Neuroscience Letters 771 (2022) 136398

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

The effect of Alzheimer's disease risk factors on brain aging in normal Chineses: Cognitive aging and cognitive reserve

Mengxue Wang [a,1], Qingguo Ren [a,b,1,*], Yachen Shi [a], Hao Shu [a,b], Duan Liu [a], Lihua Gu [a,b], Chunming Xie [a,b], Zhijun Zhang [a,b], Tiange Wu [a], Zan Wang [a,b,*], the Alzheimer's Disease Neuroimaging Initiative

[a] School of Medicine, Southeast University, Nanjing 210009, China
[b] Department of Neurology, Affiliated ZhongDa Hospital of Southeast University, Nanjing 210009, China

ARTICLE INFO

Keywords:
Alzheimer's disease
BrainAGE
Education
Gender
APOE-ε4

ABSTRACT

Aging has been recognized as a major driving force of the Alzheimer's disease's (AD) progression, however, the relationship between brain aging and AD is still unclear. There is also a lack of studies investigating the influence of AD risk factors on brain aging in cognitively normal people. Here, the "Brain Age Gap Estimation" (*BrainAGE*) framework was applied to investigate the effects of AD risk factors on individual brain aging. Across a total of 165 cognitively normal elderly subjects, although no significant difference was observed in the *BrainAGE* scores among the three groups, AD risk dose (i.e., the number of AD risk factors) is tend to associated with an increased *BrainAGE* scores (high-risk > middle risk > low risk). Female exhibited more advanced brain aging ($P = 0.004$), and higher education years were associated with preserved brain aging ($P < 0.001$). APOE-ε4 ($P = 0.846$) and family history (FH) of dementia ($P = 0.209$) did not increase *BrainAGE* scores. When comparing 52 aMCI patients with 38 cognitively normal controls from ADNI dataset, aMCI patients showed significantly increased *BrainAGE* scores. *BrainAGE* scores were negatively correlated with CSF Aβ42 levels in the aMCI group ($r = -0.275$, $P = 0.048$). With an accuracy of 68.9%, *BrainAGE* outperformed APOE-ε4 and hippocampus gray matter volume (GMV) in predicting aMCI. In conclusion, AD is independently associated with structural changes in the brain that reflect advanced aging. Potentially, *BrainAGE* combined with APOE-ε4 and hippocampus GMV could be used as a pre-screening tool in early-stage AD.

1. Introduction

Alzheimer's disease (AD), the most common cause of dementia is emerging as a global epidemic. The global prevalence of AD is expected to double every 20 years. It is primarily a disease of the elderly and the incidence rate increases with age. A large number of risk factors are associated with an increased risk of developing AD. Unfortunately, to date, neither a cure nor a treatment is optional to alter its progression [1]. The main neuropathological features of AD are widely described as the extracellular accumulation of 42-amino-acid amyloid-beta (Aβ) plaques and tau intracellular inclusions generating neurofibrillary tangles which causes severe cognitive impairment [2,3]. Various pathological changes develop years or decades before the onset of cognitive decline [4]. As well, abnormal brain structural changes already occur in amnestic mild cognitive impairment (aMCI). Over the past several years, there has been great progress in the development of biomarkers for detecting underlying AD [5].

Aging is associated with a higher risk of various diseases throughout the body, however, each individual ages at a different rate, biologically [6,7]. The Geroscience hypothesis states that aging is the result of the degeneration of multiple organ systems and this degeneration is the root cause of age-related diseases. In terms of brain degeneration, accelerated aging and the ensuing cognitive decline have a huge impact on disability and loss of independence in older adults. Consistent with the Geroscience hypothesis, recently, it has been found that the areas of brain atrophy detectable in patients with AD are largely similar to the areas of

* Corresponding authors at: Department of Neurology, Affiliated ZhongDa Hospital, School of Medicine, Southeast University, 87 Dingjiaqiao, Gulou, Nanjing, Jiangsu 210009, China.
E-mail addresses: renqingguo1976@163.com (Q. Ren), ujs_yingxiang0402@126.com (Z. Wang).
[1] Mengxue Wang and Qingguo Ren contributed equally to this work.

https://doi.org/10.1016/j.neulet.2021.136398
Received 3 August 2021; Received in revised form 22 November 2021; Accepted 12 December 2021
Available online 17 December 2021

normal age-related atrophy shown in healthy control subjects [8,9]. Davatzikos et al. supported that pathologic atrophy in AD is an accelerated aging process [10]. Cognitive decline was recently found to progressively accelerate, years before being diagnosed with AD, and to be correlated with the atrophy rates in specified brain regions. To quantify this age-related pathological structural change in the brain, "brain-age" has been proposed to measure the rate of brain aging. This technique was introduced as a powerful biomarker that can be used to estimate an individual's neuroanatomical age.

Brain age gap estimation *(BrainAGE)* refers to the difference between the predicted age obtained by an age prediction model based on brain imaging data and the chronological age of subjects [11]. A positive brain prediction age difference score indicates that an individual's brain is predicted to be "older" than his actual age, which reflects the accelerated aging state of the brain to some extent [12]. *BrainAGE* is sensitive to a variety of neurological and psychiatric diseases, such as AD, multiple sclerosis and schizophrenia etc. [13,14]. Initial studies suggest that people with AD have advanced *BrainAGE* scores. Furthermore, this access may be able to predict cognitive decline and conversion to AD in older adults. Even more meaningful, *BrainAGE* was superior to all cognitive scales and CSF biomarkers in predicting the transition from MCI to AD [15]. Elliottin et al. proved that in a longitudinal birth cohort, *BrainAGE* in midlife is also associated with cognitive decline. From a systems-integrity perspective, the link between *BrainAGE* and cognitive function exists from childhood [16]. A number of different biological processes cause the variations in brain age. For example, distinct genetic influence, smoking and environmental will all likely contribute to accelerate the brain aging [17]. However, the study of brain age is still in its infancy. Most of the existing studies have focused on patients with cognitive impairment, but few have studied the individual differences of *BrainAGE* in cognitively normal elderly. In addition, attempts to use *BrainAGE* to predict cognitive impairment are still being explored.

