Multiscale functional connectivity patterns of the aging brain learned from rsfMRI data of 4,259 individuals of the multi-cohort iSTAGING study

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Abstract

To learn multiscale functional connectivity patterns of the aging brain, we built a brain age prediction model of functional connectivity measures at seven scales on a large fMRI dataset, consisting of resting-state fMRI scans of 4259 individuals with a wide age range (22 to 97 years, with an average of 63) from five cohorts. We computed multiscale functional connectivity measures of individual subjects using a personalized functional network computational method, harmonized the functional connectivity measures of subjects from multiple datasets in order to build a functional brain age model, and finally evaluated how functional brain age gap correlated with cognitive measures of individual subjects. Our study has revealed that functional connectivity measures at multiple scales were more informative than those at any single scale for the brain age prediction, the data harmonization significantly improved the brain age prediction performance, and harmonization in the tangent space worked better than in the original space. Moreover, brain age gap scores of individual subjects derived from the brain age prediction model were significantly correlated with clinical and cognitive measures. Overall, these results demonstrated that multiscale functional connectivity patterns learned from a large-scale multi-site rsfMRI dataset were informative for characterizing the aging brain and the derived brain age gap was predictive of cognitive and clinical measures.

Keywords: resting-state fMRI, multiscale brain functional network, functional brain age, harmonization, tangent space parameterization, brain age gap

Introduction

Brain age derived from non-invasive magnetic resonance imaging (MRI) data using machine learning provides a novel means to quantify brain development and aging process (Douaud et al., 2014; Cole and Franke, 2017). Brain age gap (BAG), quantifying the difference between the brain age and the chronological age, has demonstrated promising performance for elucidating atypical brain development and aging (Cole and Franke, 2017; Truelove-Hill et al., 2020).

Most brain age modeling studies focused on structural MRI data and have shown that brain age is associated with changes in both gray matter (GM) (Erus et al., 2015; Chung et al., 2017; Minkova et al., 2017; Truelove-Hill et al., 2020) and white matter (WM) (Prins and Scheltens, 2015; Habes et al., 2016; Habes et al., 2021). Particularly, it has been demonstrated that the brain age derived from structural MRI data can accurately delineate trajectories of brain development and identify

individuals with cognitive precocity or delay (Erus et al., 2015). Similarly, it has been shown that brain development during adolescence is associated with widespread, regionally hierarchical gray matter loss and white matter increase (Truelove-Hill et al., 2020). A recent brain age modeling study also revealed brain aging trajectories in a large cohort (Habes et al., 2021). Moreover, large-scale neuroimaging studies have revealed that brain disorders are associated with brain age gap estimated from structural neuroimaging data (Kaufmann et al., 2019; Bashyam et al., 2020; Dinsdale et al., 2021).

The brain age has also been investigated based on functional neuroimaging data (Dosenbach et al., 2010; Dennis and Thompson, 2014; Li et al., 2018a; Zonneveld et al., 2019; Truelove-Hill et al., 2020). It has been demonstrated that brain maturity can be accurately estimated based on individual subjects' functional connectivity (FC) measures computed from functional MRI (fMRI) data (Dosenbach et al., 2010). Multiple studies have reported that the brain age is associated with changes in widespread functional network connectivity measures over the course of adolescence (Fair et al., 2008; Di Martino et al., 2014; Truelove-Hill et al., 2020). A large population-based aging study has revealed that brain aging is associated with weak FC within the anterior default mode network (DMN), ventral/salience attention network (VAN), and somatomotor network (SMN) and strong FC within the visual network (VN) (Zonneveld et al., 2019). However, most existing functional neuroimaging-based brain aging studies typically focused on data from single datasets (Dosenbach et al., 2010; Chan et al., 2014; Liang et al., 2019; Zonneveld et al., 2019), lacking diversity in the study cohorts.

In this study, we investigated functional connectivity patterns of the aging brain based on fMRI scans of a diverse cohort (n = 4259) from five different sites in a brain age modeling framework. We computed functional connectivity measures of individual subjects at multiple scales using a personalized functional network computational method (Li et al., 2017), harmonized the multiscale functional connectivity measures of different sites in their tangent space using ComBat-GAM (Pomponio et al., 2020), built a regression model on the harmonized functional connectivity measures to estimate the brain age and characterize the brain age gap, and finally we identified clinical and cognitive measures that were significantly correlated with the brain age gap in order to investigate whether the functional brain age gap is predictive of cognitive functions and biological measures.

Materials and methods

The overall design of this study for characterizing multiscale FC patterns of the aging brain is schematically illustrated in Figure 1, including computing multiscale FC measures of individual subjects, harmonizing the FC measures of multiple datasets, building a brain age prediction model to identify informative FC measures, and finally evaluating how the brain age gap correlated with cognitive/biological measures of individual subjects.

