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Traumatic stress load and stressor reactivity score associated with accelerated gray matter maturation in youths indexed by normative models

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Understanding how traumatic stress affects typical brain development during adolescence is critical to elucidate underlying mechanisms related to both maladaptive functioning and resilience after traumatic exposures. The current study aimed to map deviations from normative ranges of brain gray matter for youths with traumatic exposures. For each cortical and subcortical gray matter region, normative percentiles of variations were established using structural MRI from typically developing youths without any traumatic exposure ($n = 245$; age range = 8–23) from the Philadelphia Neurodevelopmental Cohort (PNC). The remaining PNC participants with neuroimaging data ($n = 1129$) were classified as either within the normative range (5–95%), delayed (>95%) or accelerated (<5%) maturational ranges for each region using the normative model. An averaged quantile regression index was calculated across all regions. Mediation models revealed that high traumatic stress load was positively associated with poorer cognitive functioning and greater psychopathology, and these associations were mediated by accelerated gray matter maturation. Furthermore, higher stressor reactivity scores, which represent a less resilient response under traumatic stress, were positively correlated with greater acceleration of gray matter maturation ($r = 0.224$, 95% CI = [0.17, 0.28], $p < 0.001$), suggesting that more accelerated maturation was linked to greater stressor response regardless of traumatic stress load. We conclude that traumatic stress is a source of deviation from normative brain development associated with poorer cognitive functioning and more psychopathology in the long run.

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INTRODUCTION

Adolescence is a sensitive and challenging period characterized as a transition from parental dependence to increased independence, and further maturation of the neural systems that subserve executive function and social cognition [1–3]. However, more than half of U.S. adolescents reported experiencing one or more traumatic events by age 17 [4]. Traumatic stress, in turn, has a significant impact on brain function and structure [5]. Furthermore, the consequences of traumatic exposures have been hypothesized to contribute to the peak onset of major psychiatric disorders during adolescence [6, 7], and a growing body of research has shown that psychopathology may be associated with deviations from normative neurodevelopment [8–10]. Understanding how traumatic stress affects typical brain development during adolescence is critical to further elucidate mechanisms underlying emergence of psychopathology and cognitive deficits after traumatic stress.

Exogenous environmental stimuli contribute to brain maturation during childhood and adolescence [11, 12]. In particular, traumatic stress early in life has long been recognized as a risk factor for behavioral challenges, emotional distress, social problems, and psychopathology later in life [13, 14]. The Stress Acceleration Hypothesis posits that early life stress accelerates development by increasing absorption of socio-environmental information to increase survival skills [15]. A recent meta-analysis and systematic review examined the evidence for accelerated biological aging after exposure to early life traumatic stress and found that accelerated pubertal timing, cellular aging as measured by both leukocyte telomere length and DNA methylation age, and brain cortical thinning were linked to early life adversities [16].

The loss of cortical gray matter volume and thickness during adolescence has been reported in cross-sectional [10] and longitudinal studies [17, 18]. Associations between traumatic stress and global cortical thinning, particularly in the frontoparietal, default mode, and visual networks, have been reported [16]. A recent study reported that threat but not deprivation-related adversities were particularly associated with the ventromedial prefrontal cortex (vmPFC) [19], with the coupling between

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amygdala and vmPFC being involved in multiple forms of emotion processing [20]. Prior neuroimaging studies have revealed cortical thinning in individuals with traumatic exposures when compared to those without [14]. However, these differences have not been investigated using normative models to explicitly quantify deviations from typical development during adolescence.

Not all individuals experience psychological health problems after being exposed to trauma. Thus, an important question is whether altered neurodevelopmental patterns associated with traumatic stress could be associated with not only cognitive deficits and psychopathology but also resilience. A recent review suggested that greater access to novel positive experiences and cognitively enriched environment slows brain maturation [11]. Indeed, protective factors such as psychological or physical caregiving and peer support reduce trauma-related stress after high cumulative adversity in children [21]. The resilience framework operationally defines resilience as an active process that leads to a benign outcome, or even positive growth, despite traumatic exposure [22, 23]. Therefore, individual differences in psychological health outcome after accounting for traumatic stress load can be interpreted as an expression of stressor reactivity (or resilience on the other end) [24]. Such an individual stressor reactivity score can serve as a proxy for resilience and investigate whether slower acceleration is noted in more resilient individuals.

Normative modeling could provide direct evidence in support of the stress acceleration hypothesis. The current study aims to examine whether youths who have experienced traumatic life events exhibit accelerated structural brain development. We directly tested the stress acceleration hypothesis with normative modeling using quantile regression. Quantile regression is reliable [25, 26] and computationally efficient [27] in modeling normative brain growth. We hypothesized that accelerated brain maturation mediates the association between traumatic stress load and poorer psychological outcomes, including cognitive functioning and psychopathology. Another aim of the study is to investigate whether relatively slower brain maturation under trauma stress is associated with resilience compared to those with poorer outcomes. A stressor reactivity score (SRS) was quantified by considering both cognitive functioning and psychopathology, accounting for exposure to traumatic stressful events. We hypothesized that high SRS would be associated with globally accelerated brain maturation, with lower SRS indicating resilience and associated with relatively slower brain maturation. To improve readability, key variables with abbreviations were listed in the Appendix with brief descriptions for this study.

