Sone et al., 2024) had been applied in diverse conditions such as epilepsy and interictal psychosis, demonstrating its utility in identifying deviations in white matter aging that are linked to neurological and psychiatric disorders. These findings highlight the unique contributions of DTI to understanding the complex mechanisms of brain aging, particularly in capturing subtle changes in white matter that may precede macrostructural alterations observed with conventional MRI. By integrating DTI into brain age models, future studies could leverage its sensitivity to microstructural changes, thereby enriching the predictive power and clinical applicability of brain age as a biomarker. This emphasizes how crucial it is to develop methodological frameworks that use DTI in addition to other imaging modalities in order to more accurately depict the complex nature of brain aging.

Studies have shown that individuals from different ethnic backgrounds (Moonen et al., 2022; Manly and Mungas, 2015) exhibit distinct patterns of brain aging, likely due to a combination of genetic, environmental, and lifestyle factors (Amariglio et al., 2020; Elbasheir et al., 2024; Munro et al., 2023). Meanwhile, socioeconomic status (Busby et al., 2023; Avila-Rieger et al., 2022) is also an important factor affecting the aging process. However, by focusing on an Asian population, this study provides new insights into the aging processes specific to this demographic, addressing a gap in the literature dominated by studies on European and North American populations.

We conducted cross center data collection and increased the model's generalizability through random grouping, but this study has a few limitations. Firstly, our brain atlas template was not segmented based on Asians, because in future research, we need to unify image processing methods, so we can only choose a unified segmentation template. Secondly, our MAE has not reached the minimum term under current investigation. This is because we abandoned deep learning modeling methods with black box effects (Haight and Eshaghi, 2023) and opted for traditional machine learning methods that are scalable and highly applicable. This highlights the positive significance of various brain regions for aging. Thirdly, due to material limitations, our brain age model is more applicable to the Asian population. We will promote its use in future research to enhance its generalizability. Fourth, we have observed that a greater number of visual patterns improves the accuracy of brain age regression (Niu et al., 2020); however, as indicated by the study above and the constraints of the databases, we have selected the two modes that provide the most contributions (reflecting brain fibers and structure). Simultaneously, studies utilizing additional modalities, greater sample sizes, and sophisticated data processing techniques are being conducted. The choice of analytical techniques is the subject of the sixth point. While deep learning can dramatically lower the MAE, it comes at the cost of interpretability, visualization, and control overfitting. Future research is needed to identify machine learning systems that are even more efficient. A potential limitation of this study lies in the variability introduced by the use of imaging data from multiple sites and scanner types. Additionally, differences in imaging protocols, such as sequence parameters and magnetic field strengths, may have influenced the generalizability of our findings. However, future studies could benefit from further standardization of imaging protocols or advanced harmonization techniques to better account for inter-site variability. Meanwhile, more interpretable work in the future should be included in the study of brain age models.

5. Conclusion

Multimodal brain MRI can accurately depict the degree of brain aging. The various structural parameters based on T1-w imaging and the parameters of various white matter fibers can effectively predict the brain age of healthy individuals. These parameters constitute brain age models through machine learning methods and are applicable to refined evaluate the degree of brain aging.

6. Declarations

a) Ethics approval and consent to participate.

The study has been approved by the Medical Ethics Committee of Kailuan General Hospital (IRB number: 2008 No. 1 and 2021002, respectively). All the procedures will be performed in accordance with the principles of the Declaration of Helsinki. Written informed consent must be obtained from each participant.

b) Availability of data and materials.

All data are available when are needed. The data can be accessed according to the request from corresponding authors.

c) Declaration of conflicting interests.

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.

d) Funding

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g) Declaration of Generative AI and AI-assisted technologies in the writing process

We did not use AI-assisted technologies in the writing process.

CRediT authorship contribution statement

Xinghao Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zaimin Zhu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Funding acquisition, Conceptualization. **Xinyuan Xu:** Writing – original draft, Visualization, Software, Resources, Methodology, Funding acquisition, Formal analysis, Data curation. **Jing Sun:** Writing – original draft, Validation, Software, Resources, Formal analysis, Data curation. **Li Jia:** . **Yan Huang:** Writing – original draft, Visualization, Supervision, Software, Resources, Data curation, Conceptualization. **Qian Chen:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Investigation, Funding acquisition, Formal analysis, Data curation. **Zhenghan Yang:** Validation, Supervision, Resources, Methodology, Funding acquisition, Data curation. **Pengfei Zhao:** Writing – original draft, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Xinyu Huang:** Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation. **Marcin Grzegorzek:** Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Data curation, Conceptualization. **Yong Liu:** Writing – original draft, Validation, Resources, Methodology, Funding acquisition, Data curation, Conceptualization. **Han Lv:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Funding acquisition, Data curation, Conceptualization. **Fangrong Zong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zhenchang Wang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2025.149458.

Data availability

Data will be made available on request.

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