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Lower Gyrification of the Ventromedial Prefrontal Cortex in Posttraumatic Stress Disorder: An ENIGMA-PTSD Study

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ABSTRACT

BACKGROUND: Cortical gyrification involves the formation of folds in the cerebral cortex, coinciding with key neurodevelopmental processes. Its strong correlation with increased cortical surface area and decreased cortical thickness may improve cortical signaling efficiency by decreasing cortico-cortical distance. Differences in brain structure have been found in posttraumatic stress disorder (PTSD), yet few small studies have examined cortical gyrification.

METHODS: Gyrification was quantified using FreeSurfer's Local Gyrification Index (lGI), derived from 3-dimensional T1-weighted volumetric brain magnetic resonance imaging in 1876 participants (PTSD n = 789, control n = 1087) across 24 sites from the ENIGMA-PGC (Enhancing Neuro Imaging Genetics through Meta-Analysis and Psychiatric Genomics Consortium) PTSD working group. Using a region of interest–based approach, we fitted a linear mixed-effects model with age (mean = 35.6, SD = 9.23, range = 8–95), sex (female = 967 [52%], male = 909 [48%]), pial surface area, PTSD, and random site effects to test associations between PTSD diagnosis/severity and regional lGI. We examined moderating effects of depression, childhood trauma, age, and sex.

RESULTS: PTSD diagnosis and severity were both associated with lower lGI for the right medial orbitofrontal and right rostral anterior cingulate cortices. The interaction of PTSD and age was associated with lower lGI for the rostral middle frontal cortex bilaterally. Contrasting comorbid PTSD and major depressive disorder with the PTSD-only group showed that comorbidity was associated with lower lGI in the left inferior and medial temporal cortices.

CONCLUSIONS: Lower lGI, which is associated with impaired signaling efficiency, was observed in the PTSD group compared with the control group for the ventromedial prefrontal cortex, a region that has been strongly implicated in associative fear learning and extinction. It is possible that PTSD accelerates the typical age-associated decline in lGI of the rostral middle frontal cortices.

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Posttraumatic stress disorder (PTSD) is a chronic psychiatric condition that may develop after exposure to traumatic events such as sexual assault, combat, or natural disasters (1–3). It is characterized by avoidance, intrusive memories, and alterations in arousal, mood, and cognition (4), manifesting in symptoms such as hypervigilance, insomnia, and emotional

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detachment (5–7). Lifetime trauma exposure is common, and 8.3% of people who have experienced a traumatic event develop PTSD (8).

Neuroimaging studies differentiating individuals with PTSD from trauma-exposed control participants have identified altered activity and morphology in regions including the amygdala (9,10), orbitofrontal cortex (OFC) (11,12), and anterior cingulate cortex (ACC) (12). Although a large body of structural magnetic resonance imaging (MRI) studies have examined surface area (13,14), cortical thickness (15,16), and volume in PTSD (17,18), the degree of cortical folding or gyrification has not been widely investigated in PTSD research. Cortical gyrification is a structural measure of the convolutions in the cerebral cortex. The local gyrification index (lGI) is calculated as the ratio of a region's cortical surface area to its convex hull (19). Gyrification begins before birth when the brain undergoes substantial morphological changes during the third trimester of fetal life (20) and continues through adolescence and adulthood (21). Given that neuroplasticity is pronounced during childhood (22,23), and childhood trauma impacts cortical thickness (24,25), investigating the association between childhood trauma and lGI is crucial. Gyrification is also known to decrease with age (26), and given the growing interest in studying the link between PTSD and biological aging using DNA methylation (27,28) and brain aging methods (29,30), we investigated the moderating effects of PTSD severity on the relationship between age and gyrification.

Gyrification is positively correlated with cortical surface area (31) and intracranial volume (32) and is related to the total number of neurons, their connectivity, and global signaling efficiency (33). Greater cortical folding results in an increased number of sulci, which, unlike gyri, primarily communicate with neighboring structures, suggesting that higher local gyrification may indicate enhanced local signaling efficiency (34,35). Several theories have posited the driving force behind the formation of cortical folds. For example, chemical morphogens may be responsible for the differential growth of the gyri and sulci (36). Alternatively, the axonal tension hypothesis argues that the axons within the white matter mechanically pull interconnected regions of the gray matter closer together, resulting in the formation of cortical folds (37). The leading hypothesis is that the formation of gyri is unregulated and is caused by the mechanical bulking that occurs as a consequence of differential growth rates across the 6 layers of cerebral cortex within the rigid confines of the skull (19,38).