Participants

Table 1. Demographic information and the scanning protocols of the multisite data

		BLSA	OASIS-3	CARDIA-1	CARDIA-3	CARDIA-4	PENN_ABC	UKBIOBANK
Number of Subjects		784	826	199	323	280	276	1571
Number of Males (%)		341 (43.39)	462 (55.93)	88 (44.22)	156 (48.30)	125 (44.64)	113 (40.94)	884 (44.44)
Age	Mean±std	65.97±14.89	70.24±9.42	51.27±4.26	51.51±3.77	51.10±3.91	68.37±13.37	62.63±7.31
	Min	22	43	42	43	43	23	45
	Max	95	97	61	61	61	95	75
	Median	68	70	52	52	52	70	63
Scanner		Philips Achieva 3T	Siemens TIM Trio 3T	Philips Achieva 3T	Siemens TIM Trio 3T	Siemens TIM Trio 3T	Siemens Prisma 3T	GE (Multiband acceleration)
T1w	Resolution (mm^3)	1.2×1×1	1×1×1	1×1×1	1×1×1	1×1×1	0.8×0.8×0.8	1×1×1
	TR (ms)	35	2400	1900	1900	1900	3000	2000
	TE (ms)	3	3	2.89	2.89	2.89	3.54	2.01
fMRI	Resolution (mm^3)	3×3×4	4×4×4	3.5×3.5×3.5	3.5×3.5×3.5	3.5×3.5×3.5	2×2×2	2.4×2.4×2.4
	TR (ms)	2000	2200	2000	2000	2000	720	735
	TE (ms)	25	27	25	25	25	37	39
	Duration (min.)	6	6	4	4	4	5	6
	Num. of volumes	180	164	120	120	120	420	490

We identified 4549 participants with resting-state fMRI data from the iSTAGING (Imaging-based coordinate SysTem for AGIng and NeurodeGenerative diseases) consortium (Habes et al., 2021). The fMRI scans were collected from subjects at a wide age range (22 to 97 years) from 5 different cohorts, including the Baltimore Longitudinal Study of Aging (BLSA), the Open Access Series of Imaging Studies (OASIS-3), the Coronary Artery Risk Development in Young Adults (CARDIA), the University of Pennsylvania Aging Brain Cohort (PENN_ABC), and the UK (United Kingdom) Biobank. Particularly, the CARDIA cohort was divided into three subcohorts, namely CARDIA-1, CARDIA-3, and CARDIA-4, according to their scanners/sites used for the data collection. Since identical scanners and protocols were used for brain imaging scanning in the UKBiobank (Focke et al., 2011; Chen et al., 2014; Alfaro-Almagro et al., 2018), the UKBiobank scans were considered from one single data site. In summary, the fMRI scans were modeled from seven different sites, their demographic information and scanning protocols are summarized in Table 1. This study was

approved by the supervisory committee and the institutional review board of the University of Pennsylvania School of Medicine.

Data processing

The UKBiobank scans were processed using UKBiobank preprocessing pipeline (Alfaro-Almagro et al., 2018), and other scans were processed using a modified UKBiobank preprocessing pipeline with steps, including head motion correction by FSL's MCFLIRT (Jenkinson et al., 2012), global 4D mean intensity normalization, and temporal high-pass filtering (> 0.01 Hz). After these standard pre-processing steps, random noise was removed using FIX (FMRIB's Independent Component Analysis-based Xnoiseifier) (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). Specifically, the FIX model was built upon WhII_Standard.RData from Whitehall Imaging Study (Filippini et al., 2014) due to its similarity with our rsfMRI data. The preprocessed rsfMRI scans were co-registered to their corresponding T1-weighted images using FLIRT with BBR as the cost function, and the T1-weighted images were registered to the MNI152 template using FSL's FNIRT (non-linear registration), generating rsfMRI scans with a spatial resolution of $2 \times 2 \times 2$ mm^3. A brain mask was applied in standard space to exclude white matter, cerebral spinal fluid, and cerebellum (cerebellum are not fully covered for some subjects).

Participants were excluded from subsequent analyses if their rsfMRI scans had mean relative displacement higher than 0.2 mm, more than 60% of frames with motion exceeding 0.3 mm, or temporal signal-to-noise ratio (tSNR) smaller than 100 except for the UKBiobank scans that were acquired using a multiband protocol (Alfaro-Almagro et al., 2018). In total, 290 participants were excluded, and the remaining 4259 subjects were included in the following analyses.

Computation of multiscale functional connectivity measures

Multiscale functional connectivity measures were computed from each preprocessed rsfMRI scan based on functional networks (FNs) obtained using a personalized functional network computational method (Li et al., 2017; Cui et al., 2020). Instead of computing the FNs at a specific spatial scale, we computed the FNs at seven scales using a package available at https://github.com/hmlicas/Collaborative_Brain_Decomposition, yielding seven sets of K (K=17, 25, 50, 75, 100, 125 and 150) FNs. Then, functional connectivity measure between each pair of FNs within each set was estimated as Pearson correlation between time series of the FNs (Zhou et al., 2020), yielding seven sets of functional connectivity matrices $\boldsymbol{C} \in R^{K \times K}$, K=17, 25, 50, 75, 100, 125 and 150.