Our study will further explore the relationship between AD and brain aging, that is, AD is the result of accelerated pathological brain aging by extending this research to the point before cognitive decline. Specifically, we tested the following hypotheses: (1) To explore the relationship between AD and brain aging, people with normal cognition were divided into low risk, middle risk and high risk group according to the risk factors of AD, we assumed that with the increase of risk level, the *BrainAGE* scores would be higher. (2) We ulteriorly explored the effects of AD risk factors (i.e., APOE-ε4, family history [FH] of AD), sex and education on brain aging in cognitively normal subjects. (3) We finally explored the potential value of *BrainAGE* for identification of patients with aMCI.

2. Materials and methods

2.1. Datasets

Nanjing Aging and Dementia Study (NADS) Dataset: A total of 165 cognitively normal elderly subjects were recruited through a normal community health screening and newspaper advertisements, and they underwent a standardized clinical interview, neuropsychological battery assessment, APOE genotyping and multi-modal brain MRI examination. General cognition was assessed using the mini-mental state examination (MMSE) and mattis dementia rating scale-2 (MDRS-2). Neuropsychological battery consisted of the auditory verbal learning test with a 20 min delayed recall (AVLT-DR), the logical memory test with a 20 min delayed recall, the Rey-Osterrieth complex figure test with a 20 min delayed recall, the clock drawing test, the digital symbol substitution test, trail-making test A and B, the stroop color-word test A, B and C, the verbal fluency test, the digital span test and the semantic similarity test. We further grouped the neuropsychological tests into 4 cognitive domains (i.e., episodic memory, visuospatial function, information processing speed and executive function) and transformed the raw scores into 4 composite z scores. The details about composite score analysis, APOE genotyping and MRI data acquisition were described in our previous studies and *Supplemental Materials*. The cognitively normal subjects were required to have an MMSE score $\geq$ 26, MDRS-2 score $>$ 120, and AVLT-DR score $>$ 4 for subjects with 8 or more years of education. Participants were excluded from this study if they had a history of neurological or psychiatric illness, major medical illness, severe visual or hearing loss or gross structural abnormalities revealed by MRI images. The Research Ethics Committee of Affiliated Zhongda Hospital and Southeast University approved the study, and each subject provide a written informed consent. Finally, in this present study, cognitively normal elderly subjects were grouped according the FH of dementia and APOE allele status (i.e., high risk: both FH and APOE-ε4; middle risk: either FH or APOE-ε4; low risk: neither FH nor APOE-ε4).

Alzheimer's Disease Neuroimaging Initiative (ADNI) Dataset: An independent sample including 52 amnesia-MCI (aMCI) patients and 38 cognitively normal controls was selected from the ADNI dataset (www.loni.ucla.edu/ADNI). All these participants received MMSE and Alzheimer's Disease Assessment Scale 13-item cognitive subscale (ADAS13) evaluations, CSF Aβ 42 and t-tau measurements, APOE genotyping, and multi-modal brain MRI scans. Subject descriptions and MRI acquisition protocol were provided in detail in the *Supplemental Materials*.

2.2. T1-Weighted MRI preprocessing

For each participant, a grey-matter (GM) volume map in the Montreal Neurological Institute (MNI) space was generated using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). In this process, all images were spatially normalized using combinations of affine linear transform and nonlinear registration to the standard MNI template and segmented into GM, white-matter, and cerebrospinal fluid. Segmented GM images were modulated to compensate the volumetric effects of expansion or shrinking employed in spatial normalization by multiplying the voxel intensity with the Jacobian determinants reflecting the parameters for fitting a voxel in native space to corresponding voxel in template space. The modulated images were then smoothed with a 10-mm full width half maximum isotropic Gaussian kernel and resampled to 3 mm isotropic voxels. These procedures created a whole-brain voxel-based GMV map for each participant. Then, we calculated the average GMV of each region in the Automated Anatomical Labelling atlas, which includes 90 prior cortical and subcortical regions in total. These 90 regional average GMV values were used as a feature vector to perform the following prediction analyses.

2.3. Brain age prediction using multivariate relevance regression (RVR) analysis

RVR is performed capturing the multidimensional aging patterns throughout the whole-brain and thus modeling structural brain aging. In order to generate the brain age model, the brain structural features (i.e., whole-brain GMV) were used to build an RVR model with the chronological ages as dependent variables. To quantify prediction accuracy, we applied leave-one-out cross-validation (LOOCV) to estimate the out-of-sample generalizability of the models. The correlation coefficient r and mean absolute error (MAE) between the estimated and chronological ages were used to quantify the prediction accuracy. Permutation tests were then used to determine whether the coefficient r and MAE were significantly better than the results expected by chance. The P values of the mean correlation r and mean MAE were calculated by dividing the number of permutations that showed a higher value than the actual value for the real sample by the total number of permutations (i.e., 1000). Details about the RVR model generation were described in *Supplemental Materials*. Accordingly, individual's *BrainAGE* score is defined as the difference between predicted brain age and chronological age. A negative *BrainAGE* reflects preserved brain health in the face of aging; conversely, a positive *BrainAGE* reflects decrements in brain

health in the face of aging.

2.4. Validation

In order to validate the brain age model, a 10-fold cross-validation (see *Supplementary Materials*) was applied to validate our prediction results. Furthermore, we made another validation analysis with using the whole-brain normalized GMV (i.e., raw regional/total intra-cranial volume) features to generate the brain age model (*Supplementary Materials*, Fig. S1).

2.5. Statistical analysis

Across the cognitively normal elderly subjects, one-way analysis of variance (ANOVA) and χ^2 tests were used to compare the demographic data among the 3 groups (i.e., high, middle and low-risk groups). One-way analyses of covariance (ANCOVAs) were further conducted to access the neuropsychological performances and *BrainAGE* scores, with age, education and sex as covariates. In addition, a multivariate linear regression analysis was further employed to investigate the effects of Alzheimer's disease Risk factors (i.e., FH and APOE-ε4), sex and education on *BrainAGE* scores. The statistical significance was set at $P < 0.05$.

