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Covariation of preadult environmental exposures, adult brain imaging phenotypes, and adult personality traits

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ABSTRACT

Exposure to preadult environmental exposures may have long-lasting effects on mental health by affecting the maturation of the brain and personality, two traits that interact throughout the developmental process. However, environment-brain-personality covariation patterns and their mediation relationships remain unclear. In 4,297 healthy participants (aged 18–30 years), we combined sparse multiple canonical correlation analysis with independent component analysis to identify the three-way covariation patterns of 59 preadult environmental exposures, 760 adult brain imaging phenotypes, and five personality traits, and found two robust environment-brain-personality covariation models with sex specificity. One model linked greater stress and less support to weaker functional connectivity and activity in the default mode network, stronger activity in subcortical nuclei, greater thickness and volume in the occipital, parietal and temporal cortices, and lower agreeableness, consciousness and extraversion as well as higher neuroticism. The other model linked higher urbanicity and better socioeconomic status to stronger functional connectivity and activity in the sensorimotor network, smaller volume and surface area and weaker functional connectivity and activity in the medial prefrontal cortex, lower white matter integrity, and higher openness to experience. We also conducted mediation analyses to explore the potential bidirectional mediation relationships between adult brain imaging phenotypes and personality traits with the influence of preadult environmental exposures and found both environment-brain-personality and environment-personality-brain pathways. We finally performed moderated mediation analyses to test the
potential interactions between macro- and microenvironmental exposures and found that one category of exposure moderated the mediation pathways of another category of exposure. These results improve our understanding of the effects of preadult environmental exposures on the adult brain and personality traits and may facilitate the design of targeted interventions to improve mental health by reducing the impact of adverse environmental exposures.
INTRODUCTION

Numerous studies have linked exposure to environmental factors (hereafter, environmental exposures) to mental health [1], especially exposures during the critical developmental periods for the human brain and behaviour [2]. To identify the biological mechanisms underlying the associations between environmental exposures and mental health, researchers have explored the effects of environmental exposures on brain structure and function, assessed by neuroimaging techniques, and on behavioural traits (such as personality) [3, 4]. Many of the brain imaging and behavioural phenotypes influenced by environmental exposures are associated with mental health [5]. Although these studies have reported various pairwise associations of environmental exposures, brain imaging phenotypes, and behavioural traits [6, 7], these associations are not always consistent across studies, possibly due to the following two challenges faced by the research field.

One challenge is that previous studies have mainly focused on the effects of a single or a few environmental exposures on human brain imaging or behavioural phenotypes [8, 9], and thus could not provide a full picture of exposure-phenotype associations. Although several recent studies have included many environmental exposures, these exposures were assessed at only a single time point or during a relatively short period of time [10, 11]; thus, these studies are unable to accurately represent the long-term cumulative or average effects of environmental exposures. Reliable exposure-phenotype associations can only be identified by simultaneously assessing various environmental exposures over a sufficient time span. The other
The challenge is how to analyse the complex associations between multiple environmental exposures and different levels of human phenotypes (such as brain and behaviour). Although pairwise correlations can provide meaningful information, the autocorrelation structure of environmental exposures, brain imaging phenotypes, or behavioural traits may bias the results of commonly used linear regression analyses [7].

To address this issue, studies on large-scale cohorts that collect various environmental, neuroimaging, and behavioural data have applied multivariate approaches, which are insensitive to autocorrelations among variables, to identify multiple-to-multiple covariation patterns between environmental exposures and brain imaging phenotypes or between brain imaging phenotypes and behavioural traits [7, 12, 13]. However, little attention has been given to the three-way environment-brain-behaviour covariation patterns, which provide information that cannot be obtained by pairwise correlations.

To shed light on potential mechanisms underlying the effects of environmental exposures on mental health, we combined sparse multiple canonical correlation analysis (smCCA) and independent component analysis (ICA) to explore environment-brain-personality covariation patterns in 4,297 healthy young Han Chinese individuals (aged 18–30 years) who participated in the Chinese Imaging Genetics (CHIMGEN) study [14]. In the present study, we examined 59 preadult (i.e., before the age of 18) environmental exposures (PAEs) potentially associated with mental health. These PAEs were divided into 50 individual-level microenvironmental exposures (PAMiEs) and 9 community-level macroenvironmental exposures (PAMaEs) [14, 15]. Since these PAEs occurred during critical developmental periods, they are expected to have the greatest
influence on the brain and personality [16] as well as on the risk of mental disorders [17]. We also included 760 imaging phenotypes to capture the structural, functional, and connectivity properties of the adult brain, of which many have been associated with environmental exposures, personality traits, and mental disorders. We also included five personality traits associated with environmental exposures, brain imaging phenotypes, and mental disorders. The three-way covariation patterns may improve our understanding of the linked many-to-many relationships of PAEs, adult brain imaging phenotypes, and adult personality traits and facilitate the generation of hypotheses about the mechanisms underlying the effects of PAEs on mental health. Due to the interaction between the brain and personality (i.e., the brain underlies personality, and personality shapes the brain via experience-dependent plasticity [18, 19]), we were also interested in whether brain imaging phenotypes mediate the effects of PAEs on personality traits, whether personality traits mediate the effects of PAEs on brain imaging phenotypes, or both, which may reveal the intricate effects of PAEs on the adult brain and personality traits. Considering potential interactions between PAMiEs and PAMaEs, we evaluated the moderation effect of one category on the mediation pathways of another category of environmental exposures to more precisely elucidate these relationships and inform interventions for health promotion. A schematic summary is shown in Fig. 1.