METHODS

Participants

The Philadelphia Neurodevelopmental Cohort (PNC) is a population-based sample of about 9500 individuals from the greater Philadelphia area, ages 8 to 23, who received medical care at the Children's Hospital of Philadelphia (CHOP) network [28]. Participants were initially enrolled in a genetic study at the Center for Applied Genomics (CAG). Upon assent/consent, participants were genotyped during their clinical visit and provided written permission to be recontacted for studies of complex pediatric disorders. In the PNC, 1601 participants completed the MRI acquisition [29] during initial phenotyping (2009–2011). Participants with the presence of gross radiological abnormalities or medical history that might impair their brain function, and those whose T1 imaging data did not pass quality assurance, were excluded ($n = 205$; see supplementary methods for details). Additionally, 22 participants were excluded due to missing data in any target variables of the current study (i.e., socio-demographics, trauma, cognition, and psychopathology). The final sample included $n = 1374$ participants. Within this cohort, 245 participants were classified as typically developing who were free of significant psychopathology and any traumatic exposure and they were designated as training data for the normative models of gray matter maturation. The remaining participants ($n = 1129$) who presented significant psychopathology or experienced at least one traumatic stressful event were used for the main analyses.

Neurocognitive and psychiatric assessment and dimensions

The Penn Computerized Neurocognitive Battery (PennCNB) [30, 31] measures accuracy and response time for executive function, episodic memory, complex cognition, and social cognition [30]. Mean of z-transformed accuracy and median response time multiplied by −1 was calculated to represent cognitive efficiency [31]. Lifetime history of clinical symptoms across major psychopathology domains was evaluated through a structured interview, GOASSESS [32], based on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children [33]. As previously described [13, 34], symptom-level psychopathology responses from the GOASSESS (111 items across common psychopathology domains) were first examined in an exploratory factor analysis and four correlated traits were extracted (i.e., mood, psychosis, externalizing behavior, fear-phobias). To produce orthogonal scores based on the correlated factors, a bifactor confirmatory model was estimated, resulting in a general psychopathology factor and the four orthogonal factors listed above. Additionally, a confirmatory correlated-traits model was estimated for the purpose of calculating correlated scores usable when orthogonal scores were not desirable or necessary. The general psychopathology factor (from the bifactor model) and 4 correlated traits (from the correlated-traits model) were used for the current study.

Evaluation of Traumatic Stressful Load (TSL)

The GOASSESS screens lifetime exposure to eight types of traumatic experiences including (1) a natural disaster; (2) a serious accident; (3) believing that the participant or someone close to him/her could be killed or hurt badly; (4) witnessing extreme violence such as someone getting killed or badly beaten; (5) seeing a dead body; (6) being attacked or badly beaten; (7) being threatened with a weapon; or (8) being sexually forced (including but not limited to rape). As in our prior work [13], traumatic stressful load (TSL) was the total count of all event types. Age-and-sex-adjusted TSL was defined by residuals of TSL after controlling for age, sex and their interactions. See supplementary Figure S1 for the distributions of TSL.

Mental health reactivity to stressor exposure: Stressor Reactivity Score (SRS)

Impaired cognitive functioning and psychopathology are often associated with traumatic exposures. In the literature, these variables have typically been investigated separately. Here, we defined functioning of an individual as a composite score, the mean of *z*-transformed cognitive efficiency and psychopathology multiplied by −1. A lower functioning composite score reflects more cognitive deficits and/or psychopathology. Stressor reactivity score (SRS) was the residuals of reversed functioning composite score accounting for TSL [24]. That is, functioning composite score (reversed) was predicted in a linear regression using total numbers of traumatic exposures, and the residuals were used as the SRS. Thus, SRS represents a normative reactivity towards traumatic stress such that a more positive score indicates a higher vulnerability, and a more negative score indicates resilience.

Imaging acquisition and preprocessing

All MRIs were acquired on the same 3 Tesla scanner (Total Imaging Matrix Trio; Siemens; Erlangen, Germany) without any mid-study hardware or firmware upgrades [29]. A 5-min magnetization-prepared, rapid acquisition gradient-echo T1-weighted (MPRAGE) image (TR = 1810 ms, TE = 3.51 ms, FOV = 180 × 240 mm, matrix = 256 × 192, voxel resolution of 1 mm^3) was acquired for each participant. Image quality procedures were applied as previously described and details were provided in the supplementary methods [35]. Gray matter structure was quantified by cortical thickness, volume and density for cortical regions and volume for subcortical regions (see supplementary methods for details).

Normative modeling and Quantile Regression Index (QRI)

The workflow of the quantile regression index calculation based on cortical thickness, volume, gray matter density, and subcortical volume is illustrated in Fig. 1. First, we defined cortical parcels using the Glasser atlas [36] and subcortical parcels using the Aseg atlas [37]. Quantile