Furthermore, an independent ANCOVA was used to compare the *BrainAGE* scores between the aMCI patients and healthy normal control (NC) subjects, with age, education and sex as covariates. The statistical significance was set at $P < 0.05$. In addition, to explore the potential of *BrainAGE* as a pre-screening tool for identifying aMCI patients, we took the individual's *BrainAGE* scores for all aMCI patients and NC subjects as a feature in the discrimination analysis. Further, to achieve superior classification performance, a fused classifier that combines the three features (i.e., the *BrainAGE* score, APOE-ε4 and bilateral hippocampus GMV) via the sum rule was further used in this study. To test the robustness of the results, we also validated the results by using the LOOCV validation method. Accuracy, sensitivity, specificity were used as quantitative assessments of the generalizability of the classifiers. A receiver operating characteristics (ROC) graph was also employed to evaluate the performance of the classifier. The area under a ROC curve (AUC) is a commonly used quantitative assessment of the diagnostic power of a predictive model.

3. Results

3.1. Alzheimer's disease risk factors, sex and education modulate the brain aging in cognitively normal elderly individuals

Cognitively normal elderly individuals were grouped according the FH of dementia and APOE allele status (i.e., high risk: both FH and APOE-ε4; middle risk: either FH or APOE-ε4; low risk: neither FH nor APOE-ε4). As shown in Table 1 and Table S1, no significant differences were observed in the demographic information and neuropsychological performances among the three groups.

Evaluated by LOOCV, the pattern of whole-brain GMV could accurately predict the cognitively normal elders' age at the individual level. The correlation between the predicted age and chronological age was r = 0.66 (permutation test, $P < 0.001$) (Fig. 1A). Although no significant difference was observed in the *BrainAGE* scores among the three groups, AD risk dose (i.e., the number of AD risk factors) is tend to associated with an increased *BrainAGE* (i.e., high-risk > middle risk > low risk) (Table 1, Fig. 1B). Regression analysis was further conducted to investigate the effects of APOE-ε4, FH of dementia, sex and education on the *BrainAGE* (Table 2). The presence of APOE-ε4 (95% CI −0.939 to 1.144, $P = 0.846$) and FH of dementia (95% CI −0.685 to 3.104, $P = 0.209$) did not increase the risk of having increased *BrainAGE*. However, the regression model revealed that female exhibited more advanced brain aging (i.e., increased *BrainAGE*) (95% CI 0.746 to 3.911, $B = 2.328$, $P = 0.004$), and that higher education years were associated with preserved brain aging (i.e., decreased *BrainAGE*) (95% CI −0.810 to −0.260, $B = -0.535$, $P < 0.001$) (Fig. 2).

Table 1
Demographics, neuropsychological performances and brain age gap for all participants.

	Low-risk (n = 89)	Middle-risk (n = 59)	High-risk (n = 17)	F/χ2	P value
Demographics					
Age (years)	67.1 ± 7.5	66.6 ± 7.2	64.8 ± 5.4	0.690	0.503 [a]
Gender (male/female)	47/42	29/30	6/11	1.762	0.414 [b]
Education (years)	12.1 ± 2.9	11.8 ± 3.1	11.7 ± 2.0	0.267	0.766 [a]
General cognition					
MMSE	28.42 ± 1.15	28.37 ± 1.36	28.47 ± 1.46	0.011	0.989 [c]
MDRS-2	138.03 ± 3.73	138.41 ± 3.14	138.59 ± 3.41	0.292	0.747 [c]
Composite z scores of each cognitive domain					
Episodic Memory	−0.05 ± 0.68	0.03 ± 0.72	0.16 ± 0.62	0.888	0.413 [c]
Visuospatial Function	−0.02 ± 0.81	0.05 ± 0.61	−0.09 ± 0.92	0.379	0.685 [c]
Information Processing Speed	−0.03 ± 0.74	−0.06 ± 0.81	0.37 ± 0.90	1.954	0.145 [c]
Executive Function	−0.05 ± 0.56	0.00 ± 0.68	0.23 ± 0.69	1.749	0.177 [c]
***BrainAGE* scores** (years)	−0.50 ± 5.52	0.14 ± 4.87	1.29 ± 6.82	0.851	0.429 [a]

Data are presented as the mean ± standard deviation. The level of each cognitive domain is denoted by the composite Z scores. Low-risk group demotes the subjects who possessed neither family history (FH) of dementia nor APOE-ε4. Middle-risk group demotes the subjects who possessed FH of dementia or APOE-ε4. High-risk group demotes the subjects who possessed both family history (FH) of dementia and APOE-ε4. *BrainAGE* is defined as the differences between predicted brain age and chronological age. A negative *BrainAGE* reflects preserved brain health in the face of aging; conversely, a positive *BrainAGE* reflects decrements in brain health in the face of aging.

[a] *P* values were obtained by one-way analysis of variance (ANOVA).
[b] *P* values were obtained by χ^2 test.
[c] *P* values were obtained by one-way analysis of covariance (ANCOVA).

3.2. Advanced brain aging in aMCI and identification of aMCI using the BrainAGE model

An independent sample including aMCI patients and cognitive normal controls was selected from the ADNI dataset. Evaluated by LOOCV, the pattern of whole-brain GMV could also accurately predict all individual age; the correlation between the predicted age and chronological age was r = 0.38 (permutation test, $P < 0.001$) (Fig. 3A). And, the aMCI patients showed significantly increased *BrainAGE* scores as compared with cognitively normal controls ($F = 7.255$, $P = 0.009$), implying systematically advanced brain aging (Fig. 3B). Interestingly, the *BrainAGE* scores were negatively corrected with CSF Aβ42 levels in the aMCI group (r = −0.275, $P = 0.048$) (Fig. 3C).