MATERIALS & METHODS

Participants
The 4,297 participants were recruited from the CHIMGEN study [14], which collected genomic, neuroimaging, environmental, and behavioural data from 7,306 healthy young Han Chinese participants aged 18–30 years from 32 research sites. The inclusion and exclusion criteria are presented in Supplementary Table 1, and the participant recruitment procedures, standard operating procedures, and data quality control can be found at http://chimgen.tmu.edu.cn/. The CHIMGEN study was approved by the local ethics committee at each research site, and written informed consent was obtained from each participant. The procedures for participant selection are shown in Supplementary Fig. 1.

Personality and environmental assessments

The Big Five personality traits, including agreeableness, conscientiousness, extraversion, neuroticism, and openness to experience, were assessed. Here, PAEs were defined as environmental exposures of the participants before the age of 18. We examined 79 PAEs, including early-life events (e.g., factors related to pregnancy and delivery; \( n = 8 \)); indoor (e.g., air quality and temperature; \( n = 7 \)) and outdoor (air pollution and noise pollution; \( n = 2 \)) environments before the age of 15; objective (family income, parental education and occupations; \( n = 5 \)) and subjective (unemployment pressure, financial difficulties, financial crises, living conditions, and neighbourhood relationships; \( n = 5 \)) socioeconomic status (SES) before the age of 10; adolescent self-rating events (e.g., interpersonal and academic stress; \( n = 6 \)); adverse childhood experiences (e.g., neglect and peer bullying; \( n = 13 \)); parental bonding (care, encouragement and control; \( n = 6 \)); family history (such as family members’ physical
conditions; \( n = 13 \); childhood trauma (emotional, physical and sexual abuse, as well as emotional and physical neglect; \( n = 5 \)); urbanicity score of the residential area (\( n = 1 \)) before the age of 18; and averaged natural environmental exposures (the normalized difference vegetation index (NDVI), the normalized difference built-up index (NDBI), night-time lights (NL), nitrogen dioxide (NO\(_2\)), particulate matter (PM\(_{2.5}\)), population density, the Palmer drought severity index (PDSI), and temperature clemency; \( n = 8 \)) before the age of 18. The measurements of these PAEs are provided in the Supplementary Information, and the categories of PAEs (PAMaEs and PAMiEs) are shown in Supplementary Table 2.

Of the 7,306 CHIMGEN participants, we excluded 2,547 participants without PAE or personality assessments. We also excluded 20/79 PAEs (Supplementary Table 3) with zero variance or near zero variance using the \textit{nearZeroVar} function of the \textit{caret} package in R (https://topepo.github.io/caret/). The remaining 59 PAEs were fed into outlier detection, and outliers were defined as those more than \( 3 \times \) the interquartile range (IQR) of the variable of interest in the remaining 4,759 participants. Outliers were set as missing values, and missing values (Supplementary Table 4) were imputed using the expectation-maximization (EM) method (25 iterations) implemented in Statistical Product and Service Solutions (SPSS, version 21) based on the relations of PAEs [20]. The descriptive statistics of PAEs and personality traits are presented in Supplementary Table 5.

**Neuroimaging data acquisition and processing**

Neuroimaging data were acquired with 10 types of 3.0-T magnetic resonance imaging
(MRI) scanners (Supplementary Tables 6–8), and the distribution of participants across sites is provided in Supplementary Table 9. Structural MRI data were used to calculate the gray matter volume (GMV), surface area (SA), and cortical thickness (CT) of each brain region; diffusion MRI data were used to compute the fractional anisotropy (FA) and mean diffusivity (MD) of each white matter tract; and resting-state functional MRI data were used to estimate the functional connectivity strength (FCS) and regional homogeneity (ReHo) of each brain region. The neuroimaging data preprocessing and phenotype calculation are provided in the Supplementary Information. After excluding 11 cerebellar imaging phenotypes with less than 10 voxels to calculate mean values, we finally included 760 brain imaging phenotypes (124 GMV, 151 CT, 151 SA, 48 FA, 48 MD, 119 FCS, and 119 ReHo; Supplementary Tables 10–13). Of the participants with eligible PAE and personality data, we included only the 4,297 participants with neuroimaging data in all three modalities. For brain imaging phenotypes, ComBat harmonization [21] was performed to adjust for the scanner effect (Supplementary Information) and achieved acceptable effectiveness (Supplementary Figs. 2–4); then normal score transformation was applied to improve data normality.

**Potential confounders**

To exclude the effects of confounders, we regressed out age, age², sex, age × sex, age² × sex, education level, body mass index, and genetic population effects for all brain imaging phenotypes and personality traits before smCCA. We further regressed out mean framewise displacement [22] for FCS and ReHo, total intracranial volume for regional GMV, total SA for regional SA, and mean CT for regional CT phenotypes. The
calculation of genetic population effects is described in the Supplementary Information, and descriptive statistics of the confounders are shown in Supplementary Table 14.

Multivariate covariation analyses

Using the PMA package (version 1.2.1) in R [23], we conducted smCCA to investigate the three-way PAE-brain-personality covariation patterns. The z-normalized PAEs, brain imaging phenotypes, and personality traits were input into the model, and then 1,000 permutations were run to select the sparse parameters. For each set of variables, 10 candidate values ranging from $1/\sqrt{p}$ to 1 with 10% increments (where $p$ is the number of variables in the set) were used to generate 1,000 parameter combinations. The optimal sparse parameters were derived from the parameter combination with the minimum $p$ value (Supplementary Information). With the optimal sparse parameters, a 10-fold cross-validation was performed to estimate the sum of canonical correlations for each model in real data. For each model, the sample was randomly divided into 10 subsets, of which nine were used for training and the remaining one was used for testing. In each loop, smCCA was performed on the training dataset, and the obtained canonical weights were applied to the testing samples to obtain their canonical variates. Then, the correlation coefficients between canonical variates were calculated and summed. Finally, the sums of canonical correlations were averaged across the 10 folds. This cross-validation was repeated 100 times, and the mean sums of canonical correlations were used to calculate the $p$ value for this model [13]. The significance of each model was determined by a permutation test ($n = 1,000$). In each permutation, 10-fold cross-validation was used to obtain the maximum sum of canonical correlations of the model.
The maximum sums of canonical correlations from 1,000 permutations were used to construct a null distribution. A $p$ value was calculated by dividing the number of maximum sums of permuted canonical correlations $\geq$ the mean sums of real canonical correlations by the number of permutations, and models with $p < 0.05$ were retained. With the FastICA package in MATLAB [24], we performed ICA (Supplementary Information) to estimate subject weights for each significant model (Supplementary Fig. 5). The contribution of each variable to each model was assessed by the correlation between this variable and subject weights across the 4,297 subjects [12, 13].