Cortical gyrification has been linked with behavior and cognition. Generally, hypergyrification of the frontal lobe (31,39) has been positively associated with general cognitive ability and better performance on executive functions such as working memory and processing speed. Lower gyrification in the left superior parietal cortex is associated with higher trait anxiety (40), and hypergyrification in the left inferior temporal and superior parietal gyri is associated with generalized anxiety disorder (41). Investigating gyrification in PTSD provides an opportunity to discover unique neurobiological markers that may not be consistently identified when examining other structural metrics such as surface area. Although gyrification, a surface-based measure, is positively correlated with surface area, studies on autism spectrum disorder (42) and generalized anxiety disorder (41) have demonstrated that gyrification (not surface area) was able to detect group differences.

Only 2 studies have investigated gyrification in PTSD. The first study showed that PTSD patients with a history of motor vehicle accidents had decreased gyrification of the left lateral OFC, but the magnitude of gyrification was not significantly correlated with PTSD symptom severity (43). The study had a sample size of 36 participants (n_{PTSD} = 18) and enrolled trauma-naïve rather than trauma-exposed control participants. Although Chu *et al.* (43) noted that the sample size was a limitation, the study was the first to investigate gyrification in patients with PTSD. The second study, with a slightly larger sample size of 48 participants, found hypergyrification of the precuneus in PTSD (44). Considering these promising but inconsistent findings from underpowered studies, possible markers of hypo- and/or hypergyrification across the brain in PTSD have remained elusive. To address concerns about low statistical power and homogeneous samples that are likely to compromise reproducibility, we leveraged PTSD data in a large sample from multiple sites with diverse trauma types, age, and other sociodemographic variables. Our aim was to test associations between lGI and PTSD diagnosis, PTSD severity, and the magnitude of childhood trauma exposure.

METHODS AND MATERIALS

Sample

The clinical, demographic, and neuroimaging participant data analyzed in this study were shared by the ENIGMA-PGC (Enhancing Neuro Imaging Genetics through Meta-Analysis and Psychiatric Genomics Consortium) PTSD working group. The sample (N = 1876) included 789 participants with PTSD and 1087 control participants (n = 813 [74.8%] trauma-exposed) ascertained at 24 sites. Sample characteristics can be found in Table 1, age distribution by site is provided in Figure S1, and a map of the contributing institutions is provided in Figure S2. Trauma-exposure data are provided in Table S1, exclusion and inclusion criteria are provided in Table S2, and race and ethnicity data are provided in Table S3. Each site acquired T1-weighted images, clinical assessments, and demographic data as part of site-specific studies that were subsequently shared with ENIGMA-PGC PTSD for joint analyses. All sites received approval from their local institutional review boards (IRBs), and all participants provided written informed consent. The data analysis was deemed exempt by the Duke University Medical Center IRB.

Harmonization of Symptom Severity

Scores were harmonized to a 0 to 1 range using minimum-maximum normalization:

$$X_{norm} = \frac{X - S_{min}}{S_{max} - S_{min}} \quad (1)$$

where X is the original score, and S_{min} and S_{max} are the original minimum and maximum scores for a given assessment, respectively. The only assessment used for childhood trauma exposure was the Childhood Trauma Questionnaire (CTQ)

