Brain age gap as a potential biomarker for schizophrenia: A multi-site structural MRI study

Weiqi Man[1,2], Hao Ding[2,3], Chao Chai[2], Xingwei An[1], Feng Liu[2], Wen Qin[2], and Chunshui Yu[1,2,3,4]

Abstract— Gray matter atrophy in schizophrenia has been widely recognized; however, it remains controversial whether it reflects a neurodegenerative condition. Recent studies have suggested that the brain age gap (BAG) between the predicted and chronological ones may serve as a biomarker for early-stage neurodegeneration. Nevertheless, it is unknown its value for schizophrenia diagnosis and the potential meaning. We included structural MRI datasets from 8 independent sites in the current study, including 501 schizophrenia patients (SZ) and 512 healthy controls (HC). We first applied support vector regression (SVR) to train the age prediction model of the controls using the gray matter volume (GMV) and apply this model to predict the age of the SZ. Meta-analysis identified the SZ had significantly higher BAG than the HC (Cohen's d = 0.38, 95% confidence level = [0.19, 0.57]), and this trend was reliably repeated in each site. Furthermore, logistic regression demonstrated BAG can significantly discriminate the SZ from the HC $(OR = 1.07, P = 7.14 \times 10^{-8})$. Finally, the linear regression study demonstrated a significant negative correlation between the BAG and gray matter volume in both groups, especially at the subcortical regions and prefrontal cortex (P<0.05, corrected using the family-wise error method).

Clinical Relevance— This multi-site study suggested that the brain age gap derived from machine learning can be taken as a potential biomarker for schizophrenia, which is significantly associated with brain gray matter atrophy.

I. INTRODUCTION

Schizophrenia is a severe psychiatric disorder with a lifetime prevalence of about 1%, rendering it a leading cause of disability worldwide, with 26 million people affected [1]. Numerous studies have found that patients with schizophrenia exhibit age-related gray matter atrophy[2-3]. Converging evidence has accumulated suggesting that schizophrenia may be disorders associated with accelerated aging [4-6]. The extent to which someone deviates from healthy brain-aging trajectories could potentially indicate underlying problems in outwardly healthy people and relate to the risk of cognitive aging or age-associated brain disease. Hence, reliable biomarkers of brain aging could be of great neuroscientific and clinical value [7]. However, the relationships between brain structure and aging in patients with schizophrenia require further disentanglement.

In recent years, many machine learning methods have been used to predict the biological age of an individual's brain (i.e., brain age) [8]. Cole et al. believed that predicted age difference, the brain age gap (BAG), defined as the difference between predicted brain age and chronological age, can be considered as the deviation from a normal trajectory of brain structural changes due to aging, representing an excess of aging effect of the brain [9]. A recent meta-analysis framework reported that schizophrenia and bipolar disorders had abnormal BAG using multi-center diffusion tensor imaging [10]. Although it is widely acknowledged that machine learning can be used to predict brain age, the biological significance of the indicator remains unclear.

In this study, to test whether BAG can be used as a potential biomarker for schizophrenia, we included structural MRI datasets from 8 independent sites, including 501 schizophrenia patients (SZ) and 512 healthy controls (HC). We applied support vector regression (SVR) to train the age prediction model of the HC using the gray matter volume (GMV) and apply this model to predict the brain age and calculate the BAG. We found a significantly higher BAG in the SZ, which can be reliably repeated in each site. Furthermore, logistic regression demonstrated that BAG could significantly distinguish schizophrenia from the HC. Finally, the BAG was closely associated with the atrophy of brain gray matter.

II. MATERIALS AND METHODS

A. Participants

This study included structural MRI datasets from 8 independent sites, in which three datasets were scanned at the local institute, and five public datasets were collected from the SchizConnect database [12]. Only the baseline datasets and participants over 18 years old were included. Finally, 501 patients with schizophrenia and 512 healthy controls were ultimately enrolled. The study was approved by the ethical committee of the Tianjin Medical University General Hospital, and written informed consent was obtained from each subject from the local institute. The demographics of each dataset was shown in Table I.

