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Brain age gap difference between healthy and mild dementia subjects: Functional network connectivity analysis

Mohammad S. E. Sendi *Student Member, IEEE*, David H Salat, Vince D. Calhoun, *Fellow, IEEE*

Abstract— **Brain age gap, the difference between an individual's brain predicted age and their chronological age, is used as a biomarker of brain disease and aging. To date, although previous studies used structural magnetic resonance imaging (MRI) data to predict brain age, less work has used functional network connectivity (FNC) estimated from functional MRI to predict brain age and its association with Alzheimer's disease progression. This study used FNC estimated from 951 normal cognitive functions (NCF) individuals aged 42-95 years to train a support vector regression (SVR) to predict brain age. In the next step, we tested the trained model on two unseen datasets, including NCF and mild dementia (MD) subjects with similar age distribution (between 50-80 years old, N=70). The mean brain age gap for the NCF and MD groups was -2.25 and 2.08, respectively. We also found a significant difference between the brain age gap of NCF and MD groups. This piece of evidence introduces the brain age gap estimated from FNC as a biomarker of Alzheimer's disease progression.**

I. Introduction

The brain is a complex network of functionally and structurally interconnected regions. Functional network connectivity (FNC), which measures the communication between brain networks, has been shown to plays a key role in complex cognitive processes. FNC can provide insight into how large-scale neuronal communication in the human brain relates to human behavior and how this relationship may be altered in neurodegenerative disease.

Besides, recently, it has been shown that the predicted brain age gap, the difference between predicted brain age and chronological age, based on the structural MRI (sMRI) reveals information about the neurophysiological phenotype of the neurological disorders [1]. Another study based on the sMRI showed that the brain age gap successfully predicts mortality rate in older subjects [2]. This proves that the acceleration or deceleration of biological age relative to chronological age could be a better indicator of the future risk of experiencing age-associated health issues. However, most previous studies used sMRI [1]–[4] and rs-fMRI [5] data for brain age prediction , less work is done on the brain age prediction based on FNC estimated from rs-fMRI . In the current study, we hypothesized that FNC would be a predictor of brain age, and the brain age gap estimated by FNC data would be a biomarker of Alzheimer's disease progression. To test this hypothesis, we trained a support vector regression (SVR) based on the FNC estimated from healthy subjects and tested that model on the FNC of the unseen healthy subjects and mild dementia patients. Next, we calculated the brain age gap of both groups.

II. Materials and Methods

A. Participants

This study used 1091 fMRI data and their chronological age when scanning from the Open Access Series of Imaging Studies (OASIS)-3 cohort. The data are collected across several ongoing studies in the Washington University Knight Alzheimer Disease Research Center over 15 years [6]. We used the clinical dementia rating scale sum of boxes (CDR-SOB) scores to evaluate the participant's cognitive stage at scanning time. Overall we had 1021 normal cognitive function (NCF, CDR-SOB=0) and 70 mild dementia (MD, 4.5≤CDR-SOB≤9) subjects [7]. The mean, standard deviation, and the range of the NCF subject's age are 69.68, 8.52, and 42-95. For the MD subjects, the mean, standard deviation, and the range of the age are 73.34, 7.51, and 50-85 (Fig.1b). Also, the mean and standard deviation of the mini-mental state examination (MMSE) score in the MD group was 22.15±4.18.

B. Data Acquisition

Two scanners of TIM Trio 3T (Siemens Medical Solutions USA, Inc) with a 20 channel head coil on 3T scanners were used to collect rs-fMRI. High resolution T2*-weighted functional images were acquired using echoplanar imaging or EP sequence with TE =27 ms, TR = 2.2 s, flip angle = 90˚, slice thickness = 4mm, slice gap (center-to-center) = 4 mm, matrix size = 64, and field of view (FOV)= 256×256×128 mm3. The duration of the scanning was 6 minutes.

C. Preprocessing and functional network connectivity estimation

The statistical parametric mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/) running in

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M, S, E, Sendi (msendi6@gatech.edu) and V. D. Calhoun (vcalhoun@gsu.edu) are with the Department of Electrical and Computer Engineering at Georgia Institute of Technology, Atlanta, Georgia, Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology and Emory University, Atlanta, Georgia, and Tri-institutional Center for Translational Research in Neuroimaging and Data Science: Georgia State University, Georgia Institute of Technology, Emory University Atlanta, Georgia.

D. H. Salat (dsalat@mgh.harvard.edu) is with Harvard Medical school, Cambridge, Massachusetts, and Massachusetts General Hospital, Boston, Massachusetts.

