Accelerated functional brain aging in major depressive disorder: evidence from a large scale fMRI analysis of Chinese participants

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common mental health conditions that has been intensively investigated for its association with brain atrophy and mortality. Recent studies suggest that the deviation between the predicted and the chronological age can be a marker of accelerated brain aging to characterize MDD. However, current conclusions are usually drawn based on structural MRI information collected from Caucasian participants. The universality of this biomarker needs to be further validated by subjects with different ethnic/racial backgrounds and by different types of data. Here we make use of the REST-meta-MDD, a large scale resting-state fMRI dataset collected from multiple cohort participants in China. We develop a stacking machine learning model based on 1101 healthy controls, which estimates a subject’s chronological age from fMRI with promising accuracy. The trained model is then applied to 1276 MDD patients from 24 sites. We observe that MDD patients exhibit a +4.43 years (p < 0.0001, Cohen’s d = 0.31, 95% CI: 2.23–3.88) higher brain-predicted age difference (brain-PAD) compared to controls. In the MDD subgroup, we observe a statistically significant +2.09 years (p < 0.05, Cohen’s d = 0.134525) brain-PAD in antidepressant users compared to medication-free patients. The statistical relationship observed is further checked by three different machine learning algorithms. The positive brain-PAD observed in participants in China confirms the presence of accelerated brain aging in MDD patients. The utilization of functional brain connectivity for age estimation verifies existing findings from a new dimension.

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estimations, it is reasonable to suspect that the conclusion drawn is algorithm sensitive. The statistically significant association originally reported may vanish when a new algorithm is applied.

To cope with these limitations, we make use of the resting-state functional magnetic resonance imaging (rsfMRI) data [33] collected by the REST-meta-MDD [34, 35], which is a coordinated multisite project from China containing over 1000 MDD patients and normal controls. We utilize three different machine learning algorithms to estimate brain age from resting-state functional connectivity [36–38]. We further propose a stacking model to combine results from the three algorithms to reach a more optimal age estimation. We conduct separate analyses on results obtained from each algorithm to check the robustness of the conclusion drawn. We confirm the existence of the positive association between accelerated brain aging and MDD based on subjects in China. The brain-PAD is significantly higher in MDD patients compared to controls and the conclusion is not affected by the machine learning algorithm applied. We separately analyze MDD patients with different depression severity, illness duration, episode status, and medication status to investigate the association between brain-PAD with demographic (age, sex) and clinical characteristics. We find a significant correlation between brain-PAD and illness duration in MDD patients as well as a higher brain-PAD in antidepressant users than in medication-free patients.

METHODS

Samples

We conduct this study through rsfMRI indices of MDD patients and matched controls (aged 12–82 years) from the REST-meta-MDD consortium, which consists of 25 research groups from 17 hospitals in China. All MDD patients are hospital diagnosed and conducted at least a T1-weighted structural scan and a rsfMRI scan. All subjects agree to provide informed consent by participants at each local site, and all data are de-identified and anonymized. Besides, approvals from the local institutional review board and ethics committee are granted at all sites.

rsfMRI data preprocessing and functional brain network construction

The Data Processing Assistant for Resting State fMRI (DPARSF) [39] is used as a standardized preprocessing pipeline. To obtain functional connectivity, we first extract 116 averaged blood oxygen level-dependent (BOLD) signals based on the Automated Anatomical Labeling (AAL) atlas. Next, we calculate the Pearson correlation coefficients between the BOLD activity time series. We use the Z-Score method [40] to normalize the functional connectivity of each subject to reduce the effect of the imaging sites. We also test the Combat method [41] whose results are presented in Supplementary Information Tables S3 and S4. In general, the Z-Score method performs better in this study. More details of the data preprocessing process are presented in Supplementary Information S2.