Harmonization of functional connectivity measures in tangent space

In order to alleviate site effect of functional connectivity measures of participants from different sites, we adopted ComBat-GAM to harmonize the functional connectivity measures (Pomponio et al., 2020). Since the functional connectivity measures themselves essentially resided on a Riemannian manifold (You and Park, 2021), we applied ComBat-GAM to the functional connectivity measures in their tangent space (Pervaiz et al., 2020). The tangent space projection of the FC matrix $\boldsymbol{C}$ was obtained through

$$\vec{\boldsymbol{C}} = \log_m\left(\boldsymbol{C}_r^{-\frac{1}{2}}\boldsymbol{C}\boldsymbol{C}_r^{-\frac{1}{2}}\right), \tag{1}$$

where $\boldsymbol{C}_r \in R^{K\times K}$ is a reference point in the manifold, K is the number FNs, $\log_m$ represents the logarithm operation on the FC matrix and $\vec{\boldsymbol{C}}$ is the resulting FC measures in the tangent space. To ensure that all projected covariance matrices lie in the same tangent plane, we chose the geometric mean as the reference point (Fletcher et al., 2004; Ng et al., 2014; Yger et al., 2017). The FC measures $\vec{\boldsymbol{C}}$ in the tangent space can be projected back to the original space by

$$\boldsymbol{C} = \boldsymbol{C}_r^{\frac{1}{2}} exp_m(\vec{\boldsymbol{C}})\boldsymbol{C}_r^{\frac{1}{2}}, \tag{2}$$

where exp_m is the exponential operation on the FC matrix.

We harmonized the FC measures in the tangent space using ComBat-GAM (Pomponio et al., 2020) with sex and age as covariates. After data harmonization, we vectorized the upper triangular part of the harmonized connectivity matrix in each scale and stacked them across scales to obtain a panel of multiscale features as illustrated in Figure 1. The data harmonization was performed using a package available at https://github.com/rpomponio/neuroHarmonize.

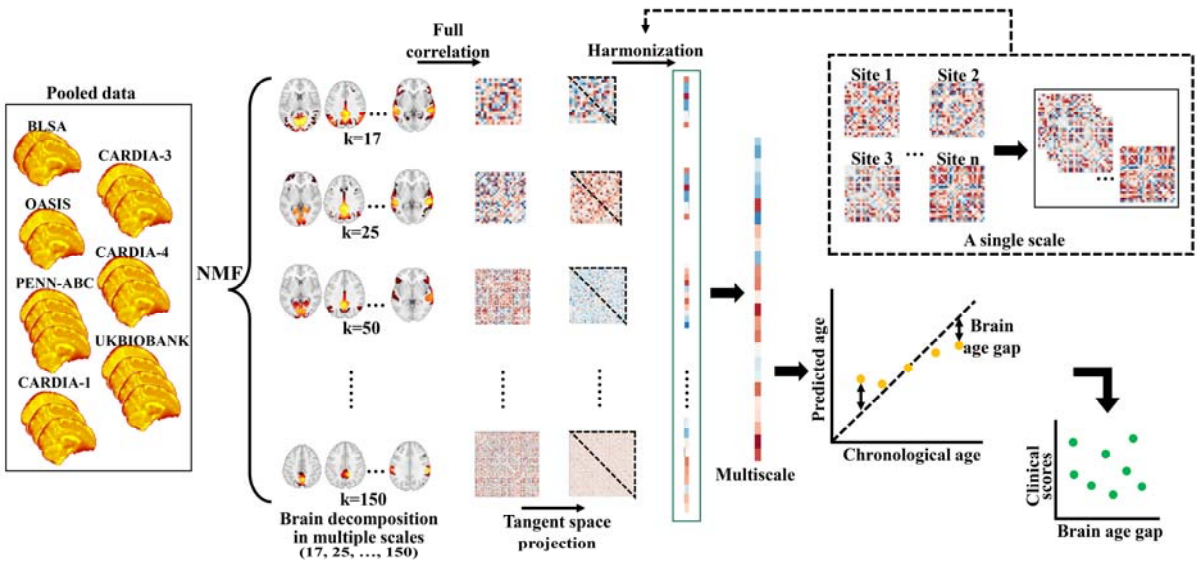

Figure 1. An overall flowchart of the present study. Multiscale functional connectivity measures were computed using a personalized functional network computing method, projected into their tangent space, harmonized using a Combat method, and finally used as input to build a brain age prediction model, from which a brain age gap score was derived to charactering the aging brain based functional MRI data of individuals.

Experimental design and statistical analysis

Brain age predictive modeling

We built a brain age prediction model on the harmonized FC measures using Ridge regression by optimizing

$$\min_{w} \sum_{i=1}^{N} (f(c_i) - y_i)^2 + \lambda \sum_{t=1}^{p} \left|\left|w_t\right|\right|^2, \qquad (3)$$

where y_i and c_i denote age and features of subject i, p denotes the number of features, w_t is a regression coefficient, $t = 1,2, \ldots, p$, and λ is a regularization parameter. We adopted a nested 5-fold cross-validation, with the inner folds determining the optimal parameter λ within the grid of $[2^3, 2^{3.5}, 2^4, \ldots, 2^{7.5}, 2^8]$ and the outer folds estimating the generalizability of the model. The cross-validation folds were generated randomly with comparable age distributions. The brain age prediction performance was quantified with mean absolute error (MAE) and correlation coefficient between the chronological age and the predicted age. The optimal λ value was determined based on MAE.