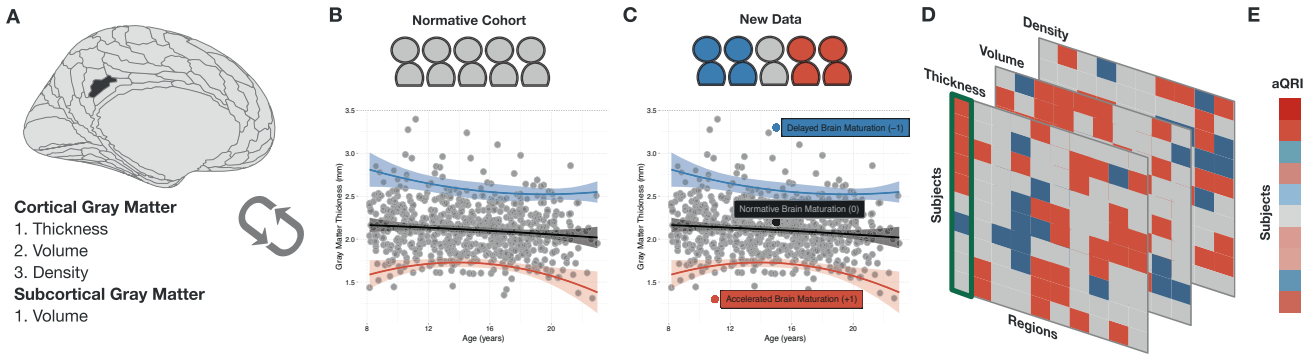

Fig. 1 Schematic Workflow for Calculating Quantile Regression Index (QRI). A The Glasser atlas was used for cortical gray matter modalities, including volume, thickness, and density, and the Aseg atlas was used for subcortical gray matter volume. **B** A normative model was estimated using quantile regression models in typically developed participants without any trauma exposure. **C** New data were fitted to the trained model and probed if it deviated from the 5% (accelerated maturation) or 95% (delayed maturation) quantile range. **D** The resulting matrices (row: subjects; columns: brain regions) are displayed. The color in each cell indicates whether a specific region of a subject deviated from the normative model (red: accelerated maturation; gray: normal; blue: delayed maturation). **E** To calculate the whole brain averaged quantile regression index (aQRI), all the columns of a subject across modalities were averaged.

regression was applied to the typically developed youths without any TSE ($n = 245$) to determine percentile curves for each cortical and subcortical parcel (Fig. 1A, B) [26, 27, 38, 39]. This method estimates the conditional quantile function as a linear combination of age and sex, implemented with the R package *quantreg* (version 5.88) [40]. For the *i*-th parcel, we fitted the 5th and 95th percentiles controlled for age and sex plus their interaction. Non-linear age effect was further adjusted using a quadratic function of age. The rest of the cohort ($n = 1129$) was compared to the trained normative brain maturation pattern (Fig. 1C). A value of −1 was assigned if the actual value of an individual was above the 95% confidence interval of the 95% quantile regression fitted line: younger than expected for that age, indicating delayed brain maturation. A value of 1 was assigned if below the 95% confident interval of the 5% quantile regression fitted line: older than expected for that age, indicating accelerated brain maturation. Anything else was assigned 0. Figure 1D shows the matrix obtained after looping all the parcels. Rows are subjects and columns are QRI of each parcel. A whole-brain QRI was the mean score across three tissue-specific cortical QRI and one subcortical volume QRI (Fig. 1E). The QRI was used and validated in previous studies [26, 27]. To further validate our approach, we compared the aQRI with the centile scores from a recent publication on normative brain charts across the lifespan using generalized additive models for location, scale and shape (GAMLSS) [10].

Statistical analysis

Kruskal-Wallis rank sum tests for continuous variables and Chi-square tests for categorical variables were employed to test the differences between normative and testing samples. Multiple comparisons were corrected by false discovery rate (FDR) with a threshold of $q = 0.05$ (two-sided).

Spearman correlation analyses were employed to examine the correlations among aQRI and TSL, psychopathology and cognition. To adjust for potential confounding effects, we further fitted a linear regression model to predict the functioning composite score with aQRI, controlling for age, sex, race, maternal education (medu) as a proxy of socioeconomic status (SES), and environmental SES (envSES) (formula: functioning composite score ~ aQRI + TSL + sex + age + sex × age + race + medu + envSES). Demographics such as sex, age and race have been recognized as contributing factors to psychopathology and functioning in our previous works [14, 28]. SES is known to be correlated with trauma exposure [14]. To study independent effect of trauma exposure, we used these variables as covariates to exclude their effects. As MRI image quality may potentially affect our results, we further controlled for the image quality in predicting functioning composite score as a sensitivity analysis (see supplementary material). Details about calculation of envSES can be found in our previous reports [14, 41]. In brief, envSES is a factor score based on census-level (American Community Survey) data for multiple features including percent of residents married, percent of residents in poverty, median family income, percent of residents with a high school education, population density, percent of residents employed, and others. For linear models, standardized parameters were obtained by fitting the model on a standardized version of the dataset. 95% confidence intervals (CIs) and *p* values were computed using the Wald approximation.

Mediation analyses were performed to examine the mediation role of brain maturation on the association between traumatic stressful load and psychopathology and cognition using R package *lavaan* (version 0.6–10) [42]. For the mediation analysis, 95% CIs were calculated using bootstrapping randomization ($n = 1000$).

Finally, Spearman correlation analyses were employed to examine the correlations among whole brain aQRI and SRS. A linear regression model was fitted to predict the SRS with aQRI, controlling for age, sex, race, medu, and envSES (formula: SRS ~ aQRI + sex + age + sex x age + race + medu + envSES). We further controlled for the MRI image quality in predicting SRS as a sensitivity analysis (see supplementary materials). To further interpret the brain maturation effects on network and region-wise levels, Spearman correlation analyses were performed within each network and each region to examine the relationship between aQRI and SRS. Multiple comparisons were corrected by FDR with a threshold of $q = 0.05$. As supplementary analyses, we also split participants into low (0–33%) and high (68–100%) SRS and compare their differences using the Wilcoxon rank sum test with $q < 0.05$.