Model training and evaluation

To obtain the input feature for the model, we reshape the upper triangle of the whole-brain correlation matrix into a one-dimensional vector with 6670 elements. To determine the brain aging pattern in healthy individuals, we first train a brain age prediction model on the training set containing 1101 normal controls. Next, we utilize the model to estimate the brain age of 1276 MDD patients on the test set. The brain age prediction is carried out by three classical supervised learning algorithms: elastic net [42, 43], bayesian ridge [44], and ridge regression [31, 45, 46]. Furthermore, we introduce a stacking model [36] from ensemble learning [47] to combine results from the three algorithms, which gives the best estimation results. The flow is shown in Fig. 1 and Supplementary Fig. S1. The four models all come to consistent conclusions in subsequent experiments. To avoid switching between different methods and make the flow of the paper more concise, we use the results from the stacking method in the main text. Analyses based on the other three algorithms are included in Supplementary Table S5.

We evaluate our model performance in the control and MDD groups separately. We first evaluate the model on the entire training set with five-fold cross-validation. Then, the same model in each fold is used to predict the brain age of MDD patients on the entire test set. The performance of the four models is evaluated based on the following three metrics: mean absolute error (MAE), mean squared error (MSE), and mean coefficient of determination (R²). All models are implemented through the Python-based sklearn package with all parameters set as the default value.

Statistical analyses

To determine whether brain aging is accelerated in MDD patients relative to controls, we split the entire controls to get a fixed training set and a validation set using the hold-out method [48]. While modest in size, this hold-out validation set consists of normal controls from all sites with the entire age span, providing an unbiased age representation of Rest-meta-MDD. To overcome this limitation, we estimate the difference in brain age between normal controls and MDD patients, we separately estimate the brain age in the two groups. The model is trained and tested in the hold-out validation set composed of normal controls. The trained model is then applied to all MDD patients in the test set to estimate their brain ages. The chronological age is subtracted from the estimated age to get the brain-PAD as the outcome variable for statistical analysis. The five-fold cross-validation is used to compare the overall performance of different models. The hold-out validation set is used as a normal control group for brain-PAD comparison. Due to factors such as regression dilution and non-Gaussian age distribution [49], we need to perform an age-bias correction. We apply a post hoc correction for the residual age effect on the test set [45, 50–53]. Following Peng et al. [54], we train a linear regression model for brain age bias correction. We calculate the regression line between the chronological age and the estimated age on the hold-out validation set. Then the slope and intercept of the regression line are used to adjust brain-predicted age values in the testing set. The steps of this process are shown in Supplementary Information S4. The brain-PAD is independent of chronological age after the age-bias correction (Supplementary Figs. S2 and S3). We apply the univariate generalized linear model (GLM) with gender, diagnosis, age, and age as covariates to explore the relationship between brain-PAD and clinical characteristics [27]. Furthermore, the two-sample t-test is used to compare the brain-PAD in different subgroups. Multiple comparisons are corrected by false discovery rate correction. The threshold for statistical significance is set at p < 0.05.

RESULTS

Model performance

The models obtained from each fold of the training set are used to estimate the brain age of individuals for the rest of the controls in the validation set as well as the MDD patients in the test set. Table 1 shows the performance of four models with 882 training subjects, 219 validation subjects, and 1276 test subjects. Among the three classical machine learning algorithms, the bayesian ridge achieves the best performance. But the stacking model with ensemble learning outperforms all of them, giving rise to the lowest MAE and MSE in both the validation and test set. The performance of other widely used models, such as XGBoost [26], SVM [27], and MLP [13] is not as good as the three models applied under default parameters (Supplementary Table S5). The correlation between chronological age and predicted age on the validation set and test set are presented in Fig. 2a, b.

The relative feature importance for normal controls

We calculate the correlation between the functional connectivity features and the chronological age (Supplementary Fig. S4). Among all the total 6670 functional connectivity features, 3196 features show positive correlations with age (mean correlation = 0.0645 ± 0.0495, range (6.1691e–05, 0.3017)). 3474 features show negative correlations.
with age (mean correlation = $-0.0691 \pm 0.0545$, range ($-0.3334, 3.7818 \times 10^{-5}$)). In particular, the most positive correlation is found for the precentral gyrus-Heschel gyrus [55, 56]. The most negative correlation is found for the median cingulate and paracingulate gyrus-inferior parietal gyrus, excluding supramarginal and angular gyri [57, 58]. In addition, we identify brain regions that the machine learning algorithm considers to be significant in brain age estimation using the feature importance [59]. The feature importance values are normalized to give the top 20 functional connectivity features (Fig. 3). The main brain regions include the cerebellum [60] superior and vermis8, the medial superior frontal gyrus and middle temporal gyrus [61], the amygdala and lenticular nucleus putamen. These brain regions are associated with brain development and atrophy, which are consistent with previous studies.