We also built brain age prediction models on FC measures in their original space, with and without the data harmonization, as well as FC measures in the tangent space without the data harmonization,

respectively. In addition to the brain age prediction models built on the multiscale functional connectivity measures, we also built brain age prediction models on FC measures of individual scales with 17, 25, 50, 75, 100, 125 and 150 FNs, respectively. All the brain age prediction models were built and evaluated with the same nested 5-fold cross-validation. The performance difference between the prediction models built on FC measures with and without the data harmonization was assessed with Wilcoxon signed-rank test across individual scales and their combination.

Functional network connectivity measures informative for brain age prediction

A permutation test was performed to evaluate the statistical significance of individual FC measures and the accuracy of the brain age prediction model (Mourao-Miranda et al., 2005; Cui et al., 2018). Particularly, we permuted the age labels of all subjects and repeated the whole cross-validation process (splitting the whole dataset into training and testing subsets) with the optimal λ parameter for 1000 times, yielding 1000 null brain age prediction models. Each model's regression coefficients were projected back to the original space of their associated FC measures for quantifying their contribution to the brain age prediction. Furthermore, correlation between individual FC measures and the chronological age was also calculated to identify FC measures significantly associated with aging.

Exploration of association between the brain age gap and clinical/cognitive score

We computed correlations between the BAG and cognitive and physiological functioning measures of individual subjects. As summarized in Table 3, the cognitive and physiological functioning measures included attention, executive function, working memory, and verbal, spanning several cognitive domains, as well as Systole, Diastole, and BMI (Body Mass Index). Pearson's correlations between the BAG and these measures were computed with sex, age, and site as covariates (Dinsdale et al., 2021). The BAG was computed with the brain age prediction bias corrected using a linear regression method (Beheshti et al., 2019).

Results

Brain age prediction results

The prediction performance of all the brain age prediction models under comparison is summarized in Table 2 and illustrated in Figure 2, indicating that the brain age prediction model built on the

harmonized multiscale FC features in the tangent space obtained the best age prediction performance, with a mean MAE of 5.57 years and a mean correlation coefficient of 0.78. The permutation test indicated that its prediction performance was statistically significant with $p < 0.001$ in terms of both MAE and correlation coefficient. The data harmonization did improve the performance if the models were built on FC measures in the tangent space ($p = 0.025$ for MAE and $p = 0.006$ for correlation coefficient, Wilcoxon signed-rank test across individual scales and their combinations) but did not consistently improve the models built on FC measures in their original space.