1 Academy of Medical Engineering and Translational Medicine, Tianjin University, Tianjin, 300072, China

2 Department of Radiology and Tianjin Key Lab of Functional Imaging, Tianjin Medical University General Hospital, Tianjin 300052, China

3 School of Medical Imaging, Tianjin Medical University, Tianjin 300070, China

4 Chinese Academy of Sciences (CAS) Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai, China

Corresponding author: Wen Qin (wayne.wenqin@gmail.com) and Chunshui Yu (chunshuiyu@tmu.edu.cn)

TABLE I.   DEMOGRAPHICSTYLES

Dataset Name	Number of subjects per group	gender (m/f)	Age (SD)	TIV (SD)
BrainCluSchi	76(SZ)	67/9	36.14(14.09)	1514.56(143.14)
	85(HC)	58/27	38.02(12.27)	1489.09(138.62)
COBRE	83(SZ)	66/17	38.07(13.23)	1498.65(139.29)
	83(HC)	61/22	38.52(11.93)	1501.33(156.52)
fBIRN	43(SZ)	26/17	39.21(10.01)	1429.31(160.46)
	58(HC)	32/26	37.05(10.92)	1425.99(139.04)
MCIC	36(SZ)	28/8	32.28(9.82)	1463.16(164.98)
	29(HC)	19/10	37.45(11.27)	1535.06(132.55)
NMorphCH	43(SZ)	30/13	32.84(7.23)	1438.97(133.14)
	44(HC)	22/22	31.30(8.48)	1435.62(167.07)
Local1	117(SZ)	63/54	34.88(9.06)	1520.63(170.70)
	117(HC)	47/70	33.51(11.01)	1482.63(146.16)
Local2	33(SZ)	19/14	31.55(7.86)	1473.63(173.83)
	62(HC)	35/27	33.56(11.17)	1476.92(131.22)
Local3	70(SZ)	30/40	34.10(5.82)	1493.21(147.74)
	34(HC)	11/23	32.62(6.12)	1514.23(133.20)

(SZ-Schizophrenia Patients, HC-Healthy Controls, SD-standard deviation, TIV-total intracranial volume)

B. MRI Data preprocessing

3D T1-weighted structural MRI images were first corrected for bias-field inhomogeneities using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and CAT12 (http://www.fil.ion.ucl.ac.uk/spm). Then images were segmented into gray matter, white matter, and cerebrospinal fluid. The segmented components were spatially normalized into the Montreal Neurological Institute (MNI) space using the DARTEL algorithm and resampled to a voxel size of 1.5mm $\times$ 1.5mm $\times$ 1.5mm [13]. The gray matter volume (GMV) was calculated by multiplying the normalized gray matter component with the Jacobian determinant. All GMV images were harmonized by a Combat technique to remove the system bias across sites [15]. GMV images were spatially smoothed using a Gaussian kernel with 8-mm full-width at half-maximum (FWHM)[14].

C. Brain Age Prediction

The GMV images of all 512 HC were used to train an SVR model to predict a subject's age. Considering that Gaussian smoothing can affect the features' independence, the GMV images we used to build an SVR model were only processed after Harmonization. All the HC were split into training and test datasets using 5-fold cross-validation. We collected all 512 healthy subjects' chronological age and predicted age from test datasets, then computed the Pearson correlation (r), root-mean-square error (RMSE), and mean absolute error (MAE) to evaluate the performance of the model. We also obtained the predicted age of the SZ using the pre-trained SVR model based on the HC. Then we calculated the BAG to characterize brain-aging trajectories for each individual (both HC and SZ) in the test datasets. Previous studies had shown that age and gender could affect brain age prediction. Thus the BAG was further undertaken confounders regression, and the corrected (residual) BAG was used for further evaluation [10][16].

D. Statistic analysis

Cohen's d was calculated to estimate the effect sizes of differences in BAG between the SZ and HC. A meta-analysis was used to assess the significance and generalizability of differences between the two groups[17] (P<0.05). Next, logistic regression was performed to assess the risk of BAG in discriminating the SZ from HC. Finally, a voxel-wise general linear model (GLM) was used to explore the correlation between BAG and GMV (P<0.05, family-wise error [FWE] correction), and the correlation interaction between the two groups .