**Mediation analyses**

To test whether brain imaging phenotypes mediated the association between PAEs and personality traits or whether personality traits mediated the association between PAEs and brain imaging phenotypes, we performed model-based mediation analyses using a Quasi-Bayesian Monte Carlo simulation with 1,000 iterations using the R package mediation (version 4.4.6) [25]. Here, the canonical variate from each smCCA model was used to represent each set of variables. The significance was defined as $p < 0.05$.

**Moderated mediation analyses**

We performed moderated mediation analyses using Model 59 in PROCESS for R (version 4.3) [26] and tested four possibilities: (a) whether the association between PAMiEs (independent variable, X) and personality (dependent variable, Y) was mediated by brain imaging phenotypes (mediator, M) and moderated by PAMaEs (moderator, W); (b) whether the association between PAMiEs (X) and brain imaging phenotypes (Y) was mediated by personality (M) and moderated by PAMaEs (W); (c)
whether the association between PAMaEs (X) and personality (Y) could be mediated by brain imaging phenotypes (M) and moderated by PAMIes (W); or (d) whether the association between PAMaEs (X) and brain imaging phenotypes (Y) was mediated by personality (M) and moderated by PAMIes (W). The moderator (PAMaEs or PAMIes) was divided into three levels: low was defined as values < one standard deviation (SD) from the mean; moderate was defined as values ± 1 SD from the mean; and high was defined as values > one SD from the mean. A bias-corrected bootstrapping method (n = 1,000) was used to estimate the distribution of mediation effects and their 95% confidence intervals (CIs). A significant mediation effect was considered if the 95% CI did not include zero. Here, the canonical variates from the second smCCA model were used to represent the sets of variables because the PAMaE variables were too sparse in the first smCCA model.

Sex-specific covariation patterns

To test sex-specific covariation patterns, we constructed smCCA models separately for males (n = 1,480) and females (n = 2,817) and reran the above analyses without regressing out the sex effect. The results for males and females were compared with the results for the full sample (n = 4,297).

Reliability and stability assessments

To assess the robustness of our results, we conducted the following analyses. (a) To test the impact of different scanner-effect adjusting methods on the imaging canonical variates, we performed Pearson’s correlation analyses of imaging canonical variates, derived from ComBat harmonization and scanner regression. (b) To assess the stability
of canonical variates of the significant models estimated by the 10-fold cross-validation, for each of the 1,000 testing samples from the 100 times of 10-fold cross-validation, we performed Pearson’s correlation analyses of the relationship between canonical variates of the testing sample estimated by the cross-validation and those estimated by the model constructed based on the full sample. (c) To assess the stability of the smCCA model with different sample sizes, we repeated the algorithm in 1,500 subsamples from 100 randomly generated subsets (each contained 10–150% of the full sample in 10% increments, creating 15 subsamples) and recalculated the sum of canonical correlations [7, 10, 27]. (d) To verify the reliability of the three-way covariate patterns, we randomly and evenly divided the sample into a discovery subsample (n = 2,149) and a replication subsample (n = 2,148). Then we reran the smCCA algorithm separately in the two subsamples, and tested whether the covariate patterns in the discovery subsample could be replicated in the replication subsample. (e) To generalize our findings, we conducted an external validation using the second follow-up (FU2) data of the IMAGEN project (Supplementary Information and Supplementary Fig. 6). After identifying correlations between any two main contributors (PAEs, brain imaging phenotypes and personality traits) in CHIMGEN, we tested these correlations in IMAGEN-FU2. We also calculated and tested the Pearson correlation between correlation coefficients derived from both datasets. (f) To test the influence of the imputation of missing environmental exposure values on model stability, we applied the sparsity parameters and canonical weights from the significant smCCA models based on the imputed sample (n = 4,297) to the nonimputed sample (n = 3,510) and repeated all analyses.
RESULTS

Participants

Data from a total of 4,297 healthy participants, including 1,480 males (34.4%) and 2,817 females (65.6%), were finally included. Their mean age was 23.51 years with a standard deviation (SD) of 2.42 years and a range of 18–30 years. We compared demographic variables between the included and excluded participants and found significant differences \( p < 0.05 \) in age, sex, and education level (Supplementary Table 15); these variables were adjusted for in the statistical analyses.

Two three-way covariation models

The optimal sparsity parameters are presented in Supplementary Table 16. The mean (SD) sums of the canonical correlations for the five models were \( r = 0.573 (0.019) \) for Model 1, \( r = 0.534 (0.015) \) for Model 2, \( r = 0.384 (0.029) \) for Model 3, \( r = 0.231 (0.035) \) for Model 4, and \( r = 0.229 (0.072) \) for Model 5. Model 1 and Model 2 were significant \( (p = 0.001, 1,000 \) permutations, Supplementary Fig. 7).

Model 1 showed a linked covariation pattern, with preadult support and stress associated with adult brain imaging phenotypes and personality traits (Figs. 2–4 and Supplementary Tables 17–18). Individuals exposed to more stressors and receiving less support (e.g., less parental care and encouragement and more parental control; more academic, interpersonal and health stressors; more disharmonious neighbourhood relationships; and more severe emotional and physical neglect and abuse) before the age of 18 showed stronger ReHo in subcortical nuclei, greater CT of the occipital and
temporal lobes, larger GMV of the occipital and parietal lobes, and reduced FCS and ReHo in the default mode network (DMN), mainly including the posterior cingulate cortex, praecuneus, medial prefrontal cortex (mPFC), and angular gyrus. These individuals also showed higher neuroticism and lower agreeableness, conscientiousness, and extraversion.