Table 1. Sample Characteristics by Site From the ENIGMA-PTSD Working Group

Site	*n*	Age, Years	Sex		Diagnosis		Diagnostic Tool	PTSD Severity		Severity Tool
			Female	Male	PTSD	Control		PTSD	Control	
Amsterdam AMC	70	39.6 (9.96)	32	38	36	34	CAPS-4	0.5 (0.1)	0.04 (0.03)	CAPS-4
Beijing	77	47.79 (10.32)	47	30	36	41	PCL-5	0.54 (0.13)	0.2 (0.11)	PCL-5
Columbia	76	35.86 (12.46)	34	42	24	52	SCID	0.45 (0.12)	0.1 (0.12)	CAPS-5
Duke	132	39.98 (9.94)	26	106	33	99	CAPS-4, CAPS-5	0.47 (0.16)	0.07 (0.12)	CAPS-4, CAPS-5
Emory	59	40.22 (11.73)	59	0	12	47	CAPS-4	0.43 (0.08)	0.14 (0.11)	CAPS-4, MPSS
Ghent	59	36.76 (11.71)	59	0	6	53	MINI	–	–	
Groningen	35	37.83 (9.52)	35	0	35	0	CAPS-4	0.5 (0.09)	–	CAPS-4
Leiden	22	14.91 (1.93)	19	3	7	15	ADIS-C/P	0.44 (0.25)	0.13 (0.12)	PTSD subscale of the TSCC
Mannheim	49	35.86 (11.64)	49	0	49	0	SCID	0.54 (0.2)	–	DTS
Masaryk	268	52.12 (18.92)	162	106	108	160	PCL-C	0.33 (0.11)	0.08 (0.06)	PCL-C
Michigan	53	30.58 (7.56)	0	53	36	17	CAPS-4	0.52 (0.13)	0.07 (0.07)	CAPS-4
Minneapolis VA	98	32.59 (7.64)	3	95	24	74	CAPS-4	0.45 (0.15)	0.14 (0.09)	CAPS-4
Minnesota	61	43.07 (9.44)	5	56	12	49	CAPS-4	0.39 (0.08)	0.07 (0.07)	CAPS-4
Münster	34	25.68 (6.39)	30	4	18	16	SCID4	–	–	
Nanjing	139	57.25 (5.91)	73	66	50	89	SCID4	0.35 (0.09)	0.13 (0.08)	CAPS-4
Stanford	101	36.42 (10.59)	57	44	67	34	CAPS-4	0.51 (0.12)	0.02 (0.02)	CAPS-4
Tours	38	27.55 (9.87)	38	0	8	30	CAPS-4	0.43 (0.1)	0.21 (0.1)	CAPS-4
Vanderbilt	50	31.34 (4.63)	9	41	15	35	CAPS-5	0.34 (0.06)	0.03 (0.03)	CAPS-5
Waco VA	28	41.11 (10.99)	4	24	13	15	PCL-5	0.61 (0.14)	0.14 (0.14)	PCL-5
Washington	145	12.83 (2.64)	72	73	31	114	CAPS-5, CAPS-4	0.18 (0.04)	0.01 (0.03)	CAPS-5
West Haven VA	60	35.02 (9.71)	7	53	31	29	CAPS-4	0.49 (0.11)	0.11 (0.11)	CAPS-4
Western Ontario	63	36.6 (13.33)	39	24	35	28	CAPS-4, CAPS-5	0.51 (0.1)	0.01 (0.03)	CAPS-4, CAPS-5
Wisconsin-Madison-Cisler	104	32.82 (8.28)	104	0	84	20	CAPS-5, SCID4	0.54 (0.19)	0.02 (0.03)	PCL-5, PCL-C
Wisconsin-Madison-Grupe	55	30.51 (6.4)	4	51	19	36	CAPS-4	0.48 (0.11)	0.16 (0.13)	CAPS-4
24 Sites[a]	1876	35.6 (9.23)	967	909	789	1087	–	0.45 (0.12)	0.09 (0.08)	–

Values are presented as *n* or mean (SD). PTSD assessments: CAPS-4 (100), CAPS-5 (62), DTS (101), MPSS (102), PCL-5 (103), PCL-C (104), and the PTSD subscale of the TSCC (105), SCID/SCID4 (106), MINI (107), ADIS-C/P (108).

ADIS-C/P, Anxiety Disorders Interview Schedule for DSM-IV for Child and Parent version; AMC, Academic Medical Center; CAPS-4, Clinician Administered PTSD Scale for DSM-IV; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; DTS, Davidson Trauma Scale; ENIGMA, Enhancing Neuro Imaging Genetics through Meta-Analysis; MINI, Mini-International Neuropsychiatric Interview; MPSS, Modified PTSD Symptom Scale; PCL-5, PTSD Checklist for DSM-5; PCL-C, PTSD Checklist-Civilian Version; PGC, Psychiatric Genomics Consortium; PTSD, posttraumatic stress disorder; SCID/SCID4, Clinical Interview for DSM-IV Axis I disorders; TSCC, Trauma Symptom Checklist for Children; VA, Veterans Affairs.