III.   RESULTS

A. SVR performance measures

SVR demonstrated that the MAE was 5.00 years, RMSE was 7.82 years, and the correlation coefficient (r) between the predicted brain age and chronological age was 0.82 (P = 5.39 $\times 10^{-128}$)for healthy controls, whose predicted performance was better than the patients with schizophrenia (MAE = 6.18; RMSE = 7.82; r = 0.70, P = 9.16 $\times 10^{-74}$). The Scatter plot of predicted brain age and chronological age for the HC are shown in Fig. 1.
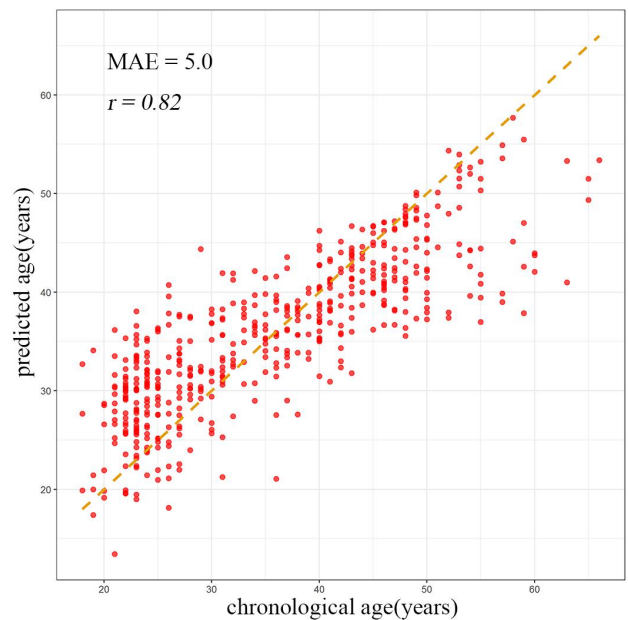

Fig. 1 Scatter plot of brain age and chronological age in 512 healthy controls.

B. Group-level Differences in Brain Age Gap

As is shown in Fig. 2, the histogram of BAG for schizophrenic patients (blue) was generally higher than that in healthy controls (red), indicating a tendency of large BAG for the SZ. Furthermore, the discrimination pattern of the age- and gender-corrected BAG (two-sample t-test, T = 5.55, p < 3.63 $\times 10^{-8}$) (Figure 2b) was better than the original one (two-sample t-test, T = 4.0, P = 7.0 $\times 10^{-5}$) (Figure 2a).
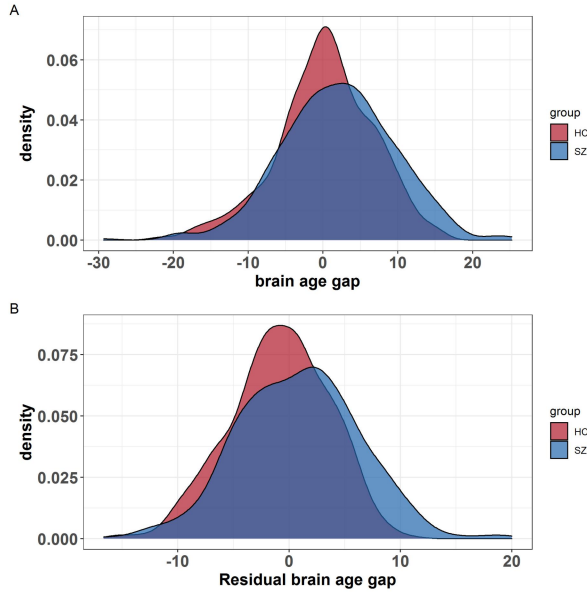
Fig. 2 The histogram of the brain age gap in schizophrenia and healthy controls. a) original brain age gap, b) age- and gender-corrected brain age gap. The blue color indicates schizophrenia, and the red color represents healthy controls.

Meta-analysis showed statistical higher BAG in the SZ than the HC (random effect model, Cohen's d = 0.38, 95% confidence level = [0.19, 0.57]). Furthermore, the forest plot demonstrated that all sites had the same effect directions, indicating good repeatability of the BAG across sites (Figure 3).
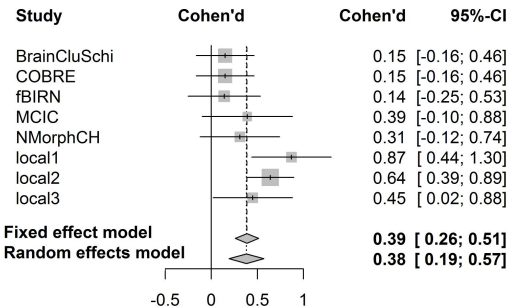

Fig. 3 Forest plot summarizing the results from the meta analysis. Cohen's d was used to calculate the effect size.