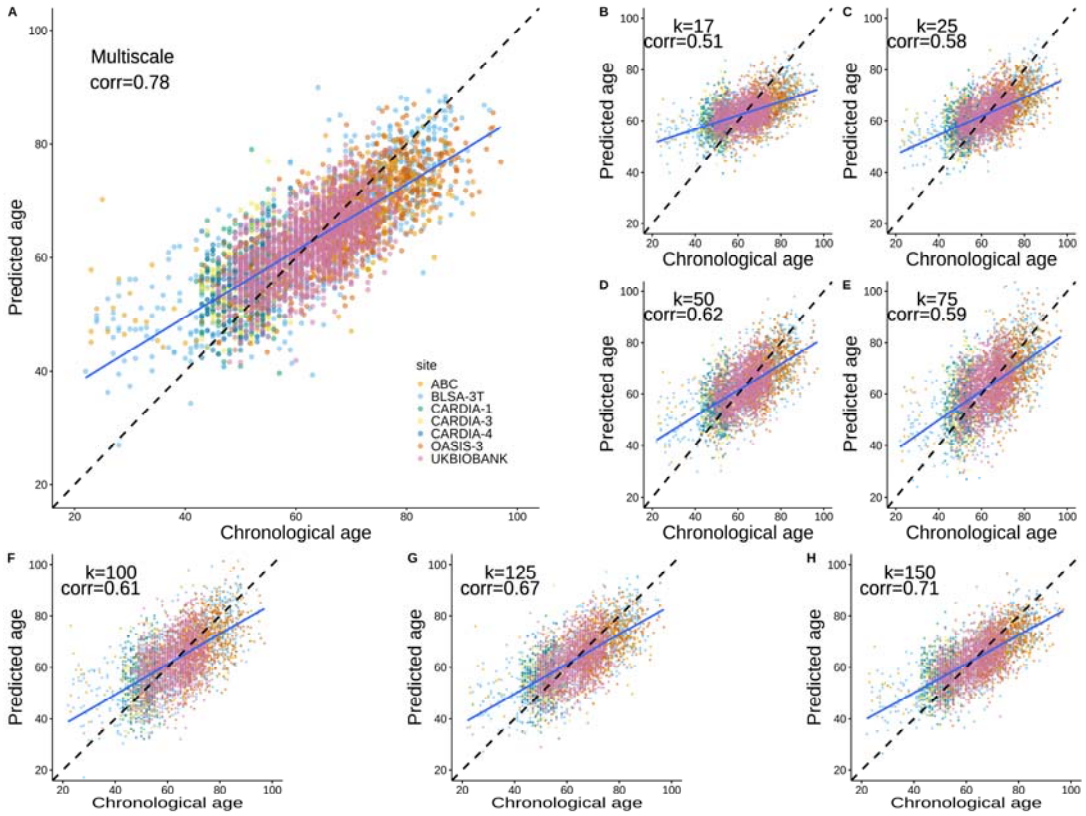

Figure 2. Correlations between the chronological age and the predicted age obtained by prediction models built upon functional connectivity measures of individual scales and their combination. In each subplot, x-axis represents the chronological age while y-axis denotes the predicted age. (A): brain age was predicted by the prediction model built upon the functional connectivity measures of all individual spatial scales; (B)-(F): brain age was predicted by the prediction model built upon the functional connectivity measures between functional networks computed with the settings of 17, 25, 50, 75, 100, 125, and 150 FNs separately. In each subplot, the black dashed line is the identity line while the blue solid line indicates the best linear fit of the predicted age to the chronological age.

Figure 2 shows scatter plots and associated correlation coefficients between the predicted and chronological ages obtained by the brain age prediction models built on the harmonized FC measures of individual scales and their combination in the tangent space, indicating again that the brain age prediction model built on the harmonized multiscale FC features in the tangent space obtained the best age prediction performance.

Table 2. Brain age prediction performance (MAE and correlation between the predicted and chronological ages) of all brain age prediction models built on FC measures of individual scales and their combination with and without the data harmonization (H+ and H- denote the models built on the FC measures harmonized or not, respectively)

Scales	MAE (year) between predicted age and chronological age				Correlation coefficient between predicted age and chronological age			
	Original Space		Tangent Space		Original Space		Tangent Space	
	H-	H+	H-	H+	H-	H+	H-	H+
17	8.45±0.12	8.34±0.14	8.01±0.11	7.96±0.12	0.42±0.03	0.42±0.03	0.49±0.03	0.51±0.03
25	7.88±0.16	8.12±0.17	7.38±0.15	7.43±0.18	0.52±0.03	0.47±0.03	0.58±0.03	0.58±0.02
50	7.67±0.14	8.23±0.12	7.21±0.16	7.33±0.16	0.56±0.03	0.46±0.02	0.64±0.01	0.62±0.02
75	7.92±0.18	8.74±0.27	7.91±0.11	8.17±0.19	0.55±0.02	0.41±0.03	0.61±0.08	0.59±0.01
100	8.28±0.13	9.30±0.16	8.02±0.08	7.80±0.10	0.53±0.02	0.36±0.02	0.60±0.07	0.61±0.01
125	8.26±0.24	8.88±0.25	7.19±0.12	6.96±0.15	0.54±0.03	0.42±0.04	0.65±0.02	0.67±0.02
150	8.56±0.19	8.86±0.09	6.70±0.09	6.45±0.09	0.52±0.04	0.42±0.03	0.68±0.02	0.71±0.02
Multiscale	7.65±0.17	8.29±0.18	5.92±0.11	5.57±0.11	0.59±0.03	0.46±0.03	0.76±0.02	0.78±0.01

Informative functional connectivity measures for predicting brain age

Figure 3 shows a hierarchical organization of the FNs from coarse to finer scales and FC measures contributed to the brain age prediction model built on the harmonized multiscale FC features in the tangent space with statistical significance (43 FC measures in total, $p < 0.05$, permutation test), illustrating that FC measures at multiple scales were informative for the brain age prediction. Particularly, FC measures between DMN, frontoparietal network (FPN), VN, VAN, SMN, dorsal attention network (DAN) and limbic network (LN) played vital roles. Among 43 informative FC measures identified by the brain age prediction model, 19 were correlated with aging with statistical significance ($p < 0.05$) and most of them were connections between SMN, DMN or FPN, as illustrated in Figure 4.