Model 2 captured another covariation pattern of preadult urban environmental exposure and SES with adult brain imaging phenotypes and personality traits (Figs. 2–4 and Supplementary Tables 19–20). Individuals with higher SES (e.g., greater parental education and white-collar occupations; less family financial difficulties and financial crises) and greater exposure to urban settings (higher urbanicity score, population density, and night-time lights, and lower NDVI) showed higher FCS and ReHo in the sensorimotor network (SMN), including the precentral and postcentral gyri and Rolandic operculum; lower GMV, SA, FCS, and ReHo in the mPFC; and lower white matter integrity in the corticospinal tract, cerebellar peduncle, and pontine crossing fibres. These individuals also had higher openness to experience.

**Mediation analyses**

We tested the bidirectional mediation effects of brain imaging phenotypes (environment-brain-personality) and personality (environment-personality-brain) using canonical variates to represent the three sets of variables (PAEs, brain imaging phenotypes and personality traits). In Model 1, the canonical variate of PAEs was correlated with those of brain imaging phenotypes \(r = 0.164\) and personality traits \(r = 0.552\); the latter two canonical variates were also correlated \(r = 0.133\) (Fig. 5A).
The mediation analysis showed that brain imaging phenotypes partially mediated the association between PAEs and personality traits (portion of mediated = 1.3%, \( \beta = 0.0049 \), \( p < 2.0 \times 10^{-16} \), 95% CI = 0.002 to 0.01, Fig. 5B). Using the canonical variate of personality traits as the mediator, we found significant partial mediation effects of personality traits on the association between PAEs and brain imaging phenotypes (portion of mediated = 20.6%, \( \beta = 0.0253 \), \( p < 2.0 \times 10^{-16} \), 95% CI = 0.011 to 0.04, Fig. 5B).

In Model 2, the canonical variate of PAEs showed significant correlations with those of brain imaging phenotypes (\( r = 0.276 \)) and personality traits (\( r = 0.208 \)), and the latter two canonical variates were also correlated (\( r = 0.0932 \)) (Fig. 5C). Using the canonical variate of brain imaging phenotypes as the mediator, we found that brain imaging phenotypes partially mediated the association between PAEs and personality traits (portion of mediated = 5.1%, \( \beta = 0.0049 \), \( p = 1.8 \times 10^{-2} \), 95% CI = 0.001 to 0.01, Fig. 5D). When using the canonical variate of personality traits as the mediator, we also found a partial mediation effect of personality traits on the association between PAEs and brain imaging phenotypes (portion of mediated = 2.8%, \( \beta = 0.0096 \), \( p = 1.6 \times 10^{-2} \); 95% CI = 0.0019 to 0.02, Fig. 5D).

**Moderated mediation analyses**

Since PAMaE variables were too sparse to conduct the analysis based on Model 1 (Fig. 2A), we performed moderated mediation analyses based only on Model 2. Using PAMaEs as the moderator, we found that the mediation effects of brain imaging phenotypes and personality were not significant at low levels of PAMaEs (PAMiEs-
brain-personality: $\beta = 0.003$, 95% CI = -0.003 to 0.008; PAMiEs-personality-brain: $\beta = 0.007$, 95% CI = -0.005 to 0.020), but were significant at moderate levels of PAMaEs (PAMiEs-brain-personality: proportion of mediated = 4.4%, $\beta = 0.005$, 95% CI = 0.001 to 0.009; PAMiEs-personality-brain: proportion of mediated = 3.4%, $\beta = 0.011$, 95% CI = 0.002 to 0.021) and high levels of PAMaEs (PAMiEs-brain-personality: proportion of mediated = 7.0%, $\beta = 0.007$, 95% CI = 0.001 to 0.013; PAMiEs-personality-brain: proportion of mediated = 4.2%, $\beta = 0.015$, 95% CI = 0.003 to 0.029), indicating that PAMaEs moderate the mediation pathways of PAMiEs-brain-personality and PAMiEs-personality-brain (Fig. 5E and Supplementary Table 2).