Code and data availability

All statistical analyses were implemented in R (version 4.1.5). All codes are made available at a GitHub repository https://github.com/kamione/trauma_brainmaturation. The raw data reported in this paper have been deposited in the database of Genotypes and Phenotypes (dbGaP): accession no. [phs000607.v3.p2].

RESULTS

Participant characteristics

Normative samples included participants classified as typically developing who did not experience any traumatic stressful event ($n = 245$). Table 1 shows that this cohort was generally younger ($q < 0.001$), with higher maternal education ($q < 0.001$), higher environmental SES ($q < 0.001$), lower psychopathology levels ($q < 0.001$), higher cognitive functioning ($q < 0.001$), and larger total brain volume ($q = 0.027$) compared to the rest of our dataset ($n = 1129$). Traumatic stressful load was grouped according to tertiles (i.e., low: 0–33%, moderate: 34–67%, high: 68–100%) for ease of interpretation. Individuals with a higher traumatic stressful load (TSL) were older, with a lower maternal education level ($q < 0.001$), lower environment SES ($q < 0.001$), worse functioning composite score ($q < 0.001$), and a smaller total brain volume ($q = 0.027$). More Black adolescents were identified in the high TSL cohort compared to the normative cohort ($q < 0.001$). Correlation analyses (supplementary Fig. S2) showed that higher age-and-sex-adjusted TSL was associated with higher severity of psychopathology ($r = 0.25$, 95% CI = [0.19, 0.30], $q < 0.001$), lower cognitive

Table 1. Sample characteristics of normative and testing samples.

Characteristic		Traumatic Stress Load by Rank			*p* value[b]	*q* value[c]
	Normative, $N = 245$[a]	Low, $N = 377$[a]	Moderate, $N = 376$[a]	High, $N = 376$[a]		
Age	14.3 (4.2)	13.8 (3.3)	14.9 (3.4)	16.8 (3.1)	<0.001	**<0.001**
Sex					0.5	0.5
Male	106 (43%)	182 (48%)	177 (47%)	187 (50%)		
Female	139 (57%)	195 (52%)	199 (53%)	189 (50%)		
Race					<0.001	**<0.001**
White	140 (57%)	177 (47%)	178 (47%)	120 (32%)		
Black	78 (32%)	144 (38%)	146 (39%)	223 (59%)		
Others	27 (11%)	56 (15%)	52 (14%)	33 (8.8%)		
Maternal Education	14.91 (2.48)	14.35 (2.46)	14.13 (2.47)	13.86 (2.32)	<0.001	**<0.001**
Environmental SES	0.09 (0.95)	−0.16 (1.02)	−0.19 (1.01)	−0.55 (1.04)	<0.001	**<0.001**
Functioning Composite Score	0.60 (0.58)	0.02 (0.63)	−0.07 (0.67)	−0.46 (0.69)	<0.001	**<0.001**
Psychopathology (g)	−0.94 (0.79)	0.06 (0.85)	0.18 (0.86)	0.87 (0.95)	<0.001	**<0.001**
Mood	−0.88 (0.82)	0.03 (0.83)	0.12 (0.88)	0.79 (1.00)	<0.001	**<0.001**
Psychosis	−0.88 (0.75)	0.03 (0.87)	0.19 (0.90)	0.85 (0.99)	<0.001	**<0.001**
Externalizing	−0.91 (0.76)	0.15 (0.89)	0.15 (0.90)	0.58 (0.88)	<0.001	**<0.001**
Fear-Phobias	−0.83 (0.85)	0.03 (0.90)	0.14 (0.99)	0.60 (0.99)	<0.001	**<0.001**
Cognitive Efficiency (g)	0.27 (0.84)	0.09 (0.95)	0.04 (0.95)	−0.06 (0.94)	<0.001	**<0.001**
Executive Efficiency	0.26 (0.80)	0.00 (0.98)	0.05 (0.87)	−0.07 (0.88)	<0.001	**<0.001**
Memory Efficiency	0.06 (0.95)	0.14 (0.89)	0.03 (1.14)	0.13 (0.93)	0.5	0.5
Complex Reasoning Efficiency	0.27 (0.89)	0.08 (0.97)	0.05 (0.96)	−0.11 (1.00)	<0.001	**<0.001**
Social Cognition Efficiency	0.21 (0.91)	0.09 (0.96)	0.01 (0.95)	−0.04 (0.96)	0.003	**0.004**
Total Brain Volume (Z)	0.14 (0.98)	0.02 (0.98)	−0.03 (1.00)	−0.09 (1.02)	0.024	**0.027**

[a]Mean (SD); *n* (%).
[b]Kruskal-Wallis rank sum test; Pearson's Chi-squared test.
[c]False discovery rate correction for multiple testing.

efficiency ($r = -0.09$, 95% CI = [−0.15, −0.03], $q = 0.005$), and smaller total brain volume ($r = -0.09$, 95% CI = [−0.15, −0.03], $q = 0.005$).