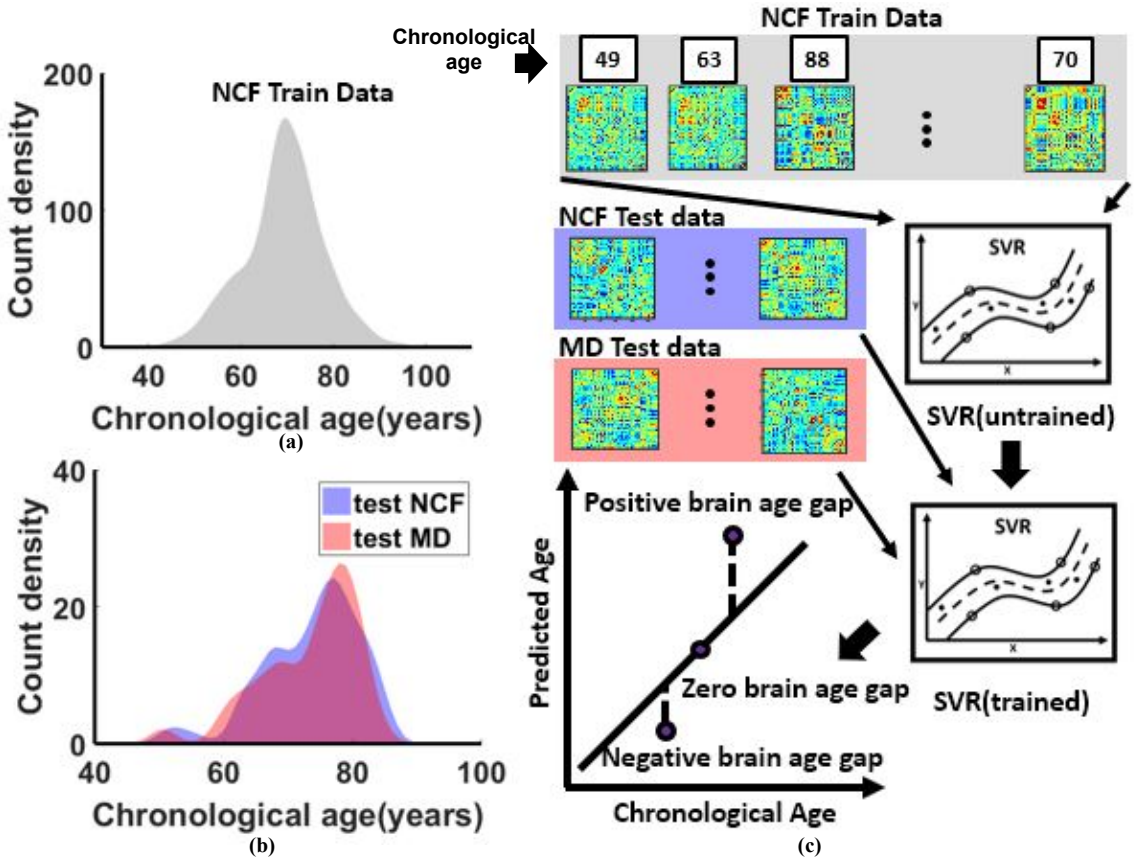

Fig.1. An overview of data ad method used in this study. a) The age distribution of normal cognitive function (NCF, N=951, age: 69.38± 8.52, range between 42-95) subjects used for training a support vector regression (SVR). b) The age distribution of unseen test data including NCF (blue, N=70, age: 73.66± 7.47, range between 50-85) and mild dementia or MD (red, N=70, age: 73.34± 7.51, range between 50-85). The age difference between two test datasets was not significant (p=0.8). c) The whole brain functional network connectivity (FNC) and the age of the NCF train data were used to train an SVR. Then, the unseen NCF and MD FNC was fed to train SVR to predict individual's brain age. Next, the difference between brain predicted age and chronological age or brain gap is calculated for both groups.

MATLAB2019 was used to preprocess the fMRI data. We removed the first five dummy scans before preprocessing.

We then used rigid body motion correction to account for subject head movement. Next, we did spatial normalization by echo-planar imaging (EPI) template into the standard Montreal Neurological Institute (MNI) space. Finally, we used a Gaussian kernel to smooth the fMRI images using a full width at half maximum (FWHM) of 6mm.

In the next step, we used the NeuroMark pipeline to extract subject-unique intrinsic connectivity networks (ICNs) with correspondence across different subjects [8]. Then, 53 ICNs was obtained for each subject and put them in seven domain networks. These domain networks included subcortical network (SCN), auditory network (ADN), sensorimotor network (SMN), visual network (VSN), cognitive control network (CCN), the default-mode network (DMN), and cerebellar network (CBN). More details on the extracted ICNs are provided in [9].