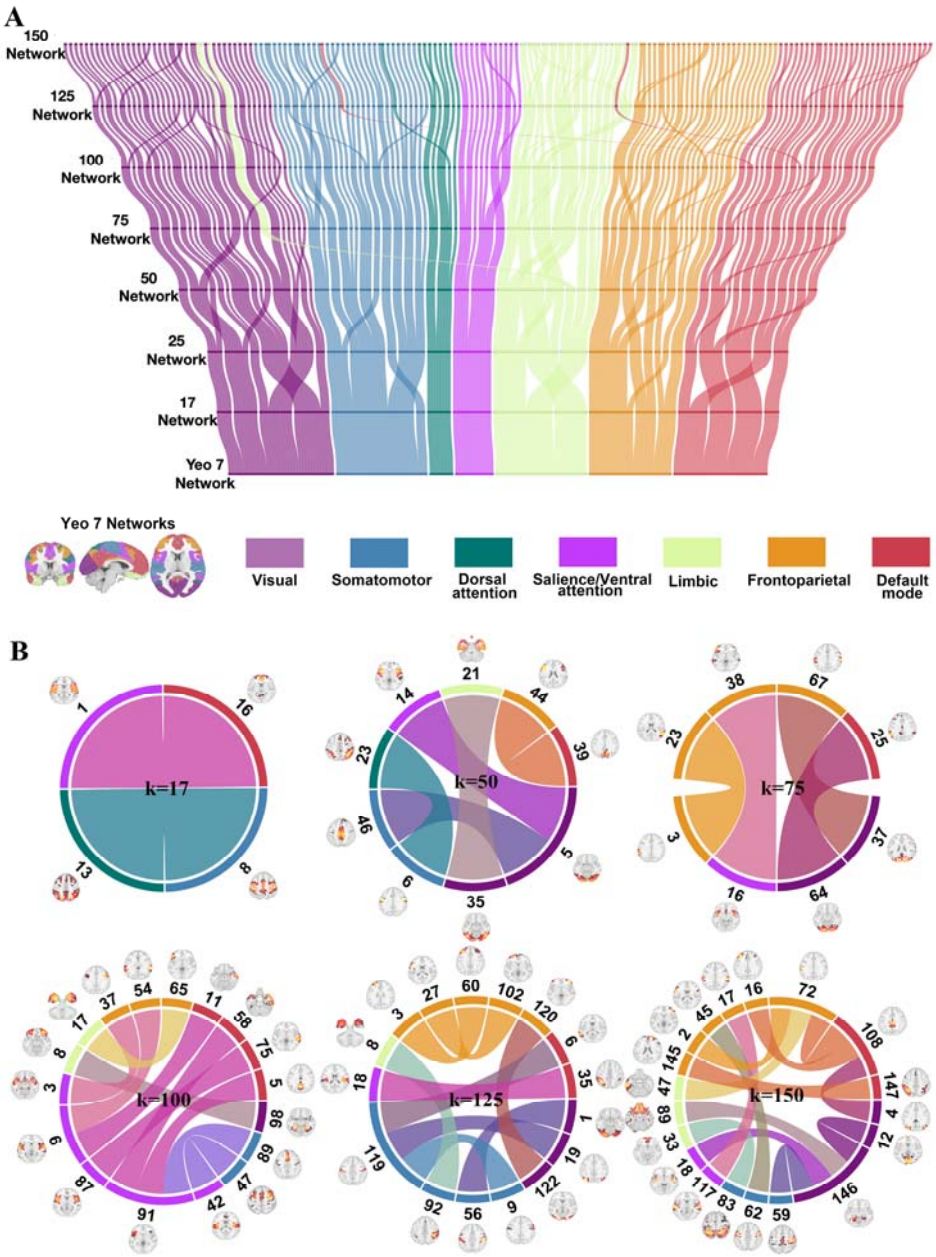

Figure 3. Functional connections informative for predicting the brain age. **(**A): A multi-scale organization of the brain networks, illustrated following the Yeo atlas of 7 networks, including VN, SMN, DAN, VAN, LN, FPN and DMN. (B): Functional connections informative for the brain age prediction. The same colors are used to denote the FNs of the Yeo atlas 7 networks.