QRI as a mediator between traumatic stress load and poor functioning

The averaged quantile regression index (aQRI) in the current study was positively associated with the centile scores of gray matter volume ($r = 0.457$, $q < 0.001$), surface area ($r = 0.371$, $q < 0.001$), cortical thickness ($r = 0.295$, $q < 0.001$), and subcortical volume ($r = 0.325$, $q < 0.001$), suggesting that our approach was comparable to a GAMLSS approach [10].

Figure 2A shows correlation between aQRI and TSL, psychopathology and cognition. Spearman correlation analysis showed that whole brain aQRI was associated with age-and-sex-adjusted TSL ($r = 0.109$, 95% CI = [0.05, 0.17], $q < 0.001$) and functioning composite score ($r = -0.30$, 95% CI = [−0.35, −0.24], $q < 0.001$). For psychopathology, aQRI was associated with general psychopathology ($r = 0.15$, 95% CI = [0.09, 0.21], $q < 0.001$), mood ($r = 0.09$, 95% CI = [0.03, 0.15], $q = 0.003$), psychosis ($r = 0.15$, 95% CI = [0.09, 0.20], $q < 0.001$), externalizing behavior ($r = 0.13$, 95% CI = [0.05, 017], $q < 0.001$), fear-phobias ($r = 0.11$, 95% CI = [0.07, 019], $q < 0.001$). For cognition, aQRI was associated with general cognitive efficiency ($r = -0.29$, 95% CI = [−0.34, −0.23], $q < 0.001$), executive efficiency ($r = -0.20$, 95% CI = [−0.26, −0.14], $q < 0.001$), complex reasoning efficiency ($r = -0.35$, 95% CI = [−0.40, −0.29], $q < 0.001$), and social cognition efficiency ($r = -0.21$, 95% CI = [−0.34, −0.23], $q < 0.001$).

We fitted a linear model to predict functioning composite score with TSL and aQRI, controlling for age, sex, race, and SES. The model explains a statistically significant and moderate proportion of variance ($F(9, 1119) = 37.71$, $p < 0.001$, $R^2 = 0.23$, adjusted $R^2 = 0.23$). Both TSL and aQRI were associated with functioning composite score after controlling for confounding variables. The effect of TSL is statistically significant and negative (standardized beta = −0.20, 95% CI = [−0.25, −0.14], $t(1119) = -6.97$, $p < 0.001$). The effect of aQRI is likewise statistically significant and negative (standardized beta = −0.07, 95% CI = [−012, - 0.01], $t(1119) = -2.34$, $p = 0.019$). The results remained robust after controlling for image quality (see supplementary material).

We further tested the mediation role of the whole brain aQRI using a mediation analysis with bootstrapping for calculating 95% confidence intervals ($n = 1000$). The effect of age-and-sex-adjusted TSL on functioning composite score was mediated by accelerated brain maturation (Fig. 2B). The indirect effect was significant ($\beta = -0.021$, 95% CI = [−0.034, −0.008], $p = 0.002$). Table 2 shows direct effects and indirect effects of all factors of psychopathology and cognitive functions as outcomes in the mediation models. Overall, we observed full or partial mediation effects of aQRI on the relationship between age-and-sex-adjusted TSL and general psychopathology (c′: $p < 0.001$, ab: $p = 0.039$), psychosis (c′: $p < 0.001$, ab: $p = 0.028$, overall cognitive efficiency (c′: $p = 0.039$, ab: $p = 0.001$), executive efficiency (ab: $p = 0.002$), complex reasoning efficiency (c′: $p = 0.001$, ab: $p = 0.001$) or social cognition efficiency (ab: $p = 0.002$).

Higher SRS was associated with accelerated brain maturation

In Fig. 3A, the hexagon plot shows that the whole brain aQRI was positively correlated with SRS ($r = 0.224$, 95% CI = [0.17, 0.28], $p < 0.001$). We fitted a linear model to predict SRS with aQRI