In addition, discrimination analyses revealed that the *BrainAGE* was superior to the hippocampus GMV and APOE-ε4 status for identifying aMCI patients with an accuracy of 68.9% (*BrainAGE*: AUC = 0.686; APOE-ε4: AUC = 0.573; hippocampus GMV: AUC = 0.414). Further exploratory discrimination model combining *BrainAGE* scores, hippocampus GMV and APOE-ε4 indicated that the success rate for detecting aMCI patients effectively increased from 68.9% to 75.6% (*BrainAGE* & APOE-ε4 & hippocampus GMV: AUC = 0.752, sensitivity = 86.5%, specificity = 60.5%) (Fig. 3D). This result demonstrated that the possibility of utilizing *BrainAGE* in combination with APOE-ε4 and hippocampus GMV as a time-effective and cost-effective pre-screening tool for

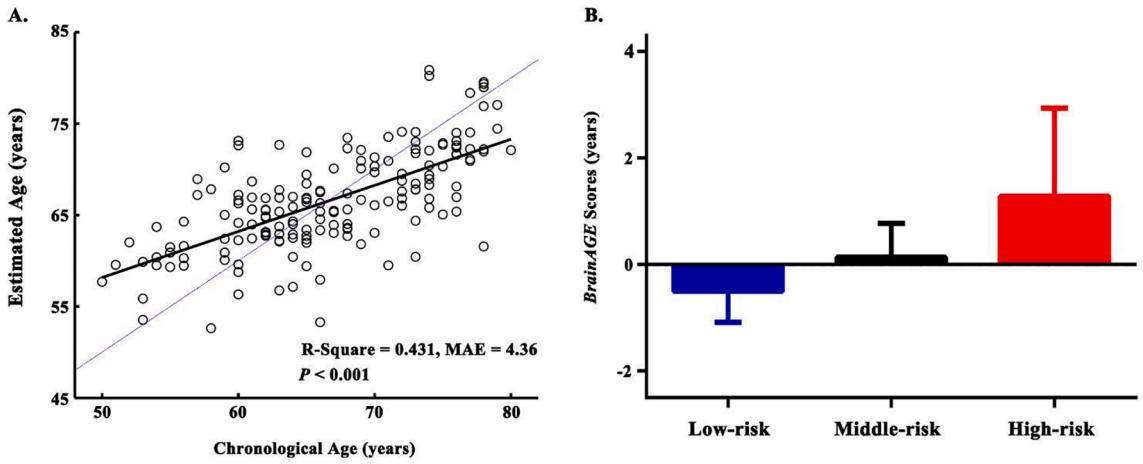

Fig. 1. (A) Age predicted according to T1-weighted image compared with actual age of each subjects in normal cognitively population. Diagonal line (i.e., blue line) indicates where the chronological age is equal to the predicted age. (B) Shown are box plots for *BrainAGE* scores of low-risk group, middle-risk group and high-risk group. The data were expressed as the mean (M) ± standard error (SE).

Table 2
Effects of APOE genotype, FH of dementia, gender and education on the *BrainAGE* with the linear regression analysis.

Predictors	Regression coefficients (95% CI)	*P* value
FH of dementia	1.210 (−0.685 to 3.104)	0.209
APOE-ε4	0.102 (−0.939 to 1.144)	0.846
Female	2.328 (0.746 to 3.911)	0.004
Education	−0.535 (−0.810 to −0.260)	< 0.001

Abbreviations: APOE, apolipoprotain E; CI, confidence interval; BrainAGE, Brain age gap estimation; FH, family history.

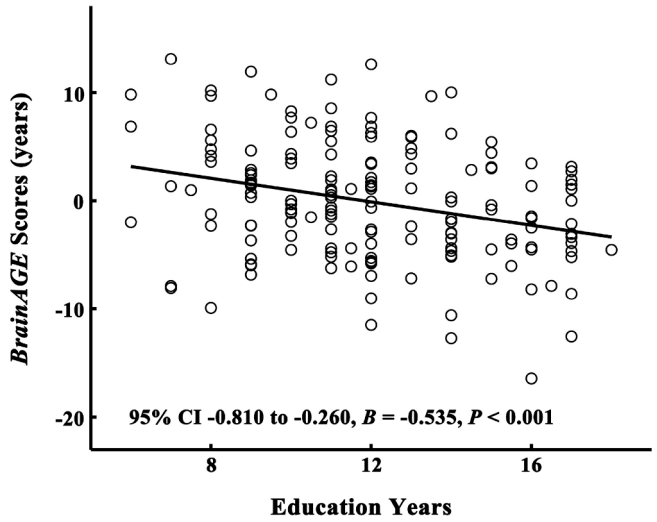

Fig. 2. Association between BrainAGE scores and education years. The regression model revealed that higher education years were associated with preserved brain aging (i.e., decreased *BrainAGE*) (95% CI −0.810 to −0.260, $B = -0.535$, $P < 0.001$).

identifying individuals with high-risk for AD.

4. Discussion

Using data from NADS and ADNI dataset, we have found the relationship between AD risk factors and brain aging. Though, the study showed that three groups' *BrainAGE* scores (high risk group, middle risk group and low risk group) were lack of statistical difference, we found a trend that as the risk factors for AD increase, so did the risk of brain aging. Specifically, when analyze the influence of education, gender, FH of dementia and APOE-ε4 genotype on brain aging, we observed that higher levels of education were correlated with lower brain age and female exhibited more advanced brain aging. The following, as a supplement to previous research, we selected aMCI to study the alterations of brain age in the early stages of AD. Consistent with our assumption, we confirm that patients with aMCI had more advanced brain aging. More interestingly, negative correlation between *BrainAGE* scores and CSF Aβ42 levels in the aMCI group was observed. Finally, it's worth noting that we combined *BrainAGE* with APOE-ε4 and hippocampus GMV, and put forward an optimal predictor markers of early screening for AD.

The brain goes through a continuous process from development to aging throughout life. However, some pathogenic factors or neurodegenerative diseases affect the aging process of the brain. During the natural course of AD, the brain is exposed to aging as well as disease effects. *BrainAGE* scores can not only represent age-related brain degeneration, but also show accelerated biological aging and early signs of cognitive decline from childhood [16]. Extending the subjects to cognitively normal people, we observed that AD risk factors can affect brain aging, which means AD may accelerate brain structure and function's changes during aging. Higher the risk factors for AD in normal people, the faster the brain shrinks. In previous studies, several risk factors for AD, such as type 2 diabetes mellitus [18], obesity and dyslipidemia [19], have been associated with advance brain aging. A large number of neurons die in patients with AD, which in turn aggravates brain atrophy, may be one of the mechanisms. Further exploring, with the increase of years of education, the score of *BrainAGE* tend to decrease and the change was statistically significant, concluding that the high cognitive reserve make the brain structure 'younger' in normal participants. Similarly, previous studies have found that higher levels of education are associated with a lower risk of dementia [20]. Acquiring a large amount of information during learning may be related to the pattern of changes in specific structural GM in specific brain regions [21]. People who practice meditation or make music for a long time have lower scores for brain age differences [22,23]. Anja et al. [24] proved that higher cognitive reserve scores are associated with better cognitive performance. The functional conclusion above is consist with our results from the perspective of structure. However, the mechanism by which reserves mediate the relationship between pathology and cognitive function is through a delay in symptom onset rather than a reduction in the rate of cognitive decline. Once MCI occurred, the higher the cognitive reserve score, the faster the cognitive decline [24].