| Model            | MAE       | MSE         | R2          |
|------------------|-----------|-------------|-------------|
| Validation set   |           |             |             |
| Elastic net      | 8.2327 ± 0.4608 | 103.7454 ± 10.9086 | 0.5670 ± 0.0486 |
| Ridge            | 8.7749 ± 0.5662 | 127.4526 ± 17.7452 | 0.4691 ± 0.0665 |
| Bayesian ridge   | 7.8057 ± 0.4420 | 97.4546 ± 10.5659 | 0.5934 ± 0.0440 |
| Stacking         | 7.7287 ± 0.5547 | 95.3625 ± 11.8727 | 0.6026 ± 0.0456 |
| Test set         |           |             |             |
| Elastic net      | 8.4156 ± 0.0582 | 110.2473 ± 12.672 | 0.4839 ± 0.0059 |
| Ridge            | 9.4921 ± 0.2447 | 143.8590 ± 6.8188 | 0.3265 ± 0.0319 |
| Bayesian ridge   | 8.3817 ± 0.0609 | 110.6582 ± 1.2202 | 0.4820 ± 0.0057 |
| Stacking         | 8.3055 ± 0.0535 | 108.4852 ± 1.2633 | 0.4837 ± 0.0071 |

**Table 1.** Performance of four models.
Accelerated functional brain aging in MDD

We compare the resulting brain-PAD scores of the MDD patients with the controls in the hold-out validation set to determine whether brain aging is accelerated in MDD patients. Overall, the brain-PAD score before age-bias correction is $-1.3731$ (SD 9.91) years in the control group and $-0.0712$ (SD 10.56) years in MDD patients. After applying an age-bias correction procedure, the brain-PAD is $+4.43$ years higher in MDD patients than in normal controls ($p < 0.0001$, Cohen’s $d = 0.31$, 95% CI: 2.23–3.88), which is shown in Fig. 4a, b. Although different estimations are obtained through different models, results from the other three models all demonstrate a consistent pattern that MDD patients have statistically significant higher brain-PAD scores compared to controls. In addition, GLM shows significant main effects for age ($p < 0.0001$), age ($p < 0.002$) and diagnosis ($p < 0.0001$), but not for gender (Table 2A).

Brain-PAD comparison for clinical characteristics

To explore the association between brain-PAD scores and clinical characteristics, we use the GLM to fit the brain-PAD of MDD patients with the following explanatory variables: sex, medication status, episode status, education years, and illness duration months (Table 2B). The medication status ($p = 0.023$) has a main effect on the brain-PAD scores of MDD patients. We further apply a two-sample t-test to determine whether the brain-PAD mean value in antidepressant users and medication-free patients are significantly different from each other (Fig. 4c, d). Brain-PAD is $+2.09$ years higher ($p = 0.0499$, Cohen’s $d = 0.13452$) in antidepressant users than in medication-free ones. Comparisons of other subgroups (sex, episode status) with controls can be found in Supplementary Table S7. While significant differences are observed in all MDD subgroups compared to normal controls, posthoc comparisons of brain-PAD in other clinical characteristics do not demonstrate any significant differences between MDD subgroups except for the medication status. For the two continuous-type clinical characteristics (education years and illness months), we divide the subgroups according to their medians (both are 12 in this study) for brain-PAD comparisons (Supplementary Table S8). Overall, MDD patients with fewer than 12 years of education have a 2.28 years higher brain-PAD than those with greater than or equal to 12 years of education ($p = 0.00679$). Brain-PAD of MDD patients with fewer than 12 months of illness is 1.69 years higher than that in patients with greater than or equal to 12 months of illness. We also calculate correlations between brain-PAD scores and illness months, education years, and HDRS scores separately. Only illness duration is found to be significantly correlated with brain-PAD scores (Spearman $R = -0.067$, $p < 0.05$, Supplementary Fig. S5).