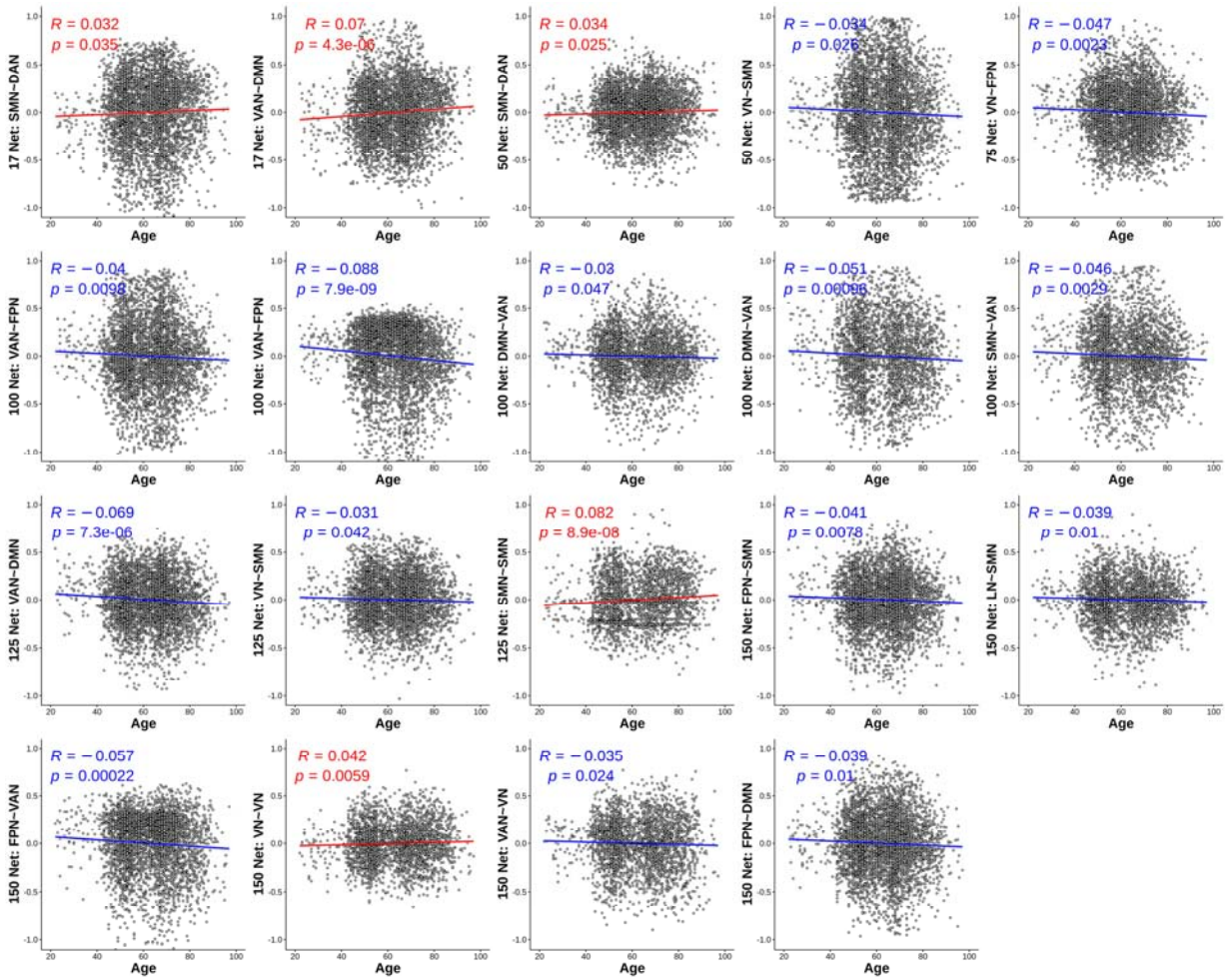

Figure 4. Functional connections with connectivity significantly correlated with the chronological age. Regression lines in red and blue indicate functional connectivity measures positively and negatively correlated with the chronological age, respectively.

Brain age gap correlation with cognitive scores

Table 3 summarizes correlation coefficients between BAG and clinical/cognitive measures. Particularly, MMSE, DSST, CVLT_IM, CVLT_Long, DSB, and DSF were negatively correlated with the BAG, while measures of 'time taken to complete a cognitive task' (TMT_A and TMT_B) were correlated positively with the BAG. The BAG was positively correlated with blood pressure (systole and diastole) and BMI.

Table 3. Correlation between BAG and cognitive/clinical measures

	Clinical or cognitive measures	correlation coefficients	*p* values
Attention	DSF (Digit Span Forward)	-0.061	0.0109
	TMT_A (Trail Making Test Part A)	0.078	**0.0012***
Executive	DSST (Digital Symbol Substitution Test)	-0.0957	**0.0002***
	TMT_B (Trail Making Test Part B)	0.0641	0.0089
	DSB (Digit Span Backward)	-0.0779	0.0138
Verbal Fluency	BNT (Boston Naming Task)	-0.1063	0.24
	ANI_Fluency (Animal Fluency)	-0.1158	0.0664
	Category_Fluency	-0.0866	0.0163
	Letter_Fluency	-0.0667	0.0646
	VEG_Fluency (Vegetable Fluency)	-0.1405	0.0137
Verbal Memory	CVLT_IM (California Verbal Learning Test Immediate)	-0.0849	0.019
	CVLT_Long (California Verbal Learning Test Long)	-0.0919	0.0113
Global	MMSE (Mini-Mental State Examination)	-0.1362	**0.0000***
	MOCA (Montreal Cognitive Assessment)	-0.146	0.0035
	WM_SUM (Working Memory Summary)	-0.1629	0.0171
Biological	Systole	0.0544	0.0032
	Diastole	0.0148	0.4213
	BMI (Body Mass Index)	0.0376	0.0301

* Significant after Bonferroni correction.

Discussion

In this study, we built a brain age prediction model of functional connectivity measures at multiple scales on a large fMRI dataset to learn multiscale functional connectivity patterns of the aging brain and characterize the functional brain. The brain age prediction model built on the harmonized data obtained promising age prediction performance and the derived brain age gap was significantly correlated with cognitive measures, consistent with established brain aging trends (Smith et al., 2019; Smith et al., 2020; Dinsdale et al., 2021).

We characterized the functional connectivity patterns at multiple scales, inspired by accumulating evidence that the brain is a multi-scale system (Betzel and Bassett, 2017; Eickhoff et al., 2018). The effectiveness of brain functional connectivity analyses at multiple spatial scales has been demonstrated in recent studies for characterizing functional brain networks (Li et al., 2018b; Iraji et al., 2021; Liu et al., 2021). We utilized a personalized functional network computational method (Li et al., 2017; Cui et al., 2020). Comparison results have demonstrated that the prediction model built upon the multiscale brain functional connectivity measures could better predict the brain age than those built upon functional connectivity measures of any single scale. As illustrated in Figure 3(A), the multi-scale brain functional networks largely follow a hierarchical organization structure with a few exceptions in finer scales with the FNs computed with settings of 75, 100, 125 and 150 FNs.