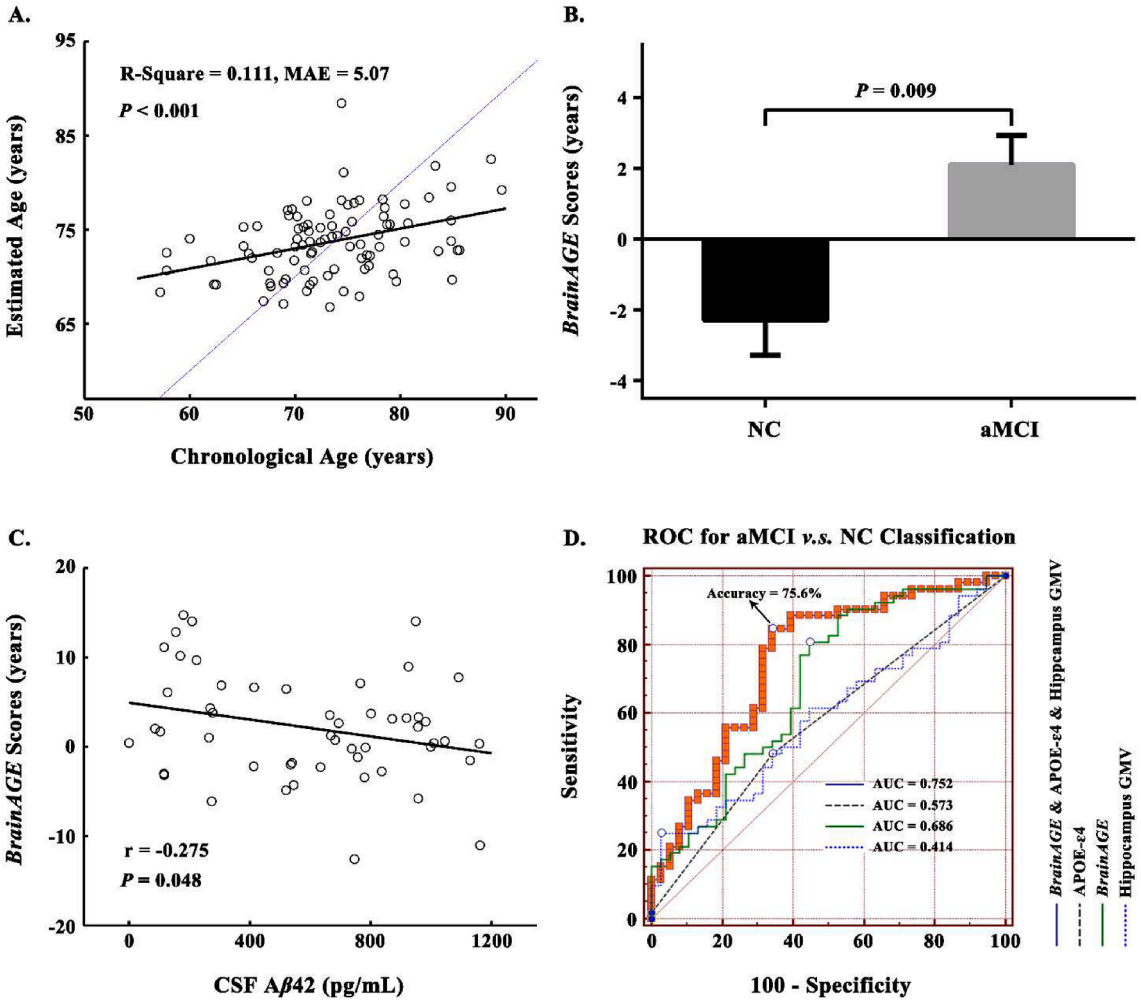

Fig. 3. (A) Age predicted according to T1-weighted image compared with actual age of each subject with aMCI. Diagonal line (i.e., blue line) indicates where the chronological age is equal to the predicted age. (B) Shown are box plots for *BrainAGE* scores of two groups ($P = 0.009$). The data were expressed as the mean (M) ± standard error (SE). (C) The line represents a negative correlations between *BrainAGE* scores and CSFAβ42. (D) ROC curves for classifying aMCI subject and NC subjects.

Sex differences play a vital role in human brain structure and physiology. Eileen Luders et al. found female brains at age 50 were estimated more than three years younger than male brains [25]. This is contrary to our findings. In the current cross-sectional study, we demonstrated that women had a statistically significant higher *BrainAGE* scores than men. It's worth noting that the women in the two studies were in different ages. Woman's brain morphology varies during the course of the menstrual cycle and *BrainAGE* is modulated by hormone levels [26]. Estrogen has a neuroprotective effect on age-related brain atrophy [27]. However, the women in our study were almost postmenopausal, whose brain volume has declined over the long term [28]. This also explain why brain aging is sex-specific. These results suggest that postmenopausal women may be at high risk for AD. In terms of metabolic brain age, women exhibit a significant "youth" advantage in adulthood, but this advantage disappears after cognitive impairment [29]. Apart from hormonal reasons, another possible mechanisms may be correlated with sex-specific associations between lifestyle-related health measures and gray matter atrophy [30]. Another multi-center study of 228 cognitively unimpaired elderly subjects demonstrated that some physiological and clinical parameters, such as markers of liver and kidney functions, that influence structural brain aging show a sex-specific pattern [31]. However, the mechanism of gender-specific needs to be further studied.