Next, Pearson correlation was used to calculate a 53×53 correlation matrix, which shows the correlation between any pair of ICNs. Overall, we had 1378 connectivity features for each subject. Fig. 2 a, b, & c show the mean FNC across all NCF train data, NCF test data, and MD test data, respectively. As shown in this figure, we observe a clear difference in VSN/SMN connectivity between NCF and patients with MD. This is consistent with our previous finding that showed less functional connectivity between VSN and SMN in the patient with MD[9].

D. Brain age prediction model

All 1378 connectivity features and the chronological age from 951 NCF training subjects (Fig.1a) were used to train an SVR model in MATLAB2019 (Fig.1c). The best hyperparameters, including kernel function, epsilon, and BoxConstraint, were selected through an optimization process. The optimized kernel function, epsilon, and BoxConstraint were linear, 0.4554, 0.008. Then, we tested the model on unseen NCF and MD datasets (Fig.1b). Finally, we calculated the difference between brain predicted age and chronological age for each individual in both unseen datasets.Nine hundred fifty-one healthy subjects were used for training the model. The model was tested on two unseen datasets. The first test dataset includes 70 NCF subjects and the second test dataset includes 70 MD patients. The age distribution of both datasets was similar.

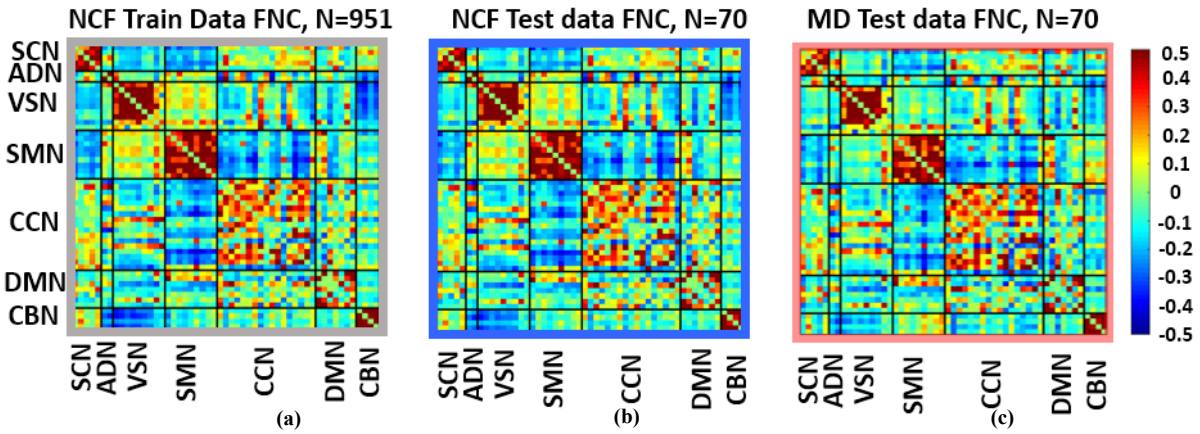

Fig.2. Functional network connectivity (FNC) shows the correlation between any pair of independent components. a) The average FNC across all normal cognitive function (NCF) subjects (N=951) in the training dataset, b) The mean FNC unseen NCF test data (N=70), c) The mean FNC unseen (mild dementia) MD test data (N=70). SCN: subcortical network, ADN: Auditory network, SMN: Sensorimotor network, VSN: Visual sensory network, CCN: Cognitive control network, DMN: Default mode network, CBN: Cerebellar network. Colorbar shows the strength of the connectivity.

III. Results

After training an SVR model using the train NCF dataset, we tested that model on unseen NCF and MD test data. Fig. 3a shows the correlation between predicted brain age and the chronological age in NCF test data ($r=0.73$, $p=5.3e^{-13}$, $N=70$). This result proves that the FNC features would be a predictor for brain predicted age. Fig. 3b shows the same correlation for the MD test data ($r=0.33$, $p=0.004$, $N=70$). This result shows that the model based on healthy subjects could better predict the healthy subject age than the MD subjects. Fig. 3 c shows the brain age gap of NCF and MD subjects. In this graph, the vertical dash lines show the mean of the brain age gap of NCF (blue) and MD (red) groups. The mean and standard deviation of the brain age gap for the NCF and MD group was -2.2581± 5.0879 and 2.0814± 7.4520. This result shows that the brain age gap was increased in MD subjects (Cohen's $d=0.68$, $p<0.001$). In addition, the range of the brain age gap of the MD group was higher than the brain age gap of the NCF group. This result shows that the brain age gap could be a biomarker of Alzheimer's disease progression. Also, we calculated the correlation between the brain age gap and MMSE score in the MD group and the correlation between chronological age and MMSE score. The correlation between the brain age gap and MMSE was $r=-0.14$ ($p=0.23$), while the correlation between the chronological age and MMSE score was $r=0.21$ ($p=0.07$). The negative correlation between the brain age gap and the MMSE score shows that a higher brain gap is associated with lower cognitive function. Although the link between the brain age gap and the MMSE score was not significant, the brain age gap was a better predictor than chronological age.