[a]Final row provides totals for participant counts (across sites, by sex, and by diagnosis) and mean PTSD symptom severity for PTSD and Control groups.

(45). See Tables S4 to S6 for details on depression and PTSD assessments.

Neuroimaging Data Acquisition and Processing

The MRI acquisition parameters for each cohort are detailed in Table S7. Cortical folding quantifies the degree of convolutions in the cerebral cortex by comparing the pial surface area of a region to its smoothed outer surface area. The lGI (46), a measure of cortical folding, was computed for each participant using the FreeSurfer software version 7.1.1 (https://surfer.nmr.mgh.harvard.edu/). An lGI of 5 indicates more cortical folding (gyrification), while an lGI value of 1 signifies a smooth cortical surface without folding. See Figure 1 for an illustration of the lGI calculation process. The FreeSurfer software performs the following key steps.

Surface Preparation. An outer smoother surface wrapping the pial surface was generated. The cortex was segmented into 68 cortical regions using the Desikan-Killiany Atlas.

Region of Interest Estimation. Circular regions of interest (ROIs) were estimated on the outer smoothed surface, and their corresponding circular areas were estimated on the pial surface.

Measurements. Local gyrification was computed for each vertex on the smooth outer surface and averaged within ROIs. For each ROI on the outer surface, the ratio of its area to the corresponding pial surface patch was calculated to derive its lGI. These lGI values were mapped back onto the pial surface, providing a detailed representation of cortical folding.

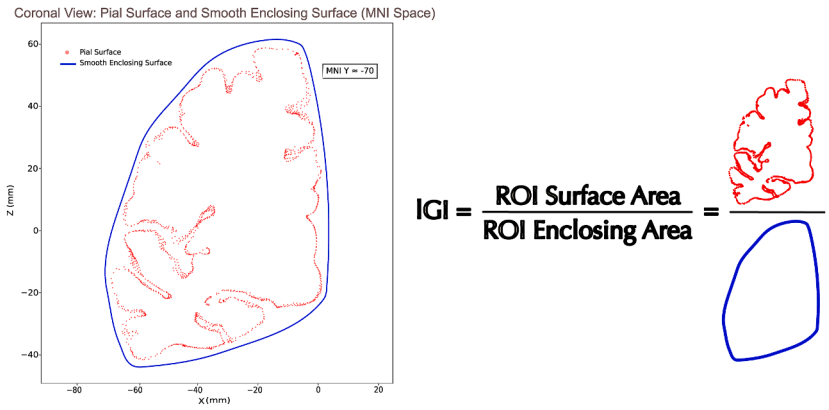

Figure 1. Illustration of local gyrification calculation. In the example illustration, the local gyrification index (lGI) is calculated by taking the ratio of the pial surface area (red) to the smoothed enclosing area (blue). MNI, Montreal Neurological Institute; ROI, region of interest.

Quality Control. Quality control was performed using FreeSurfer's QATools (47). We quantitatively inspected the gray matter signal-to-noise ratio and excluded statistical outliers falling outside ±2.698 SDs (48). This procedure resulted in the exclusion of 20 participants (1.05% of the initial sample), yielding a final sample size of 1876.

Statistical Analyses

A linear mixed-effects model was used to determine whether PTSD diagnosis was associated with lGI. The model included fixed effects of age, sex, and total cortical surface area and a random effect of site (to mitigate the possible influence of unobserved heterogeneity across sites/scanners). Analyses were performed using the lme4 package (49) in R version 4.3.2. The analyses were then repeated using PTSD severity as a continuous variable in place of a categorical variable for PTSD diagnosis. Both analyses included data from trauma-naïve, trauma-exposed, and PTSD groups with normalized mean symptom severities of 0.02, 0.1, and 0.45, respectively. Trauma-naïve participants may report mild symptoms consistent with posttraumatic psychopathology even though they have not been exposed to a traumatic event. To account for the false discovery rate (FDR) from testing of multiple ROIs ($p_{FDR} < .05$; 68 tests), the Benjamini-Hochberg procedure (50) was applied to correct the significance values. PTSD diagnosis (model 1) and PTSD severity (model 2) are the effects of interest for the primary analysis. *Y* represents the ROI.