Reliability and stability analyses

First, we tested the influence of the two scanner-effect adjusting methods and
found that imaging canonical variates, estimated based on imaging phenotypes preprocessed by ComBat harmonization and scanner regression were strongly correlated in the two models (Model 1: $r = 0.981, p < 2.2 \times 10^{-16}$; Model 2: $r = 0.992, p < 2.2 \times 10^{-16}$; Supplementary Fig. 8). Second, for each testing sample, we performed Pearson’s correlation analyses between canonical variates from the cross-validation and those estimated by the model constructed with the full sample; we found that the canonical variates of the three sets of variables estimated by the two methods showed strong correlations (mean [SD], $r = 0.954 [0.059]$ for PAEs, $r = 0.844 [0.052]$ for brain imaging phenotypes, and $r = 0.979 [0.028]$ for personality in Model 1; and $r = 0.955 [0.058]$ for PAEs, $r = 0.962 [0.043]$ for brain imaging phenotypes, and $r = 0.944 [0.066]$ for personality in Model 2; Supplementary Fig. 9A). Third, we reran the smCCA 1,500 times with different sample sizes and found that the sum of canonical correlations of the Model 1 was approximately stabilized after the sample size approached 50% of the full sample (Supplementary Fig. 9B), suggesting that the sample size used in this study was sufficient to generate stable smCCA results. Fourth, after splitting the full sample into the discovery ($n = 2,149$) and replication ($n = 2,148$) subsamples, we reran the smCCA algorithm separately in the two subsamples and found similar two significant models in both the discovery (Model 1: $r = 0.62, p = 0.001$; Model 2: $r = 0.59, p = 0.002$) and replication (Model 1: $r = 0.55, p = 0.008$; Model 2: $r = 0.52, p = 0.034$) subsamples (Supplementary Fig. 10, Supplementary Table 16). The two significant models in the discovery subsample had similar covariation patterns (Supplementary Fig. 11) with the two models in the replication subsample. The contributions of variables to models estimated based on the discovery subsample were significantly correlated with those calculated based on the replication subsample (Model 1: $r = 0.890$ for PAEs, $r = 0.935$ for brain imaging phenotypes, and $r = 0.976$ for personality traits; Model 2: $r = 0.944$ for brain imaging phenotypes, and $r = 0.976$ for personality traits; Model 2: $r = 0.944$ for brain imaging phenotypes, and $r = 0.976$ for personality traits; Model 2: $r = 0.944$ for brain imaging phenotypes, and $r = 0.976$ for personality traits).
0.939 for PAEs, \( r = 0.892 \) for brain imaging phenotypes, and \( r = 0.977 \) for personality traits, Supplementary Fig. 12). Fifth, based on the main contributors of each model in Fig. 4, we conducted correlation analyses between any two sets of main contributors in CHIMGEN, and validated these correlations in IMAGEN-FU2. CHIMGEN and FU2 participants showed similar correlation patterns between PAEs and personality traits (Supplementary Fig. 13A). We also found significant correlations (Model 1: \( r = 0.880, p = 3.41 \times 10^{-15} \); Model 2: \( r = 0.797, p = 5.80 \times 10^{-3} \), Supplementary Fig. 13B-C and Supplementary Tables 22-23) between correlation coefficients derived from both datasets. However, the correlations between datasets in correlation coefficients of brain imaging phenotypes with personality traits (Model 1: \( r = 0.266, p = 1.69 \times 10^{-2} \); Model 2: \( r = 0.192, p = 4.18 \times 10^{-1} \)) and PAEs (Model 1: \( r = 0.232, p = 5.36 \times 10^{-4} \); Model 2: \( r = 0.293, p = 2.58 \times 10^{-5} \)) were rather weak (Supplementary Fig. 13B-C and Supplementary Tables 24-27). Finally, we repeated the analyses in the 3,510 participants without any missing values and found that the two significant models were still significant (Model 1: \( r = 0.57, p = 0.001 \) and Model 2: \( r = 0.54, p = 0.001 \), Supplementary Table 16), with almost the same covariation patterns. The contributions of variables to the models estimated based on the nonimputed sample (\( n = 3,510 \)) were significantly correlated with those calculated based on the full sample (\( n = 4,297 \)) (Model 1: \( r = 0.998 \) for PAEs, \( r = 0.910 \) for brain imaging phenotypes, \( r = 0.999 \) for personality traits; Model 2: \( r = 0.999 \) for PAEs, \( r = 0.968 \) for brain imaging phenotypes, \( r = 0.999 \) for personality traits; Supplementary Fig.14). Moreover, we replicated all significant findings in the mediation and moderated mediation analyses (Supplementary Fig. 15 and Supplementary Table 28). These findings indicate that data imputation had a negligible impact on our results.
**Sex-specific covariation patterns**

We constructed smCCA models separately for females \((n = 2,817)\) and males \((n = 1,480)\) and then reran the analyses and compared the results with those estimated based on the full sample \((n = 4,297)\). In the female sample, we also found two significant models (Model 1: \(r = 0.61, p = 0.001\) and Model 2: \(r = 0.56, p = 0.001\); Supplementary Table 16 and Supplementary Fig. 16). In Model 1, we observed female-specific covariation patterns in brain imaging phenotypes, such as higher regional GMV and white matter integrity, although the PAEs and personality traits of females showed almost the same covariation patterns as those of the full sample (Supplementary Fig. 17A). In Model 2, females showed similar covariation patterns to those of full sample (Supplementary Fig. 17B). The contributions of variables to models estimated based on the female sample and those estimated based on the full sample showed strong correlations (Model 1: \(r = 0.962\) for PAEs and \(r = 0.992\) for personality traits; Model 2: \(r = 0.983\) for PAEs, \(r = 0.951\) for brain imaging phenotypes, and \(r = 0.993\) for personality traits), except for brain imaging phenotypes \((r = 0.619)\) in Model 1 (Supplementary Fig. 17C-D). The main contributors to each model based on the female sample are shown in Supplementary Fig. 18. In the male sample, we found one significant model \((r = 0.55, p = 0.037;\) Supplementary Table 16 and Supplementary Fig. 19). The PAEs and personality traits of males showed almost the same covariation patterns as those of the first model in the full sample; however, the contribution of regional GMV to the model was weaker in males than in the full sample (Supplementary Fig. 20A). Although we observed strong correlations of the contributions of environmental \((r = 0.990)\) and
personality ($r = 0.999$) variables to the model estimated based on the male sample and those estimated based on the full sample, we identified a moderate correlation ($r = 0.594$) for brain imaging phenotypes (Supplementary Fig. 20B). The main contributors to the model based on the male sample are shown in Supplementary Fig. 21. In addition, the mediation analyses in females and males showed similar mediation relationships to those in the full sample (Supplementary Figs. 22 A-D and 23), and the moderated mediation results in females were consistent with those in the full sample (Supplementary Fig. 22 E and Supplementary Table 29).