AD is a multifactorial disease with genetic (70%) and environmental (30%) causes. It is well known that the APOE-ε4 allele is an established risk factor for AD [32]. Compared with non-carriers, carriers of APOE-ε4 are approximately 8 to 15 times more likely to develop AD. APOE-ε4 also affects the clinical course of AD, leading to early onset of dementia, high degree of brain atrophy, and rapid cognitive decline [33]. The presence of the ε4 allele is associated with an earlier onset of terminal cognitive decline and a faster rate of cognitive decline before and after onset [34,35]. In the present research, *BrainAGE* scores did not differ between APOE-ε4 carriers and non-carriers in CN subjects. This is in line with Luise Christine Löwe's results suggesting that *BrainAGE* scores had no significant differences between ε4 carriers and non-carriers in MCI as well as AD patients from ADNI dataset [36]. Similar results were observed in patients with mild traumatic injury using brain morphometry and diffusion tensor imaging [37]. However, looking longitudinally, the brain ages faster in APOE-ε4 carriers than in non-carriers in progressive MCI (pMCI) and AD patients [36]. In normal control group and stable MCI (sMCI), the effect of APOE-ε4 on brain aging was significantly lower, indicating that the influence of allele on brain aging rates depends on the type of AD. One reason is that the closer to the late or end stages of AD, the influence of ε4 allele on the speed of brain aging is more obvious. Moreover, measurements used in this study may be not sensitive enough and that other objective markers of biological aging could provide additional information, such as Telomere length and epigenetic clock. Therefore, we cannot conclude that APOE-ε4 have no

effect on brain aging in cognitively normal people, which may already influence the aging rates subtly. FH and APOE4 highly co-occur and, conceivably, their effects on developing AD dementia may overlap [38]. Furthermore, APOE4 and FH have synergistic interaction effects on cerebral Aβ deposition and glucose metabolism in cognitive normal middle-aged and older adults [39]. A first-degree FH of dementia is a well-documented risk factor for AD; however, the influence of FH on brain aging across the lifespan is poorly understood. FH of AD affects mitochondrial function by modulating translocase of outer mitochondrial membrane, leading memory decline [40]. Whether or not there's a family history, no significant group differences in behavioral performance and hippocampal volume were found from the studies by M.N. Rajah et al. [41]. Similarly, we also failed to observe the effect of FH on brain age. This may be due to our small sample size, or we need to select more different stages of AD for analysis. Even so, healthy people with both FH and APOE4 need more attention for AD prevention. Future efforts will seek to design larger-scale neuroimaging studies and integrate the neuroimaging findings with deep genetic.

Katja et al. found that the mean *BrainAGE* score for the AD patients was +10 years, implying systematically advanced brain aging [10]. Consistent with the hypothesis that pathological atrophy of AD is an accelerated aging process [42], as a supplement to previous researches, we found a significant difference in the *BrainAGE* scores between aMCI patients and CN controls. Different types of AD follow different trajectories of brain aging. The brains of people with AD age at a faster rate than those with pMCI [43]. From the perspective of cognitive decline, different regional atrophy patterns are associated with different cognitive impairment profiles. Advanced brain aging in normal people were associated with lower executive function. Decrease of CSF Aβ42 levels is an important marker for early diagnosis of AD, which directly reflects the deposition of brain amyloid protein [44]. It is interesting to note a negative correlation between *BrainAGE* scores and CSF Aβ42 levels. Although aging itself appears to be associated with synaptic and nerve loss in the absence of proteinopathy [45], abnormal protein deposition in the brain of AD patients increases with age and further leads to neuronal damage and loss, accelerating brain aging. This finding further provides additional evidence for the link between AD and brain aging. Early identification of brain anatomy that differs from normal growth and atrophy patterns coupled with early intervention has important implications for improving clinical outcomes, for example in AD. In fact, hippocampal volume, whole brain volume and apparent "brain volume" are all potential biomarkers for AD [46]. In a study by Gaser et al., BrainAGE scores were used to predict the transition from MCI to AD which was more accurate than the conversion prediction based on hippocampal volume, cognitive score, and CSF biomarkers [15]. That is consistent with our findings. This study provides evidence that *BrainAGE* scores was better than hippocampal GMV and APOE-ε4 in differentiating patients with aMCI. When combining *BrainAGE* with cerebrospinal fluid biomarkers and hippocampal volume, the sensitivity and specificity were highest, expected to be the best pre-screening tool.

Our study is not without limitations. First, white matter damage due to cerebrovascular disease was not detected in the segmentation method. In future, the segmentation should be extended by methods in combination with FLAIR sequence. Besides, subjects with high *BrainAGE* scores but without cognitive impairment may have other preclinical neurodegenerative diseases. However, because such situation only occurs in a limited number of subjects that unlikely contribute to the difference in outcome. Thirdly, we were unable to observe a relationship between cognitive reserve and the rate of brain aging. Further studies should longitudinal investigate the relationship. Forth, in this present study, whole-brain raw GMVs were used to generate the brain age model, and we found that females exhibited more advanced brain aging (i.e., increased *BrainAGE*) than the males. However, with using the whole-brain normalized GMV (i.e., raw regional/total intra-cranial volume) features to generate the brain age model, we observed no significant gender difference in the *BrainAGE*. Further studies with larger independent sample were needed to validate the gender-effect on brain aging. The last, providing information on the differences in brain age analysis between different brain regions is of great value, in the years to come.

5. Conclusions

AD is a process of the brain pathological aging. Enhancing cognitive reserve may be one way to delay brain aging. *BrainAGE* has shown promising results in providing early signs of pathological brain aging before clinical symptoms of AD and even predicting future AD. Since this method requires only a single T1-weighted image of each individual, it can be easily implemented in clinical work to act as a pre-screening tool for identifying AD. In addition, research on the relationship between brain age and AD may help to develop personalized neuroprotective treatments and interventions.

Funding support

This study was funded by The National Natural Science Foundation of China (No. 81801680).

CRediT authorship contribution statement

Mengxue Wang: Conceptualization, Validation, Formal analysis. **Qingguo Ren:** Writing – original draft, Methodology. **Yachen Shi:** Investigation. **Hao Shu:** Investigation. **Duan Liu:** Visualization. **Lihua Gu:** Writing – review & editing. **Chunming Xie:** Resources. **Zhijun Zhang:** Supervision. **Tiange Wu:** Visualization. **Zan Wang:** Funding acquisition, Project administration.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neulet.2021.136398.

References

[1] R. Loera-Valencia, A. Cedazo-Minguez, P.A. Kenigsberg, G. Page, A.I. Duarte, P. Giusti, M. Zusso, P. Robert, G.B. Frisoni, A. Cattaneo, M. Zille, J. Boltze, N. Cartier, L. Buee, G. Johansson, B. Winblad, Current and emerging avenues for Alzheimer's disease drug targets, J. Intern. Med. 286 (2019) 398–437.