C. Logistic regression

A logistic regression was introduced to evaluate predicted probability of the corrected BAG in discriminate the SZ from the HC. As shown in Table II, the odds ratio was 1.07 for the BAG (P = 7.14 $\times$ 10^{-8}), indicated that for every 1 unit increase in BAG, the incidence of schizophrenia increases by 1.07 units.

TABLE II.   LOGISTIC REGRESSION

| Model | logistic regression | | |
	N (HC/PSY)	OR (95% CI)	P value
sample	1013 (512/501)	1.07 (1.05-1.10)	7.14×10^{-8}

Total number of participants (N), odds ratio (OR).

D. The association between brain age gap and GMV alterations

The association between the corrected BAG and GMV was shown in Figure 4. We found a significantly negative association between the BAG and wide distribution of `brain` GMV (P < 0.05, FWE correction), indicating BAG can characterize the gray matter atrophy in both normal subjects and patients with schizophrenia. Brain regions with more significant association included the subcortical regions, medial and lateral prefrontal cortex, etc. No brain region with correlation interaction was identified between the SZ and HC (P>0.05, FWE correction).

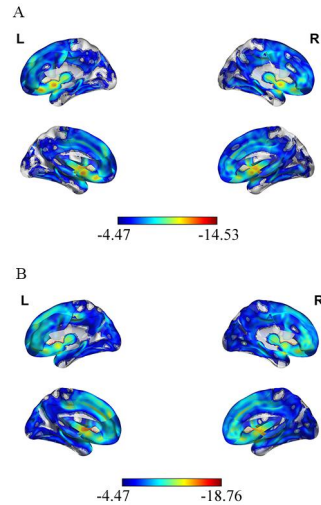Fig. 4 Brain regions with significant negative correlation between the BAG and GMV in healthy controls (A) and schizophrenia (B) (P < 0.05, FWE corrected).

In addition, we calculated the spatial correlation of the BAG-GMV association T-maps between the SZ and HC. We found a high positive correlation (r = 0.90, p < 0.001), indicating a general value of BAG in representing the GMV atrophy for both HC and SZ.
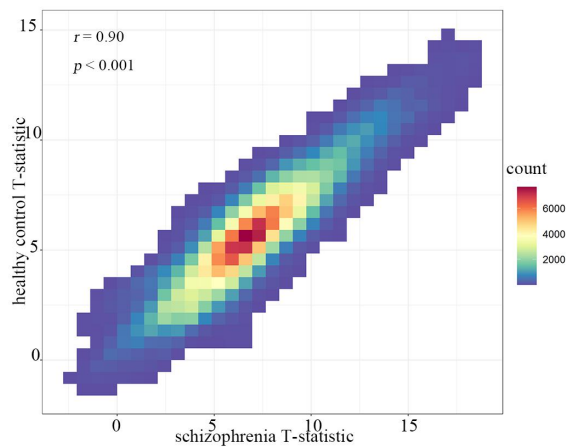
Fig. 5 Two-dimensional statistical histogram shows space correlation of GMVs reduction in derived from brain age gap between schizophrenia and healthy controls. Colorbar represents the count of voxels in each T value tile of whole brain.

IV. DISCUSSION AND CONCLUSION

Machine learning methods can capture very subtle differences between patients and normal people and are sensitive to identifying small deviations from normal trajectories [18]. However, due to the limitations of high data dimension and small sample size, the clinical application of machine learning in mental diseases is limited. This study combines the traditional machine learning and statistical model to discuss if the brain age gap, an indicator derived from machine learning, can distinguish schizophrenia patients from abnormal aging trajectories. Meanwhile, this study tried to explore the neurological explanation of the brain age gap. Based on a large sample size of structural MRI datasets from 8 independent sites, we first applied SVR to train the age prediction model of the HC using the GMV and apply this model to predict the brain age and calculate the BAG. We found a significantly higher BAG in the SZ, which can be reliably repeated in each site. Furthermore, BAG could significantly distinguish schizophrenia from healthy controls and was closely associated with the atrophy of brain gray matter. Thus, this multi-site study indicates the feasibility of BAG as potential neurobiological biomarkers for SZ individual diagnosis and reveals its neurological representation.

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