DISCUSSION

Based on 59 pre-adult environmental exposures, 760 brain imaging phenotypes, and five personality assessments in 4,297 healthy young adults, we conducted the first attempt to investigate three-way environment-brain-personality covariation patterns using multivariate analyses. We identified two covariation patterns linking distinct PAEs to brain imaging phenotypes and personality traits. We also found bidirectional mediation effects, i.e., brain imaging phenotypes partially mediated the associations between PAEs and personality traits, and personality traits also partially mediated the associations between PAEs and brain imaging phenotypes. After further dividing PAEs into PAMaEs and PAMiEs, we found that PAMaEs moderated the mediation pathways of PAMiEs-brain-personality and PAMiEs-personality-brain and that PAMiEs moderated the mediation pathways of PAMaEs-brain-personality and PAMaEs-personality-brain. The identified three-way environment-brain-personality covariation
patterns may inform the design of precise environmental interventions to promote mental health.

The first model linked preadult stressful events and lack of support to a series of brain structural, functional, and connectivity changes as well as higher neuroticism and lower agreeableness, consciousness, and extraversion in adulthood. This three-way covariation model extends previous observations regarding associations of personality traits with stress and support [28, 29] by demonstrating that stress and support were more important for these personality traits than other included environmental exposures. On the one hand, stress and reduced support associated with higher neuroticism (emotional instability), are well-known risk factors for psychiatric disorders, including depression [30], anxiety [31], addiction [32], and schizophrenia [33]. On the other hand, the lack of stress and increased support were associated with proactive personality traits including higher agreeableness (trustworthy), consciousness (responsible), and extraversion (sociable) [34], which are resilient to psychopathology [35]. Compared to pairwise association studies, the identified three-way covariation patterns of environment-brain-personality provide new insights. For example, based on the linked covariation of increased stress, weaker FCS and ReHo in the DMN regions, and higher neuroticism, we propose a stress-DMN-neuroticism covariation model to integrate the pairwise associations between stress and the DMN [36], stress and neuroticism [37], and the DMN and neuroticism [38]; this covariation model may reveal how stress increases the risk of neuroticism-related mental disorders. By combining the pairwise associations of stress, amygdala connectivity and activity, neuroticism, and mental
disorders, the identified stress-amygdala-neuroticism covariation pattern may suggest a potential pathway from stress to mental disorders. We also found covariation of increased stress, weaker mPFC functional connectivity (FCS), increased amygdala activity (ReHo), and higher neuroticism, which provides further support for the hypothesis that abnormally enhanced activity in the amygdala caused by reduced connectivity with the mPFC is a critical mechanism underlying stress- and neuroticism-related mental disorders [39, 40]. In this model, we found covariation of increased stress and reduced support with higher FCS or ReHo in the putamen, caudate and pallidum as well as higher neuroticism, which may explain the higher functionality of these regions in mental disorders [41, 42]. In addition, we found associations of increased stress and reduced support with increased thickness of primary visual and auditory cortices (brain regions with early maturation), consistent with the view that early adversity disrupts brain maturation by influencing synaptic pruning [43, 44]. This environment-brain-personality covariation model indicates that reducing preadult stress and increasing available support may benefit neurodevelopment and personality formation and ultimately reduce the risk of mental disorders.

The second model captured another three-way covariation pattern linking higher urbanicity and SES to stronger functional activity and connectivity in the SMN, weaker activity and connectivity as well as lower volume and surface area in the mPFC, and higher openness to experience. Individuals with higher openness to experience tend to be more sensitive to feelings and aesthetic experiences and more open to new ideas and values [45]; these individuals show greater cognitive flexibility, creativity, and novel-
seeking [46] but have an increased risk for mental disorders, such as borderline personality disorder [47], schizotypy [48], and addiction [49]. Several associations in the three-way covariation model have been reported previously, such as higher openness to experience in urban children than in rural children [50] and higher openness to experience in individuals with higher childhood SES [51]. We found similar associations of preadult urbanicity and SES with brain imaging phenotypes and openness to experience in this model, indicating that urbanicity and SES share environmental components critical for development. In the second model, higher urbanicity, SES, and openness to experience were consistently associated with weaker FCS and ReHo in the mPFC as well as stronger FCS and ReHo in the SMN. The mPFC is one of the core regions of the DMN and plays an important role in processing social and self-related information [52]. Structural and functional impairments in the mPFC have been related to mental disorders, such as depression [51], posttraumatic stress disorder [52], and schizophrenia [53]. The adverse effect of urbanicity on the mPFC is consistent with the reported negative correlations of urbanicity with the GMV, surface area, and functional connectivity of the mPFC [53]; the association of the mPFC with openness to experience has been reported previously [54]. In this model, we also found worse integrity (lower FA) in many white matter fibre tracts, especially the rostral part of the corpus callosum that connects the left and right mPFC. Impaired white matter integrity in the rostral corpus callosum is frequently reported in mental disorders and is also associated with air pollution [63], a feature of urban settings. Consistent with the associations of the SMN with openness and creativity [55], this model also showed a
positive relationship between functional connectivity and activity of the SMN with
openness to experience, which can be explained by mentally simulating possible future
actions [56]. Our findings extended this pairwise association to the environmental
factors of preadult urbanicity and SES, which may inform the strategies to enhance
creativity. Moreover, covariation of higher preadult urbanicity and SES, stronger SMN
activity, and higher openness to experience may explain the increased SMN activity in
patients with bipolar disorder [57], major depressive disorder [58], and schizophrenia
[59]. This model provides a full picture of the relationships of openness to experience
with urbanicity, SES, brain structure, and brain function, which may inform strategies
to improve cognition and mental health.

Comparison of the contributions of brain imaging phenotypes to the two models
revealed that some brain imaging phenotypes (such as the FCS and ReHo of the
putamen, sensorimotor cortex, and mPFC) contributed similarly to the two models but
that other brain imaging phenotypes (such as the GMV and FA of most brain regions
and white matter tracts) contributed to the two models in the opposite direction. These
results may reflect the shared and distinct environmental effects on brain imaging
phenotypes and associations between brain imaging phenotypes and personality traits,
indicating that environmental neuroscience and personality neuroscience studies should
include environmental exposures, brain imaging phenotypes, and personality
assessments as much as possible to obtain more complete pictures of their relationships.