DISCUSSION

Biological aging can be defined as a progressive process of decline involving multiple organ systems. While all individuals age chronologically at the same rate, the rate of their biological aging varies from one to the other [62]. Resting-state functional MRI is
developed as a common approach to interrogate the myriad of functional systems in the brain without the constraints of any prior assumptions [63]. Machine learning algorithms based on functional connectivity and the availability of large-scale reliable samples allow us to develop generalized models to estimate the brain age of individual subjects [64]. Here, we make use of the Rest-Meta-MDD consortium from China to verify the accelerated brain aging in MDD patients, which is previously observed in Caucasian participants using structural MRI information. We apply four machine learning algorithms based on functional connectivity features to estimate the brain age of individuals with the entire adult lifespan (12–82 years). We observe manifestly accelerated brain aging in 1276 MDD patients. Furthermore, we compare brain-PAD scores between MDD subgroups divided according to clinical characteristics such as medication status and episode status. We confirm that the conclusion drawn in this paper is not algorithm sensitive as results from different algorithms lead to the same conclusion.

Our study benefits from a reliable experimental design. The dataset contains 24 cohorts so the potential site effect is effectively avoided. Instead of using samples from some independent sites as the fixed validation set, we randomly select samples from all sites to constitute the training set and validation set. In this way, the generalizability of the model is improved and the model outcomes are evaluated more objectively [65, 66]. Moreover, we split the normal controls into a fixed training set and a hold-out validation set. We compare the brain-PAD scores of the controls in this hold-out validation set to the MDD patients in the test set. As the validation set is not involved in the development of the brain age prediction model, the risk of overfitting is effectively prevented [67]. The application of four different machine learning algorithms allows us to further validate the consistency of the patterns observed.

The accuracy of our model (Stacking, MAE = 8.3055, $R^2 = 0.4837$) is better than some previous studies, such as Peter et al. [32] (GPR, MAE = 8.587 years), and Gonneaud et al. [13] (DNN, MAE = 11.90 years). We acknowledge that algorithms used in some other studies yield more accurate age estimation than ours. But multiple factors can affect the performance of the models, such as different features considered and the age distribution of the subjects. The model tends to yield a better prediction using sMRI features than fMRI features [36]. In the meanwhile, the prediction error tends to be smaller when the age distribution of the subjects is narrower. To the best of our knowledge, our work provides a very accurate brain age estimation based on functional connectivity features in a date covering a wide age span (12–82 years).

Although multiple studies are carried out on relatively small samples, conclusions drawn from larger samples tend to be more reliable. First, machine learning algorithms are sensitive to sample size [68–71]. The small size of samples brings a bigger prediction error and a higher risk of overfitting [72]. Moreover, larger samples tend to contain subjects with a wider age distribution. While a wide range of ages makes the estimation challenging, it effectively increases the generalizability of the conclusion [73]. In this study, we make use of the Rest-meta-MDD consortium, which is the largest rsfMRI database of MDD patients. To the best of our knowledge, only one study from ENIGMA uses more subjects than
The comparisons between subgroups of MDD patients show brain-PAD than medication-free patients (Cohen discussed by Han [31]. The antidepressant users are likely to have characteristics, which is in line with the our regression analysis. In particular, the main effect of medication antidepressant use mainly for severe or chronic MDD [80]. In other words, patients with milder symptoms tend not to take antidepressants [81]. To fully understand the adaptation of brain-PAD in response to pharmacotherapy, randomized controlled intervention studies are needed which require more information on the clinical use of antidepressants, such as the dosage and duration. It is also noteworthy that the p-value in the study by Han [31] is slightly above 0.05 whereas in our study it is slightly below the threshold of statistical significance. But it is still near the boundary of the threshold line. We honestly report the result, and we also admit that it is far early to draw any conclusion based on this statistic.