$$Y \sim \text{PTSD Diagnosis} + \text{Age} + \text{Sex} + \text{Total Surface Area} + (1|\text{Site}) \quad \text{(Model 1)}$$

$$Y \sim \text{PTSD Severity} + \text{Age} + \text{Sex} + \text{Total Surface Area} + (1|\text{Site}) \quad \text{(Model 2)} \tag{2}$$

Exploratory analyses included additional variables for childhood trauma severity (51) and depression (52,53). These variables were integrated into the linear mixed-effects model to assess their potential moderating effects on the association between PTSD and lGI. The moderating effects of PTSD severity on the relationship between aging and lGI was also examined. See Figure 2 for a diagram of the exploratory

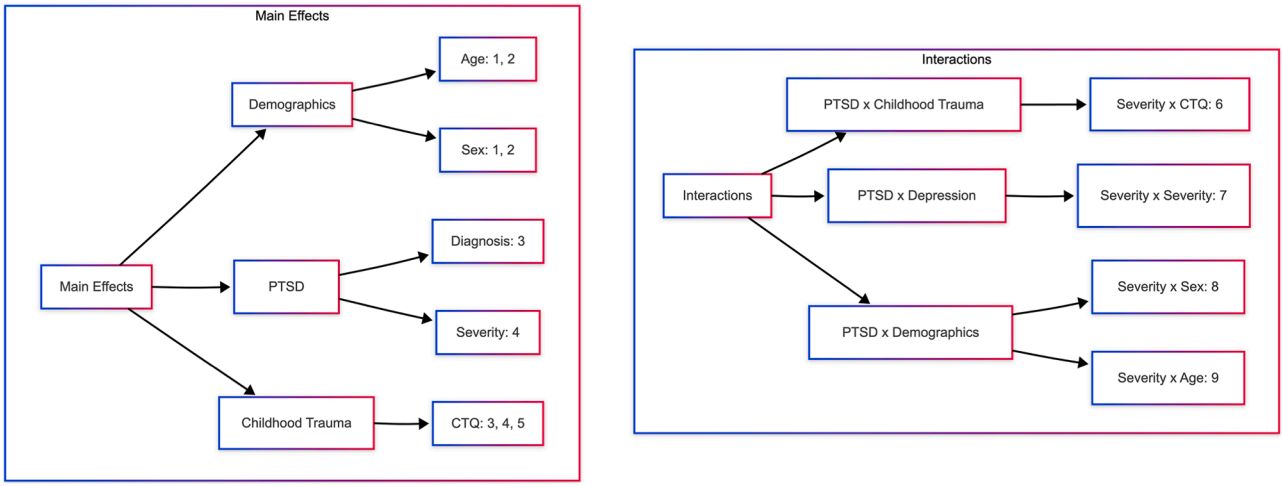

Figure 2. Diagram of exploratory analyses. A diagram of the effects of interest for exploratory analysis. The values represent the model number. Each mixed-effects model includes the main effects of age, sex, total cortical surface area, and the random effects of site. PTSD, posttraumatic stress disorder.

analyses and Figure S3 for the correlation between predictors. Descriptive statistics for the effects of interest by PTSD diagnosis can be found in Table 2. We used the Johnson-Neyman technique (54) from the interactions (55) package in R to assist with interpreting significant interaction results.

Sensitivity Analyses

Finally, post hoc sensitivity analyses were conducted to assess the robustness of primary findings against potential confounds, including alcohol use, scanner field strength (1.5T), and diagnostic instrument (Clinician-Administered PTSD Scale [CAPS]) (see Table S15). Detailed inclusion criteria for these restricted subsets, including specific cutoffs for the Alcohol Use Disorders Identification Test (AUDIT)/AUDIT-Consumption (56) and exclusion definitions, are provided in Table S14. These analyses were restricted specifically to the ROIs identified as significant in the primary analysis (see Results).

RESULTS

PTSD Diagnosis and Severity

Applying model 1, PTSD diagnosis was associated with lower lGI of the right medial OFC (mOFC) ($t_{1850} = -3.77$, $p_{FDR} = .012$) and the right rostral anterior cingulate ($t_{1850} = -3.34$, $p_{FDR} = .029$). There was also a trend-level association between PTSD diagnosis and lower lGI of the right lateral OFC ($t_{8184} = -2.96$, $p_{FDR} = .053$, $p_{unc} = .0031$), left pars orbitalis ($t_{1824} = -3.03$, $p_{FDR} = .053$, $p_{unc} = .0025$), and right frontal pole ($t_{1849} = -2.78$, $p_{FDR} = 0.075$, $p_{unc} = .0055$) (see Table S8).