IV. Discussion

In this study, we predicted brain age based on the FNC features estimated from rs-fMRI. To the best of our knowledge, this is the first study that demonstrated the usage of FNC in predicting the brain age gap in healthy subjects and mild dementia patients. We showed that the model trained based on healthy subject FNC data would better predict healthy subjects' brain age than mild dementia patients. This result proves that possibly our model could capture the deviation from normal brain trajectory in the mild dementia group. Also, we found that the brain age gap of the mild dementia group was significantly higher than the brain age gap in controls.

Alzheimer's disease is the most common age-related problem and progresses in different stages. Recent studies showed FNC changes obtained from rs-fMRI during the transition from healthy aging to Alzheimer's disease. The current study's result potentially introduces the brain age gap estimated from FNC as a potential biomarker of Alzheimer's disease progression. A similar result was shown based on the sMRI data [1]. We also showed that the brain age gap was a better predictor of the cognitive decline in mild dementia subjects than the chronological age based on the correlation between the brain age gap and MMSE. While the result was not statistically significant, a larger dataset may help with this. Theoretically, the brain age gap reflects the prediction error of the machine learning model. This error can be associated with either underlying physiology (deviation from normal brain mapping) or noise (lower model accuracy) [1]. A model trained on a bigger imaging data set with higher quality would increase the trained model's confidence and possibly reduce the noise effect. Therefore, a future study with a bigger and higher quality rs-fMRI dataset is needed to evaluate the model's accuracy. In addition, we did not separate the male and female subjects in the current study due to the limited training and test data size. A previous study showed that females show a lower brain age gap than males [2]. Future study is needed to show whether gender would affect the brain's predicted age from FNC. Also, comparing the results of sMRI feature and fMRI feature in predicting brain age is needed.

V. Conclusion

In this paper, we proved that FNC estimated from rs-fMRI could predict brain age in healthy subjects. Results also

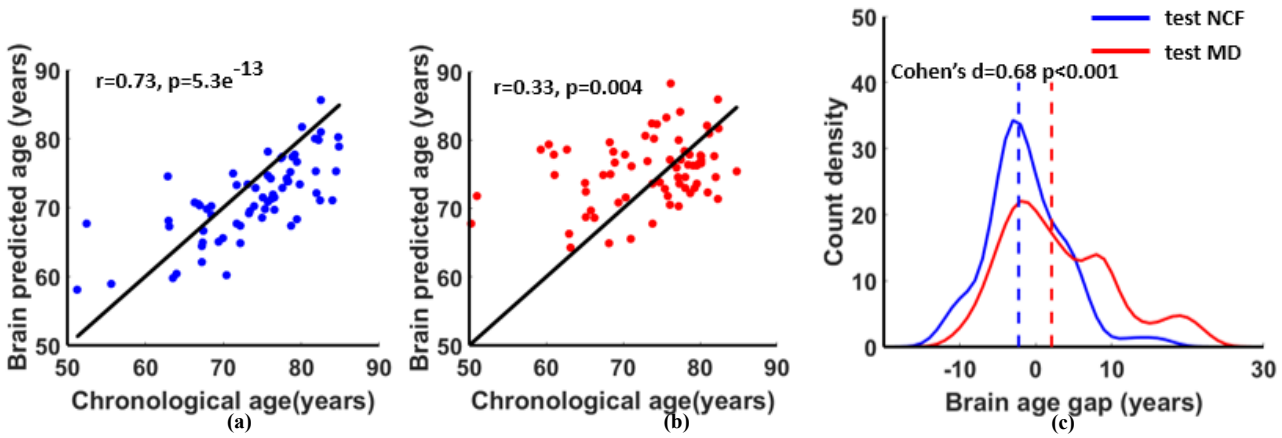

Fig.3. Brain prediction model results. a) The scatter plot of the predicted brain age versus chronological age for the normal cognitive function (NCF) unseen test data (r=0.73, p=5.3e^{-13}). The solid black line represents brain predicted age=choronological age.b) The scatter plot of the predicted brain age versus chronological age for the mild dementia (MD) unseen test data (r=0.33, p=0.004). c) The brain age gap of the test NCF and test MD dataset. The dash line represents the mean value of the brain age gap for each group. The brain age gap of MD group is significantly higher than that of NCF group (p<0.001). Also, MD brain age gap standard deviation is wider than that of NCF.

showed an acceleration in the brain predicted age on mild dementia subjects. We also found that the brain age gap of the mild dementia subjects was significantly higher than the brain age gap of the healthy subjects. This result potentially proves the brain age gap as a biomarker in the progression of Alzheimer's disease.

VI. References

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