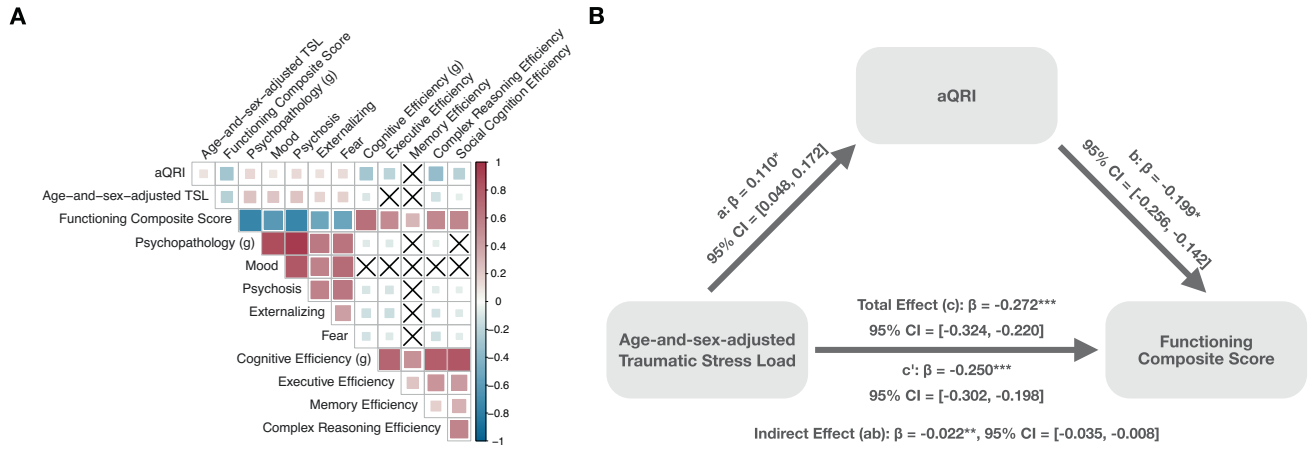

Fig. 2 Accelerated brain maturation mediated the relationship between traumatic stress load and functioning composite score. **A** Spearman correlation analyses show the significant relationships between traumatic stress load, aQRI, cognition, and psychopathology. Insignificant results were crossed out. **B** Mediation analyses show that traumatic stress load was positively associated with accelerated brain maturation and accelerated brain maturation was negatively associated with functioning composite score. Both direct and indirect effects were significant. Further mediation effects on cognitive functions and psychopathology are shown in Table 2.

Table 2. Direct and indirect effects of traumatic stress load on cognitive functioning and psychopathology mediated by accelerated brain maturation.

Outcome variables	Direct effect (c')			Indirect effect (ab)		
	Standardized Beta	95% CI	*p* value	Standardized Beta	95% CI	*p* value
Psychopathology (g)	0.302	0.255, 0.349	**<0.001**	0.009	0.000, 0.017	**0.039**
Mood	0.279	0.229, 0.328	**<0.001**	0.004	−0.003, 0.011	0.314
Psychosis	0.288	0.240, 0.336	**<0.001**	0.010	0.001, 0.018	**0.028**
Externalizing	0.187	0.138, 0.237	**<0.001**	0.005	−0.003, 0.012	0.231
Fear-Phobias	0.198	0.142, 0.253	**<0.001**	0.007	−0.001, 0.014	0.077
Cognitive Efficiency (g)	−0.062	−0.122, −0.003	**0.039**	−0.023	−0.037, −0.010	**0.001**
Social Cognition Efficiency	−0.041	−0.101, 0.020	0.187	−0.018	−0.029, −0.007	**0.002**
Complex Reasoning Efficiency	−0.096	−0.155, −0.038	**0.001**	−0.029	−0.046, −0.013	**0.001**
Memory Efficiency	0.008	−0.050, 0.066	0.783	0.002	−0.004, 0.009	0.430
Executive Efficiency	−0.041	−0.099, 0.017	0.170	−0.019	−0.031, −0.007	**0.002**

controlling for sex, age, medu, envSES, and race as well as image quality (see supplementary material). The model explains a statistically significant and weak proportion of variance ($F(8, 1120) = 18.58$, $p < .001$, $R^2 = 0.12$, adjusted $R^2 = 0.11$). The effect of aQRI is statistically significant and positive (standardized beta = 0.06, 95% CI [0.001, 0.12], $t(1120) = 2.01$, $p = 0.044$). By summarizing parcels into Yeo's 7 networks, Spearman correlation analysis revealed that the SRS was positively associated with aQRI (Fig. 3B). By grouping SRS into tertiles, we compared the high (67–100%) and low (0–33%) SRS groups as supplementary analyses. The high SRS group had greater acceleration of brain maturation in all Yeo's 7 networks compared to the low SRS group across (Fig. S4). Higher aQRI in high compared to low SRS group was found in all neuroimaging modalities including gray matter cortical and subcortical volume, cortical thickness, and gray matter density (Fig. S5). Figure 3C displays the region-wise correlations between aQRI and SRS. Correlations were found in the bilateral sensorimotor regions, superior temporal gyrus, medial prefrontal cortex, dorsolateral prefrontal cortex, occipital regions, precuneus, and midcingulate cortex. Positive correlations between aQRI and SRS were also found in bilateral thalamus proper and putamen, right caudate and amygdala. The correlation analyses were further conducted in each gray matter modality and the results suggested that the pattern could be driven by gray matter volume (Fig. S6). Top 10% of the absolute aQRI values were visualized in Fig. 3D. The top values were all positive and most of them were found in the individuals within the high SRS group. The high SRS group revealed a pattern of accelerated gray matter maturation similar to Fig. 3C.

DISCUSSION

In line with existing literature [15], our study provided direct evidence for a global acceleration of brain development associated with traumatic exposures in youths. With a normative model established with quantile regression, we demonstrated that high traumatic stress load was positively associated with poorer cognitive functioning and more psychopathology mediated by accelerated gray matter maturation. Furthermore, stressor reactivity score (SRS), representing a normative functional response after controlling for traumatic stress load, was positively associated with accelerated gray matter maturation, particularly in the visual, somatomotor, limbic, and default mode networks and subcortical regions. These results remained robust after adjusting for SES suggesting the effect of traumatic stress on brain maturation was independent of SES. Thus, while traumatic stress load was associated with more severe symptoms and poorer neurocognitive functioning, individual differences in stressor