In the mediation analyses, we identified a bidirectional mediation relationship for
the effects of PAEs on adult brain imaging phenotypes and personality traits. The
mediating roles of brain imaging phenotypes on the associations of environmental exposures with personality traits have been reported in previous studies [60, 61]. This mediation relationship can be easily understood given that brain structure and function are the substrates of personality traits [62], which can be regarded as special external phenotypes of the brain. In addition, we provided evidence of the mediating roles of personality on the associations of environmental exposures with brain imaging phenotypes. More importantly, the variance explained by personality traits (20.6%) in the environment-brain association was much greater than the variance explained by brain imaging phenotypes (1.3%) in the environment-personality association in the Model 1. These results potentially indicate that personality has an important impact on brain structure and function, which may be explained by the experience-dependent plasticity of the brain [19]. This mechanism emphasizes that the brain can be shaped by various behaviours, especially during the critical period of development; this property has been adopted by psychiatrists to develop behavioural therapies for mental disorders [63]. When dividing the 59 PAEs into macro- and microenvironmental exposures (PAMaEs and PAMiEs), we found that one category of exposure moderated the environment-brain-personality and environment-personality-brain pathways of another category of exposure, suggesting interactions between PAMaEs and PAMiEs. These interactions should be further investigated since they may indicate more precise interventions to create supportive and healthier environments for individuals and communities [64].

We also found several noticeable sex differences; for example, Model 2 was
significant only in females, and GMV and white matter integrity showed greater contributions to the female model than to the male model. The identified sex differences in the three-way covariation models may reflect sex differences in stress responsivity, which result from a complex interaction of sex chromosome genes with dynamic hormonal changes across the lifespan [65]. Since sex differences in stress responsivity at different critical developmental stages have been associated with different vulnerabilities to neuropsychiatric disorders [66], the sex-specific relationships of the environment-brain-personality disorder pathway deserve further investigation.

Although the identified three-way covariation patterns provide novel insights into the complex effects of PAEs on the brain and personality, there are still several limitations. First, despite we provide evidence for generalizing the correlations between PAEs and personality traits identified in Chinese into Europeans, the current evidence cannot generalize the identified associations of brain imaging phenotypes with PAEs and personality traits in Chinese, which still need to be verified in large-scale studies of other ancestries. Second, the scope and precision of environmental and neuroimaging indicators are limited, and more extensive and accurate environmental and neuroimaging measurements may provide additional information. Third, a panoramic picture can be obtained only from the three-way covariation models; however, the specific associations, especially the causal relationships, cannot be captured. Based on the clues provided by this study, future studies should investigate the causal effects of environmental exposures on the brain and personality. Fourth, the neuroimaging data and personality data were acquired at only a single time point during adulthood, which
prevents us from identifying the three-way covariation patterns specific to different developmental periods. Finally, our analyses considered only linear relationships, which inevitably overlooks potentially important nonlinear relationships.

Our multivariate analyses of data from 4,297 healthy participants indicated two three-way environment-brain-personality covariation patterns that are overlooked by pairwise correlation analyses, such as those conducted by previous studies. The mediating effect of personality on the relationship between environmental exposures and brain imaging phenotypes may indicate the ability of behaviour to shape the brain and thus support for behavioural therapy for brain disorders. The moderated mediation analyses of the relationship between preadult macro- and microenvironmental exposures may indicate more precise interventions to improve mental health. The sex differences in the covariation models may reflect sex differences in stress responsivity, which need to be considered when investigating the effects of environmental exposures on the brain, personality, and mental disorders. In combination with the well-known relationships of brain imaging features and personality traits with mental disorders, our results may provide candidate modifiable environmental risk factors to facilitate the development of preventive strategies for these disorders.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS
This work was funded by Natural Science Foundation of China (82030053), Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDKX-001A) and Tsinghua-Toyota Joint Research Fund. No other disclosures were reported.

CODE AVAILABILITY

Structural MRI data for VBM and SBM analyses were preprocessed separately by CAT12 (version r1364, http://dbm.neuro.uni-jena.de/cat) and FreeSurfer (version 6.0.0) (http://surfer.nmr.mgh.harvard.edu/), respectively. DTI data were preprocessed by FSL 5.0.10 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). rs-fMRI data were preprocessed by SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and Data Processing Assistant for Resting-State fMRI (http://rfmri.org/dpabi). Brain imaging phenotypes visualization was done using MRIcroGL (https://www.nitrc.org/projects/mricrogl/) and ggseg package in R (https://github.com/ggseg/ggseg). The codes for smCCA are available on the bnaras GitHub (https://github.com/bnaras/PMA). The codes for FastICA are available at https://www.fmrib.ox.ac.uk/ukbiobank/nnpaper/ukb_NN.m.

ADDITIONAL INFORMATION

Supplementary Information include Supplementary Methods, Supplementary Tables, and Supplementary Figures.

AUTHOR CONTRIBUTIONS

Kaizhong Xue, Wen Shen, Yanwei Miao, and Chunshui Yu conceptualized the study.
Kaizhong Xue conducted the analysis, and wrote the first version of the manuscript. Bo Gao, Feng Chen helped analyze data and revise the manuscript. Meiyun Wang, Jingliang Cheng, Bing Zhang, Wenzhen Zhu, Shijun Qiu, Xiaochu Zhang, Zuojun Geng, Guangbin Cui, Yongqiang Yu, Weihua Liao, Hui Zhang, Xiaojun Xu, Tong Han, Wen Qin, Feng Liu, Meng Liang, Lining Guo, Qiang Xu, Jiayuan Xu, Jilian Fu, Peng Zhang, Wei Li, Dapeng Shi, Caihong Wang, Zhihan Yan, Jing Zhang, Jiance Li, Dawei Wang, Junfang Xian, Kai Xu, Xi-Nian Zuo, Longjiang Zhang, Zhaoxiang Ye, Wen Shen, Yanwei Miao, and Chunshui Yu collected imaging data. Wen Shen, Yanwei Miao, and Chunshui Yu provided critical comments on the manuscript and approved the final version of the manuscript. All authors contributed to the manuscript. The authors read and approved the final manuscript.