Similarly, consistent with the finding obtained by Han et al. [24] using structural brain MRI, we observe a higher brain-PAD in first-episode patients (+4.19 years, N = 538) than in recurrent patients (+2.56 years, N = 282). We believe the same explanation can be applied. First, as pointed out in previous studies and observed in our work, there is a negative correlation between brain-PAD and illness duration (Spearman R = −0.067, p < 0.05). Furthermore, recurrent patients have a longer illness duration than first-episode patients. The median illness duration in recurrent patients (60 months) is 10 times greater than in first-episode patients (6 months) in our data. The corresponding median of brain-PAD score in recurrent patients (0.58 years) is 3.08 years smaller than in first-episode patients (3.66 years). The combination of the two effects gives rise to a higher brain-PAD in first-episode patients than that in recurrent patients. It is implied that there may be a clinically unstable period in first-episode patients. As more treatment is given, patients may become more stable in brain functioning. Hence the brain-PAD decreases with the illness duration [24]. But such a hypothesis needs more clinical information to be further verified through longitudinal studies.

Our results extend the generalizability of accelerated brain aging in MDD patients using the rsfMRI feature of Chinese participants. But several limitations should be considered. Although a standardized preprocessing pipeline is employed at all sites before the aggregation group analysis, some subjects still show measurement bias and missing values in the scan. We address this problem by applying various standardization methods to the features. Although the prediction error is within control, these operations may still bring impact on the final results. Next, multiple brain atlas could be considered to obtain the functional connectivity features. Different functional connectivity will have an impact on the subsequent analysis. Furthermore, different features and models could also have a dramatic effect on the final results. Several studies report the great potential of the multimodal features [82–84] and deep learning algorithms [85–87] in neuroimaging research. More comparisons of neuroimaging features and models are needed in the future to produce more convincing conclusions. Besides, all participants in Rest-meta-MDD are Chinese, the generalizability of our model to other ethnic/racial and cultural backgrounds remained to be explored. Finally, aging is a continuous process, yet few current studies address longitudinal investigations of brain aging, including stage-by-stage analyses of MDD to explore trends in brain-PAD with age to understand the progressive effects of the aging process. More clinical features are still desired in the future to determine the clinical significance of measuring brain-PAD and whether it can be considered as a clinically essential biomarker.

| Parameter estimates for all main effects and significant interactions in other clinical characteristics. |
|-----------------------------------------------|
| (A)                                           |
| Coef  | SE    | z    | p     | 0.025  | 0.975  |
| Intercept | 7.64  | 2.57 | 2.972 | 0.003  | 2.602  | 12.678 |
| Gender | −0.6052 | 0.771 | −0.785 | 0.432  | −2.116 | 0.905  |
| Diagnosis | 4.7237 | 1.045 | 4.519 | 0      | 2.675  | 6.772  |
| Age   | −0.4421 | 0.129 | −3.433 | 0.001  | −0.695 | −0.19  |
| Age2  | 0.0046  | 0.002 | 3.048 | 0.002  | 0.002  | 0.008  |

| (B)                                           |
| Coef  | SE    | z    | p     | 0.025  | 0.975  |
| Intercept | 1.8688 | 5.087 | 0.367 | 0.713  | −8.102 | 11.839 |
| Gender | −1.2863 | 1.255 | −1.025 | 0.305  | −3.746 | 1.173  |
| Episode | 2.2518 | 1.532 | 1.47  | 0.141  | −0.75  | 5.254  |
| Medication | 2.9454 | 1.291 | 2.282 | 0.023  | 0.415  | 5.475  |
| Age   | −0.0285 | 0.252 | −0.113 | 0.91   | −0.522 | 0.465  |
| Age2  | −0.0007 | 0.003 | −0.219 | 0.827  | −0.007 | 0.006  |
| Education | −0.0022 | 0.156 | −0.014 | 0.989  | −0.307 | 0.303  |
| Month | 0.006  | 0.012 | 0.511 | 0.609  | −0.017 | 0.029  |
50. Le TT, Kuplicki RT, McKinney BA, Yeh HW, Thompson WK, Paulus MP, et al. A nonlinear simulation framework supports adjusting for age when analyzing brain age. Front Aging Neurosci. 2018;10:317.