[2] U. Dube, J.L. Del-Aguila, Z. Li, J.P. Budde, S. Jiang, S. Hsu, L. Ibanez, M. V. Fernandez, F. Farias, J. Norton, J. Gentsch, F. Wang, S. Salloway, C.L. Masters, J. H. Lee, N.R. Graff-Radford, J.P. Chhatwal, R.J. Bateman, J.C. Morris, C.M. Karch, O. Harari, C. Cruchaga, An atlas of cortical circular RNA expression in Alzheimer disease brains demonstrates clinical and pathological associations, Nat. Neurosci. 22 (2019) 1903–1912.

[3] H. Braak, E. Braak, Neuropathological stageing of Alzheimer-related changes, Acta Neuropathol. 82 (1991) 239–259.

[4] R. Sperling, E. Mormino, K. Johnson, The evolution of preclinical Alzheimer's disease: implications for prevention trials, Neuron 84 (2014).

[5] G.E. Michael, K. Mee-Ohk, D.G. Michael, Clinical neurology and epidemiology of the major neurodegenerative diseases, CSH Perspect. Biol. 10 (2018).

[6] M.E. Levine, A.T. Lu, A. Quach, B.H. Chen, T.L. Assimes, S. Bandinelli, L. Hou, A. A. Baccarelli, J.D. Stewart, Y. Li, E.A. Whitsel, J.G. Wilson, A.P. Reiner, A. Aviv, K. Lohman, Y. Liu, L. Ferrucci, S. Horvath, An epigenetic biomarker of aging for lifespan and healthspan, Aging (Albany NY) 10 (2018) 573–591.

[7] F.C. Ludwig, M.E. Smoke, The measurement of biological age, Exp. Aging Res. 6 (1980) 497–522.

[8] J.H. Cole, K. Franke, Predicting age using neuroimaging: innovative brain ageing biomarkers, Trends Neurosci. 40 (2017) 681–690.

[9] M. Habes, R. Pomponio, H. Shou, J. Doshi, E. Mamourian, G. Erus, I. Nasrallah, L. J. Launer, T. Rashid, M. Bilgel, Y. Fan, J.B. Toledo, K. Yaffe, A. Sotiras, D. Srinivasan, M. Espeland, C. Masters, P. Maruff, J. Fripp, H. Volzk, S.C. Johnson, J.C. Morris, M.S. Albert, M.I. Miller, R.N. Bryan, H.J. Grabe, S.M. Resnick, D.