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Figures and Figure legends

**Fig. 1** Schematic summary of the study design. 

- **A** Extracting PAEs, IMG and NEO features for each participant.  
- **B** A permutation scheme is used to select optimal sparsity parameters for PAEs, IMG and NEO and the 10-fold cross-validation (100 iterations) is run to estimate sum of canonical correlations.  
- **C** The significance of smCCA models is tested by the permutation test \((n = 1,000)\).  
- **D** The Fast-ICA is used to estimate subject weights in each model.  
- **E** Correlation between each variable and subject weight in all individuals are used to determine the contribution of each variable to each model.  
- **F** Mediation and moderated mediation analyses of canonical variates are conducted to find mediation pathways and moderation effects.  

Abbreviations: CT, cortical thickness;
ICA, independent component analysis; FA, fractional anisotropy; FCS, functional connectivity strength; GMV, gray matter volume; IMG, brain imaging phenotypes; MD, mean diffusivity; NEO, the Revised NEO Personality Inventory; PAEs, preadult environmental exposures; PAMaEs, preadult macroenvironmental exposures; PAMiEs, preadult microenvironmental exposures; ReHo, regional homogeneity; SA, surface area.
**Fig. 2** Two significant three-way covariation models. A The first significant model. B The second significant model. The x axis shows variables, and the y axis represents the contribution of each variable to the model. PAEs with larger contributions ($r > 0.2$) are marked with names. Abbreviations: ACE-IQ, adverse childhood experiences international questionnaire; ASLEC, adolescent self-rating life events check list; CTQ: childhood trauma questionnaire; ELCs, early-life conditions; FCS, functional connectivity strength; FH, family history; GMV-TIV, gray matter volume-total intracranial volume; ICs, indoor conditions; IMG, imaging measures; ICA, independent component analysis; lh, left hemisphere; NEO, the Revised NEO Personality Inventory; NDBI, normalized difference built-up index; NDVI, normalized difference vegetation index; NL, night-time lights; NO$_2$, Nitrogen Dioxide; OCs, outdoor conditions; OSES, objective socioeconomic status; PAEs, preadult environmental exposures; PBIF, parental bonding instrument-father; PBIM, parental bonding instrument-mother; PDSI, palmer drought severity index; PM$_{2.5}$, particulate matter; ReHo, regional homogeneity; rh, right hemisphere; SSES, subjective socioeconomic status; TBSS-FA, tract-based spatial statistics-fractional anisotropy; TBSS-MD, tract-based spatial statistics-mean diffusivity; TC, temperature clemency.
Fig. 3 The contribution of brain imaging phenotypes to each model. A Contribution of cortical imaging phenotypes. B Contribution of subcortical and cerebellar imaging phenotypes. C Contribution of white matter imaging phenotypes. Although FCS and ReHo phenotypes contribute similarly to the two models (such as positive contribution of the SMN and putamen and negative contribution of the mPFC), GMV and FA phenotypes (positive contribution in Model 1 and negative contribution in Model 2) show opposite contributions. Abbreviations: CT, cortical thickness; FCS, functional connectivity strength; FA, fractional anisotropy; GMV, gray matter volume; MD, mean diffusivity; M, model; mPFC, medial prefrontal cortex; ReHo, regional homogeneity; SA, surface area; SMN, sensorimotor network.
Fig. 4 The main contributors of each model. A The main contributors of Model 1. B The main contributors of Model 2. The contribution of each variable to each model is assessed by the correlation between the variable and subject weight across subjects. Red and blue represent positive and negative correlations, respectively. The top PAEs ($r > |0.2|$) and IMG (10 positive and 10 negative) variables are ordered by their contributions. All NEO variables are presented, and the grey colors represent traits with contribution < $|0.1|$. Abbreviations: ACE-IQ, adverse childhood experiences international questionnaire; ASLEC, adolescent self-rating life events check list; CT, cortical thickness; CTQ, childhood trauma questionnaire; ELCs, early-life conditions; FCS, functional connectivity strength; IMG, brain imaging phenotypes; ICA, independent component analysis; NDVI, normalized difference vegetation index; NEO,
the Revised NEO Personality Inventory; OSES, the objective socioeconomic status;
PAEs, pre-adult environmental exposures; PBIF, parental bonding instrument-father;
PBM, parental bonding instrument-mother; ReHo, regional homogeneity; SSES, the
subjective socioeconomic status.
Fig. 5 Mediation and moderated mediation analyses for significant models. A Correlations between any two canonical variates of PAEs, IMG, and NEO from the Model 1 in the full sample (n = 4,297). B IMG mediates the association between PAEs
and NEO, and NEO mediates the association between PAEs and IMG in the Model 1. C Correlations between any two canonical variates of PAEs, IMG, and NEO from the Model 2. D IMG mediates the association between PAEs and NEO, and NEO mediates the association between PAEs and IMG in the Model 2. E In moderated mediation analyses, PAMaEs moderate the mediation pathways of PAMiEs-IMG-NEO and PAMiEs-NEO-IMG, and PAMiEs moderate the mediation pathways of PAMaEs-IMG-NEO and PAMaEs-NEO-IMG. The grey column means nonsignificant mediation at the corresponding level of the moderator. Abbreviations: IMG, brain imaging phenotypes; NEO, the Revised NEO Personality Inventory; PAEs, preadult environmental exposures; PAMaEs, preadult macroenvironmental exposures; PAMiEs, preadult microenvironmental exposures.