51. Liang H, Zhang F, Niu X. Investigating systematic bias in brain age estimation with application to post-traumatic stress disorders. Technical report. Wiley Online Libr. 2019;40:3143–52.

52. Cole JH. Multimodal neuroimaging brain-age in UK biobank: Relationship to biometrical, lifestyle, and cognitive factors. Neurobiol Aging. 2020;92:34–42.

53. Aycheh HM, Seong JK, Jin SH, Na DL, Kang B, Seo SW, et al. Biological brain age prediction using cortical thickness data: A large scale cohort study. Front Aging Neurosci. 2018;10:252.

54. Peng H, Gong W, Beckmann CF, Vedaldi A, Smith SM. Accurate brain age prediction with lightweight deep neural networks. Med Image Anal. 2021;68:101817.

55. Kovalev VA, Kugelg F, von Cramon DY. Gender and age effects in structural brain asymmetry as measured by MRI texture analysis. Neuroimage. 2003;19:895–905.

56. Amoroso N, La Rocca M, Bellantuono L, Diacono D, Fanizzi A, Lella E, et al. Deep learning and multiplex networks for accurate modeling of brain age. Front Aging Neurosci. 2019;11:115.

57. MacDonald SW, Nyberg L, Sandblom J, Fischer H, Backman L. Increased response-time variability is associated with reduced inferior parietal activation during episodic recognition in aging. J Cogn Neurosci. 2008;20:779–86.

58. Rivera SM, Reiss A, Eckert MA, Menon V. Developmental changes in mental arithmetic: Evidence for increased functional specialization in the left inferior parietal cortex. Cereb Cortex. 2005;15:1779–90.

59. Nunes A, Schnack HG, Ching CR, Agartz I, Akudjedu TN, Alida M, et al. Using structural MRI to identify bipolar disorders-13 site machine learning study in 3020 individuals from the enigma bipolar disorders working group. Mol Psychiatry. 2020;25:2130–43.

60. Tienmeier H, Lenroot RK, Greenstein DK, Tran L, Pierson R, Giedd JN. Cerebellum development during childhood and adolescence: A longitudinal morphometric mri study. Neuroimage. 2010;49:63–70.

61. Tomoda A, Kinoshita S, Korenaga Y, Mabe H. Pseudohypopacardia in childhood and adolescence is associated with increased gray matter volume in the medial frontal gyrus and superior temporal gyrus. Cortex. 2012;48:492–503.

62. Elliott ML, Caspi A, Routs AM, Ambler A, Broadbent JM, Hancox RJ, et al. Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk policy and Nat Aging. 2021;1:295–308.

63. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, et al. Toward discovery of human brain function. Proc Natl Acad Sci USA. 2010;107:4734–9.

64. Franke K, Gaser C. Ten years of brainage as a neuroimaging biomarker of brain aging: What insights have we gained? Front Neuranol. 2019;10:789.

65. Ortu’ G, Monaro M, Conversano C, Gemignani C, Sartori G. Machine learning in psychometrics and psychological research. Front Psychol. 2020;11:2970.

66. Cai XL, Fung W, Beckmann CF, Vedaldi A, Smith SM. Accurate brain age prediction with lightweight deep neural networks. Med Image Anal. 2021;68:101817.

67. Kovalev VA, Kugelg F, von Cramon DY. Gender and age effects in structural brain asymmetry as measured by MRI texture analysis. Neuroimage. 2003;19:895–905.

68. Amoroso N, La Rocca M, Bellantuono L, Diacono D, Fanizzi A, Lella E, et al. Deep learning and multiplex networks for accurate modeling of brain age. Front Aging Neurosci. 2019;11:115.

69. MacDonald SW, Nyberg L, Sandblom J, Fischer H, Backman L. Increased response-time variability is associated with reduced inferior parietal activation during episodic recognition in aging. J Cogn Neurosci. 2008;20:779–86.