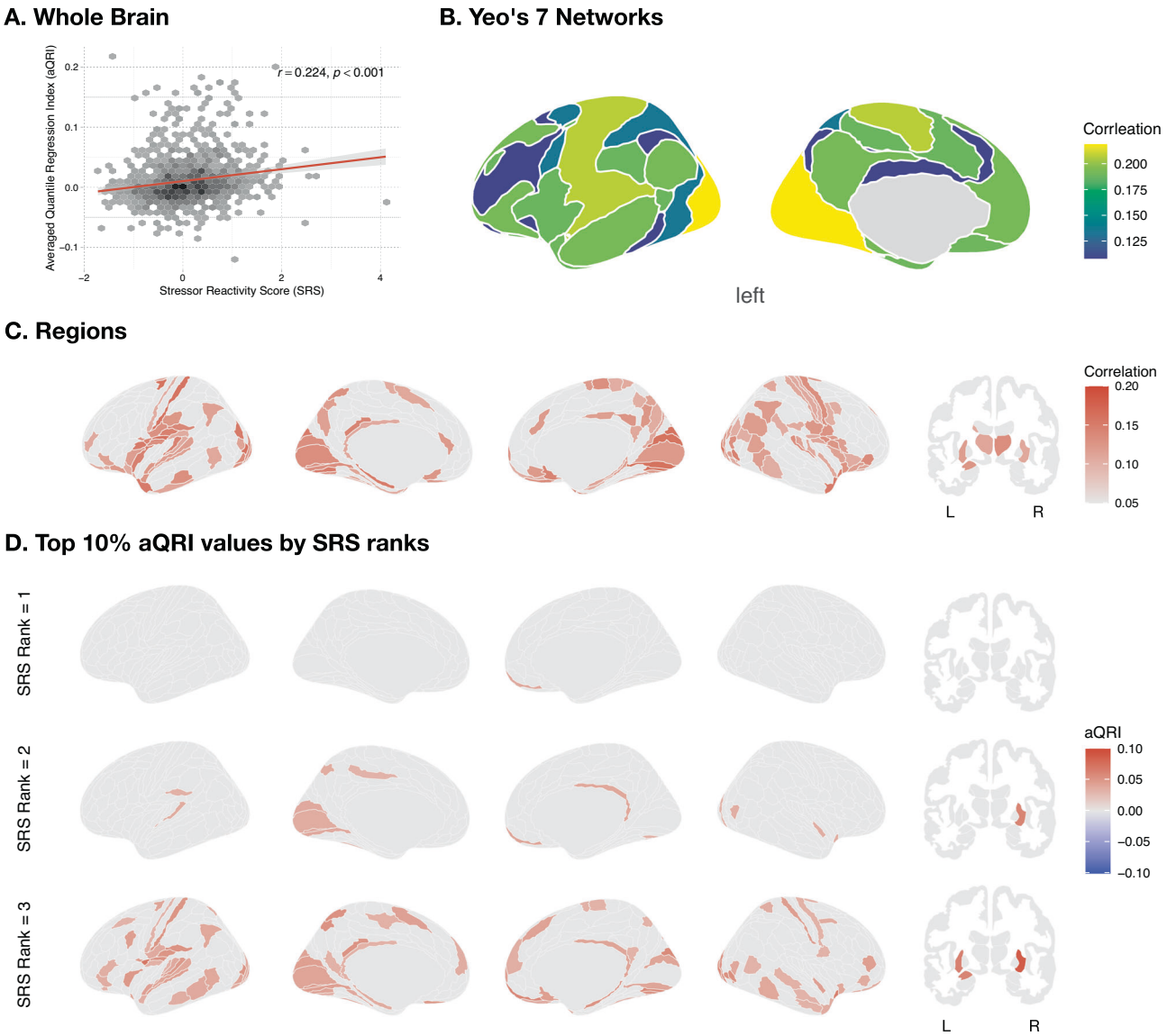

Fig. 3 Accelerated brain maturation was associated with stressor reactivity score. A A scatter plot illustrated a positive relationship between accelerated brain maturation and stressor reactivity score (SRS). **B**, **C** Spearman correlations between SRS and aQRI within networks organized into Yeo's 7 networks or regions defined by the Glasser and Aseg atlas. Only correlation coefficients with an FDR corrected *p* value (i.e., *q*) smaller than 0.05 are displayed. **D** Top 10% of absolute aQRI values were visualized and most of them were in individuals with high SRS, particularly in the occipital cortex, sensorimotor areas, temporal gyrus, orbitofrontal cortex, DLPFC, mPFC, amygdala, and hypothalamus.

reactivity were associated with brain maturation rates, suggesting vulnerability and resilience indicators.

Accelerated development is arguably a result of brain adaptations to manage early adverse events. According to the Stress Acceleration Hypothesis, such a rapid development may help to adapt to adverse events [43, 44]. However, this strategy becomes uncertain for a long-term adaptation to the everchanging environment. Supporting the stress acceleration hypothesis, our mediation models demonstrated global accelerated brain maturation associated with traumatic stress exposures in community youths. This acceleration is further linked to poorer cognitive functioning and psychopathology. Gray matter thinning could be the result of selective pruning of inefficient synaptic connections and increases in myelination [45]. Early life adversity could accelerate these processes leading to atypical development.