Specifically, one FN of the LN computed with the setting of 50 FNs switches to the VN computed with the setting of 75 FNs, while two FN of the DMN computed with the setting of 100 FNs switch to SMN and LN computed with the settings of 125 FNs. These results indicated that less stable brain decompositions were generated at finer scales, consistent with findings in structural imaging studies (Varikuti et al., 2018; Patel et al., 2020).

Data harmonization is a prerequisite step in neuroimaging studies with data from multiple sites (Shinohara et al., 2017). To improve the generalization ability of machine learning models and increase statistical power, we adopted a Combat-based data harmonization technique that has been successfully applied to different imaging features, including diffusion tensor imaging measures, cortical thickness, regional volume measures, and functional connectivity measures (Fortin et al., 2017; Fortin et al., 2018; Yu et al., 2018). Since the functional connectivity measures reside in a manifold space, we harmonized the FC measures in their tangent space. As summarized in Table 2, the comparison results have demonstrated that the data harmonization on the tangent space parameterized FC measures improved the prediction performance, while the same data harmonization method applied to the FC measures in their original space did not improve the prediction performance. These results indicated that it is necessary to take into consideration of inter-correlation between features when applying Combat methods for data harmonization (Johnson et al., 2007; Orlhac et al., 2022).

In order to identify informative functional connectivity features for the brain age prediction, we performed permutation tests (Golland et al., 2005) and univariate correlation based significance tests. The statistically significant functional connectivity measures identified by both the tests included 19 connections between SMN, DMN, and FPN, as illustrated in Figure 4. Specifically, many functional network connectivity measures exhibited decreased strength with aging, such as those connections with SMN, DMN, and FPN, consistent with findings of the existing studies (Chan et al., 2014; Grady et al., 2016; Zonneveld et al., 2019; Truelove-Hill et al., 2020). Interestingly, the within network connections of the VN and SMN increased with aging. Similar findings were also reported in several existing studies (Song et al., 2014; Seidler et al., 2015; Zonneveld et al., 2019). We also noticed that the connectivity between DMN (network 16, the anterior cingulate) and VAN (network 1, the insula) computed with the setting of 17 FNs increased with aging, consistent with findings reported in previous studies (Cao et al., 2014; Fan et al., 2020), as well as increased connectivity between SMN and DAN computed with the settings of 17 and 50 FNs.

A highly consistent finding in the aging literature is decreasing DMN connectivity with aging (Ferreira and Busatto, 2013; Dennis and Thompson, 2014; Damoiseaux, 2017; Stumme et al., 2020). Aging is also associated with substantial declines in motor functioning as well as higher-order cognitive networks, such as the FPN. In addition to these findings, we also observed that aging was associated with increased within-network connectivity in the VN and SMN, contradictory with findings of existing studies (Stumme et al., 2020). Particularly, it was observed that aging is associated with decreased functional connectivity within the primary processing networks, including the VN and SMN (Stumme et al., 2020). A variety of factors might contribute to such discrepancies, including different atlases or brain parcellations used for computing the functional connectivity measure (Arslan et al., 2018) and the sample size and diversity (Marek et al., 2022). It is worth noting that fMRI data of 4259 subjects were included in our study.

Statistically significant correlations between the brain age gap and multiple clinical and cognitive scores were observed as summarized in Table 3. Not surprisingly, MMSE, DSST, CVLT_IM, CVLT_Long, DSB, and DSF were negatively correlated with the brain age gap, while measures of 'time taken to complete a cognitive task' (TMT_A and TMT_B), blood pressure (systole and diastole), and BMI were correlated positively with the brain age gap, indicating that the brain age gap measure derived from our brain age prediction model was biologically informative and has a great potential to be a clinically useful biomarker for characterizing brain aging.

Our study has following limitations. First, the present study has focused on functional connectivity within FNs. Functional connectivity within networks across different scales may provide additional informative functional connectivity measures for characterizing the aging brain (Iraji et al., 2021). Second, the present study has focused on functional connectivity information alone. The functional connectivity measures can be further enhanced by functional network topology measures that are informative for charactering the brain development (Cui et al., 2020). Moreover, integration of brain anatomy, structural connectivity, and functional connectivity measures may further improve the brain age prediction as well as the characterization of brain aging (Truelove-Hill et al., 2020). Third, the present study identified informative functional connectivity measures using a combination of permutation test and univariate correlation analysis. It merits further investigation to establish explainable and interpretable brain age prediction models (Tian and Zalesky, 2021).

In summary, the present study revealed that functional connectivity measures at multiple scales were more informative than those at any single spatial scale for the brain age prediction and the data harmonization in the tangent space of functional connectivity measures significantly improved the

brain age prediction performance. Moreover, the derived brain age gap score was predictive of cognitive and clinical measures.

Competing Financial Interests

Dr. Nasrallah was an educational speaker for Biogen. Dr. Wolk has received grant support from Merck, Biogen, and Eli Lilly/Avid and consultation fees from Neuronix and GE Healthcare and is on the Data and Safety Monitoring Board for a clinical trial run by Functional Neuromodulation.

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Data and code availability

The data of this study is available upon request and subject to approval by the ISTAGING Consortium's supervisory committee. All the codes will be deposited in an open access platform upon the acceptance of this manuscript.

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