70. Rivera SM, Reiss A, Eckert MA, Menon V. Developmental changes in mental arithmetic: Evidence for increased functional specialization in the left inferior parietal cortex. Cereb Cortex. 2005;15:1779–90.

71. Nunes A, Schnack HG, Ching CR, Agartz I, Akudjedu TN, Alida M, et al. Using structural MRI to identify bipolar disorders-13 site machine learning study in 3020 individuals from the enigma bipolar disorders working group. Mol Psychiatry. 2020;25:2130–43.

72. Tienmeier H, Lenroot RK, Greenstein DK, Tran L, Pierson R, Giedd JN. Cerebellum development during childhood and adolescence: A longitudinal morphometric mri study. Neuroimage. 2010;49:63–70.

73. Tomoda A, Kinoshita S, Korenaga Y, Mabe H. Pseudohypopacardia in childhood and adolescence is associated with increased gray matter volume in the medial frontal gyrus and superior temporal gyrus. Cortex. 2012;48:492–503.

74. Elliott ML, Caspi A, Routs AM, Ambler A, Broadbent JM, Hancox RJ, et al. Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk policy and Nat Aging. 2021;1:295–308.

75. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, et al. Toward discovery of human brain function. Proc Natl Acad Sci USA. 2010;107:4734–9.

76. Franke K, Gaser C. Ten years of brainage as a neuroimaging biomarker of brain aging: What insights have we gained? Front Neuronal. 2019;10:789.

77. Ortu’ G, Monaro M, Conversano C, Gemignani C, Sartori G. Machine learning in psychometrics and psychological research. Front Psychol. 2020;11:2970.

78. Cai XL, Fung W, Beckmann CF, Vedaldi A, Smith SM. Accurate brain age prediction with lightweight deep neural networks. Med Image Anal. 2021;68:101817.

79. Kovalev VA, Kugelg F, von Cramon DY. Gender and age effects in structural brain asymmetry as measured by MRI texture analysis. Neuroimage. 2003;19:895–905.

80. Amoroso N, La Rocca M, Bellantuono L, Diacono D, Fanizzi A, Lella E, et al. Deep learning and multiplex networks for accurate modeling of brain age. Front Aging Neurosci. 2019;11:115.

81. MacDonald SW, Nyberg L, Sandblom J, Fischer H, Backman L. Increased response-time variability is associated with reduced inferior parietal activation during episodic recognition in aging. J Cogn Neurosci. 2008;20:779–86.

82. Rivera SM, Reiss A, Eckert MA, Menon V. Developmental changes in mental arithmetic: Evidence for increased functional specialization in the left inferior parietal cortex. Cereb Cortex. 2005;15:1779–90.

83. De Lange AMD, Anatu¨rk M, Suri S, Kaufmann T, Cole JH, Griffanti L, et al. Mul- timodal brain-age prediction and cardiovascular risk: The Whitehall ii MRI sub- study. Neuroimage. 2020;222:117292.

84. Rokicki J, Wolters T, Nordhay W, Tesli N, Quintana DS, Almas D, et al. Multimodal imaging improves brain age prediction and reveals distinct abnormalities in patients with psychiatric and neurological disorders. Hum Brain Mapp. 2021;42:1714–20.

85. J'onnson BA, Bjornsdottir G, Thorgeirsson T, Ellingsen LM, Walters GB, Gudbjar- jonsson D, et al. Brain age prediction using deep learning uncovers associated sequence variants. Nat Commun. 2019;10:1–10.

86. Koppe G, Meyer-Lindenberg A, Durstewitz D. Deep learning for small and big data in psychiatry. Neuropsychopharmacology. 2021;46:176–90.

87. Abrol A, Fu Z, Salman M, Silva R, Du Y, Pils S, et al. Deep learning encodes robust discriminative neuroimaging representations to outperform standard machine learning. Nat Commun. 2021;12:1–17.

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AUTHOR CONTRIBUTIONS

YSL: design of the work, data analysis and interpretation, and drafting the manuscript. WYC: data analysis and interpretation. JQ: revising the manuscript. TJ: conception and design of the work, drafting the manuscript, and revising the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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