In addition to associations with a general psychopathology factor, a significant partial mediation effect of accelerated brain maturation on psychosis spectrum symptoms (compared to mood, externalizing behavior, or fear-phobias symptom dimensions) was observed. Our findings suggest that traumatic stress events could have a particular effect on development of psychosis through accelerated brain development [45–47]. Literature has established the relationship between early life adversity and psychosis symptoms or diagnosis even controlling for genetic liability (e.g., family history of psychosis) [48]. A study employing a network framework revealed that general psychopathology symptoms, including anxiety and impulse control, mediate the relationship between childhood trauma and psychotic symptoms [49]. Childhood trauma was linked to decreased hippocampal and amygdalar volume in first episode schizophrenia patients [50]. The authors suggested that childhood adversity, relatively independent of psychotic symptoms, may contribute to brain morphology in psychosis. One possible mechanism could be heightened perception of threats in traumatized individuals and increased likelihood of future development of delusions and hallucination symptoms [51]. Our study can suggest a potential mechanism linking response to traumatic stress with neurodevelopmental disruptions and psychosis spectrum symptoms.

Although the current community samples did not specifically recruit individuals diagnosed with post-traumatic stress disorder (PTSD), studies about neural circuits related to PTSD could further inform the impact of atypical brain development on SRS. A recent PTSD study under the ENIGMA network, gathering case-control studies across the globe, revealed that participants with PTSD had lower volumes in multiple regions including prefrontal regulatory, emotion, and sensory processing cortical regions [16]. Lateral orbitofrontal gyrus was robustly associated with post-traumatic stress symptoms even adjusting for depressive symptoms. Their findings confirmed the deficits in emotion brain circuits in PTSD. Cortical thinning in orbitofrontal cortex was also linked to accelerated cellular aging based on DNA methylation in PTSD [52, 53], suggesting a higher epigenetic-based mortality risk in individuals with lifetime trauma and PTSD. Similarly, our results revealed a comparable pattern of accelerated brain maturation in the high SRS group in a community cohort (see Fig. 3B, D), suggesting that a similar pattern of structural brain abnormality may develop regardless of a formal diagnosis of PTSD.

Could slower brain maturation be associated with resilience after exposures to traumatic stress in early life? Our results may inform this question. Our operational definition of stressor reactivity was by normative responses towards traumatic stressful events. Therefore, low stressor reactivity could inform resilience of individuals. Our results showed that SRS was positively associated with accelerated brain maturation across gray matter modalities. On a macroscopic perspective of closer examination, individuals with low SRS showed slower brain maturation compared to those with high SRS in the visual, somatomotor, limbic, and default mode networks even adjusting for SES [52]. A preregistered systematic review found that in interventions improving family or social support, resilience factors may reduce the risk of psychopathology following childhood adversity [54]. Rare and positive events that trigger surprise could lead to slower maturation and enhanced plasticity [53]. Future longitudinal studies could examine brain development in traumatized individuals with enriched social environmental support. These studies could provide better understanding of how resilience develops after trauma [55].

Several limitations should be taken into consideration. First, the developmental patterns were estimated using cross-sectional data. Although this estimation shared similarities with longitudinal data, there are still some discrepancies [56]. Longitudinal data should be acquired in the future to confirm the current findings. Second, detailed information of stressors, including duration and temporal relationships, was not available. Such information could help estimate more precise, outcome-based resilience scores. Third, the limited sample size of training data for the normative model prevented us from building a sex and race-stratified training model [57]. Although we have adjusted the race effect as a confounding effect in the subsequent analyses, a larger and race-stratified sample could be helpful to generalize our results. Fourth, while the operational normative ranges (5–95% percentiles) in the current study followed the previous literature [27], this definition is subjective. Future studies could establish optimal and minimum thresholds that can differentiate atypical from normative growth. Fifth, the prevalence rate of traumatic exposure of the PNC cohort was lower than the national survey [4, 58]. This could be due to operational definitions of traumatic exposure and/or that the PNC samples focus on a specific region whereas the national survey samples represented different regions of the US. Sixth, although PennCNB provided an overall reliable measurement of general cognition, cognitive functions that might be enhanced by stress are not included, such as detection of threat cues, fear learning, enhancing effect of emotion on episodic memory. Future study could examine the effect of accelerated brain maturation on these relevant cognitive functions.

CONCLUSIONS

Accelerated brain maturation associated with traumatic stress could link to adverse outcomes in youths in the long run, while slower maturation could indicate the effects of a protective factor. Understanding typical and atypical neurodevelopment in youths with adversity could inform etiology of vulnerability and resilience to psychopathology and help inform efforts at early prevention programs for youths at risk after life adversity.

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AUTHOR CONTRIBUTIONS

TYW: Conceptualization, methodology, software, formal analysis, data curation, writing—original draft, writing—review & editing, visualization. TMM: Data curation, formal analysis, writing—review & editing. JS: Formal analysis, writing—review & editing. KSLY: Writing—review & editing. KR: Resources, data curation, writing—review & editing. RB: Writing—review & editing. MEC: Writing—review & editing. AFA-B: Writing—review & editing. TDS: Resources, writing—review & editing. REG: Resources, writing—review & editing, supervision, project administration, funding acquisition. RCG: Conceptualization, resources, writing—review & editing, supervision, project administration, funding acquisition.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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APPENDIX. ABBREVIATION TABLE FOR KEY VARIABLES

Key Variable	Abbreviation	Brief Description
Traumatic Stress Load	TSL	Sum of traumatic stressful events
Averaged Quantile Regression Index	aQRI	Whole brain maturation index calculated by quantile regression models
Stressor Reactivity Score	SRS	Residuals of functioning composite score regressing out traumatic stressful load, a score indicating vulnerability or resilience to poorer outcomes under stress