A. Wolk, C. Davatzikos, The Brain Chart of Aging: Machine-learning analytics reveals links between brain aging, white matter disease, amyloid burden, and cognition in the iSTAGING consortium of 10,216 harmonized MR scans, Alzheimers Dement. 17 (2021) 89–102.
[10] K. Franke, G. Ziegler, S. Kloppel, C. Gaser, Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters, Neuroimage 50 (2010) 883–892.
[11] T.T. Le, R.T. Kuplicki, B.A. McKinney, H.W. Yeh, W.K. Thompson, M.P. Paulus, A Nonlinear simulation framework supports adjusting for age when analyzing BrainAGE, Front. Aging Neurosci. 10 (2018) 317.
[12] K. Franke, C. Gaser, Ten years of BrainAGE as a neuroimaging biomarker of brain aging: what insights have we gained? Front. Neurol. 10 (2019) 789.
[13] J.H. Cole, J. Raffel, T. Friede, A. Eshaghi, W.J. Brownlee, D. Chard, N. De Stefano, C. Enzinger, L. Pirpamer, M. Filippi, C. Gasperini, M.A. Rocca, A. Rovira, S. Ruggieri, J. Sastre-Garriga, M.L. Stromillo, B. Uitdehaag, H. Vrenken, F. Barkhof, R. Nicholas, O. Ciccarelli, Longitudinal assessment of multiple sclerosis with the brain-age paradigm, Ann. Neurol. 88 (2020) 93–105.
[14] I. Nenadic, M. Dietzek, K. Langbein, H. Sauer, C. Gaser, BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder, Psychiatry Res. Neuroimaging 266 (2017) 86–89.
[15] C. Gaser, K. Franke, S. Kloppel, N. Koutsouleris, H. Sauer, BrainAGE in mild cognitive impaired patients: predicting the conversion to Alzheimer's disease, PLoS ONE 8 (2013), e67346.
[16] M.L. Elliott, D.W. Belsky, A.R. Knodt, D. Ireland, T.R. Melzer, R. Poulton, S. Ramrakha, A. Caspi, T.E. Moffitt, A.R. Hariri, Brain-age in midlife is associated with accelerated biological aging and cognitive decline in a longitudinal birth cohort, Mol. Psychiatry (2019).
[17] S.M. Smith, L.T. Elliott, F. Alfaro-Almagro, P. McCarthy, T.E. Nichols, G. Douaud, K.L. Miller, Brain aging comprises many modes of structural and functional change with distinct genetic and biophysical associations, ELIFE 9 (2020).
[18] K. Franke, C. Gaser, B. Manor, V. Novak, Advanced BrainAGE in older adults with type 2 diabetes mellitus, Front. Aging Neurosci. 5 (2013) 90.
[19] M. Kolenic, K. Franke, J. Hlinka, M. Matejka, J. Capkova, Z. Pausova, R. Uher, M. Alda, F. Spaniel, T. Hajek, Obesity, dyslipidemia and brain age in first-episode psychosis, J. Psychiatr. Res. 99 (2018) 151–158.
[20] R.S. Wilson, L. Yu, M. Lamar, J.A. Schneider, P.A. Boyle, D.A. Bennett, Education and cognitive reserve in old age, Neurology 92 (2019) e1041–e1050.
[21] B. Draganski, C. Gaser, G. Kempermann, H.G. Kuhn, J. Winkler, C. Buchel, A. May, Temporal and spatial dynamics of brain structure changes during extensive learning, J. Neurosci. 26 (2006) 6314–6317.
[22] L. Eileen, C. Nicolas, G. Christian, Estimating brain age using high-resolution pattern recognition: younger brains in long-term meditation practitioners, Neuroimage 134 (2016).
[23] L. Rogenmoser, J. Kernbach, G. Schlaug, C. Gaser, Keeping brains young with making music, Brain Struct. Funct. 223 (2018) 297–305.
[24] A. Soldan, C. Pettigrew, Q. Cai, J. Wang, M.C. Wang, A. Moghekar, M.I. Miller, M. Albert, Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease, Neurobiol. Aging 60 (2017) 164–172.
[25] E. Luders, N. Cherbuin, C. Gaser, Estimating brain age using high-resolution pattern recognition: younger brains in long-term meditation practitioners, Neuroimage 134 (2016) 508–513.
[26] K. Franke, G. Hagemann, E. Schleussner, C. Gaser, Changes of individual BrainAGE during the course of the menstrual cycle, Neuroimage 115 (2015) 1–6.
[27] J.L. Eberling, C. Wu, M.N. Haan, D. Mungas, M. Buonocore, W.J. Jagust, Preliminary evidence that estrogen protects against age-related hippocampal atrophy, Neurobiol. Aging 24 (2003) 725–732.
[28] J.L. Eberling, C. Wu, R. Tong-Turnbeaugh, W.J. Jagust, Estrogen- and tamoxifen-associated effects on brain structure and function, Neuroimage 21 (2004) 364–371.
[29] I. Beheshti, S. Nugent, O. Potvin, S. Duchesne, Disappearing metabolic youthfulness in the cognitively impaired female brain, Neurobiol. Aging 101 (2021) 224–229.
[30] Y. Taki, S. Kinomura, K. Sato, K. Inoue, R. Goto, K. Okada, S. Uchida, R. Kawashima, H. Fukuda, Relationship between body mass index and gray matter volume in 1,428 healthy individuals, Obesity (Silver Spring) 16 (2008) 119–124.
[31] K. Franke, M. Ristow, C. Gaser, Gender-specific impact of personal health parameters on individual brain aging in cognitively unimpaired elderly subjects, Front. Aging Neurosci. 6 (2014) 94.
[32] L. Bertram, C.M. Lill, R.E. Tanzi, The genetics of Alzheimer disease: back to the future, Neuron 68 (2010) 270–281.
[33] B.D. Hoyt, P.J. Massman, C. Schatschneider, N. Cooke, R.S. Doody, Individual growth curve analysis of APOE epsilon 4-associated cognitive decline in Alzheimer disease, Arch. Neurol. 62 (2005) 454–459.
[34] L. Yu, P. Boyle, J.A. Schneider, E. Segawa, R.S. Wilson, S. Leurgans, D.A. Bennett, APOE epsilon4, Alzheimer's disease pathology, cerebrovascular disease, and cognitive change over the years prior to death, Psychol. Aging 28 (2013) 1015–1023.
[35] E.H. Corder, A.M. Saunders, W.J. Strittmatter, D.E. Schmechel, P.C. Gaskell, G. W. Small, A.D. Roses, J.L. Haines, M.A. Pericak-Vance, Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families, Science 261 (1993) 921–923.
[36] L.C. Löwe, C. Gaser, K. Franke, The effect of the APOE genotype on individual brainAGE in normal aging, mild cognitive impairment, and Alzheimer's Disease, PLoS ONE 11 (2016).
[37] T. Hellstrom, N. Andelic, A.G. de Lange, E. Helseth, K. Eiklid, L.T. Westlye, Apolipoprotein varepsilon4 status and brain structure 12 months after mild traumatic injury: brain age prediction using brain morphometry and diffusion tensor imaging, J. Clin. Med. 10 (2021).
[38] D. Scarabino, G. Gambina, E. Broggio, F. Pelliccia, R.M. Corbo, Influence of family history of dementia in the development and progression of late-onset Alzheimer's disease, Am. J. Med. Genet. B Neuropsychiatr. Genet. 171B (2016) 250–256.
[39] D. Yi, Y. Lee, M.S. Byun, J.H. Lee, K. Ko, B.K. Sohn, Y.M. Choe, H.J. Choi, H. Baek, C.H. Sohn, Y.K. Kim, D.Y. Lee, Synergistic interaction between APOE and family history of Alzheimer's disease on cerebral amyloid deposition and glucose metabolism, Alzheimers Res. Ther. 10 (2018) 84.
[40] A.A. Willette, J.L. Webb, M.W. Lutz, B.B. Bendlin, A.M. Wennberg, J.M. Oh, A. Roses, R.L. Koscik, B.P. Hermann, N.M. Dowling, S. Asthana, S.C. Johnson, Family history and TOMM40 '523 interactive associations with memory in middle-aged and Alzheimer's disease cohorts, Alzheimers Dement. 13 (2017) 1217–1225.
[41] M.N. Rajah, L. Wallace, E. Ankudowich, E.H. Yu, A. Swierkot, R. Patel, M. M. Chakravarty, D. Naumova, J. Pruessner, R. Joober, S. Gauthier, S. Pasvanis, Family history and APOE4 risk for Alzheimer's disease impact the neural correlates of episodic memory by early midlife, Neuroimage Clin. 14 (2017) 760–774.
[42] C. Davatzikos, F. Xu, Y. An, Y. Fan, S.M. Resnick, Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: the SPARE-AD index, Brain 132 (2009) 2026–2035.
[43] K. Franke, C. Gaser, Longitudinal changes in individual BrainAGE in healthy aging, mild cognitive impairment, and Alzheimer's disease, GeroPsych J. Gerontopsychol. Geriatric Psychiatry 25 (2012).
[44] K. Blennow, H. Zetterberg, Biomarkers for Alzheimer's disease: current status and prospects for the future, J. Intern. Med. 284 (2018) 643–663.
[45] R. Benavides-Piccione, I. Fernaud-Espinosa, V. Robles, R. Yuste, J. DeFelipe, Age-based comparison of human dendritic spine structure using complete three-dimensional reconstructions, Cereb. Cortex 23 (2013) 1798–1810.
[46] S.G. Popescu, A. Whittington, R.N. Gunn, P.M. Matthews, B. Glocker, D.J. Sharp, J. H. Cole, Nonlinear biomarker interactions in conversion from mild cognitive impairment to Alzheimer's disease, Hum. Brain Mapp. 41 (2020) 4406–4418.