Consistent with the PTSD diagnosis analysis, PTSD severity (model 2) was associated with lower lGI of the right mOFC ($t_{1722} = -4.12$, $p_{FDR} = .0027$) and right rostral ACC ($t_{1721} = -3.52$, $p_{FDR} = .015$) (see Figures 3 and 4). There was a trend-level association between PTSD severity and lower lGI of the right frontal pole cortex ($t_{1723} = -2.99$, $p_{FDR} = .065$, $p_{unc} = .0029$) (see Table S9).

The effect sizes measured by Cohen's *d* for the right mOFC were $d_{PTSD\ Diagnosis} = -0.18$ and $d_{PTSD\ Severity} = -0.2$ and for the right rostral ACC were $d_{Diagnosis} = -0.16$ and $d_{Severity} = -0.17$. We note that the Cohen's *d* estimates are approximations because a mixed-effects model has different variance for each site.

When adjusting for CTQ scores, PTSD diagnosis (model 3) and severity (model 4) were both still associated with lower lGI of the right mOFC (diagnosis: $t_{655} = -3.30$, $p_{FDR} = .035$; severity: $t_{636} = -3.58$, $p_{FDR} = .017$) and the right rostral ACC (diagnosis: $t_{655} = -3.35$, $p_{FDR} = .035$; severity: $t_{635} = -3.51$, $p_{FDR} = .017$).

Exploratory Analyses and Confounding Factors

We found no significant main effects of childhood trauma (CTQ) on lGI in models 3, 4, and 5 ($p_{FDR} > .25$). Similarly, no significant interactions were observed between PTSD severity and CTQ scores (model 6; $p_{FDR} > .56$) or depression severity (model 7; $p_{FDR} > .35$) for any region.

Comorbid PTSD and Major Depressive Disorder

To investigate the effects of PTSD and major depressive disorder (MDD) comorbidity, participants were organized into 4 groups: 1) a comorbid group of patients with both PTSD and MDD diagnosis, 2) a group of patients with only a PTSD diagnosis, 3) a group of patients with only an MDD diagnosis, 4) and a control group who had neither. Following an analysis of covariance, we conducted a post hoc pairwise test and corrected for multiple comparisons using Tukey's method. There was a significant difference when we contrasted the comorbid group and the PTSD-only group, with the comorbid group being associated with lower lGI for the left inferior temporal cortex ($t_{1868} = 3.04$, $p = .013$) and the left middle temporal cortex ($t_{1867} = 3.79$, $p < .001$). When we contrasted participants with PTSD and control participants, the PTSD group was associated with increased left middle temporal lGI ($t_{1865} = -2.69$, $p = .036$).

Sex

Applying model 1, female participants had significantly greater lGI for most regions (see Table S10) including the left mOFC ($\beta = 0.05$, $t_{1727} = 9.37$, $p_{FDR} < .001$) and the left supramarginal cortex ($\beta = 0.083$, $t_{1658} = 8.57$, $p_{FDR} < .001$). Applying model 2,

Table 2. Descriptive Statistics of Cohort by Diagnosis

Variable	Trauma-Exposed and Trauma-Naïve Group	PTSD Group	Statistics
Age, Years, *N* = 1876	37.59 ± 16.72	38.77 ± 14.52	$t_{1874} = -1.62$, $p = .105$
Sex, Female/Male, *N* = 1876	505/582	462/327	$\chi^2 = 26.30$, $p < .001$
PTSD Severity, *n* = 1741	0.08 ± 0.10	0.45 ± 0.16	$t_{1739} = -55.63$, $p < .001$
Available/missing	976 (89.8%)/111 (10.2%)	765 (97.0%)/24 (3.0%)	
MDD Diagnosis, No MDD/MDD, *N* = 1876	895/192	331/458	$t_{1874} = 19.19$, $p < 0.001$
Depression Severity, *n* = 1469	0.16 ± 0.18	0.40 ± 0.19	$t_{1467} = -24.01$, $p < .001$
Available/missing	838 (77.1%)/249 (22.9%)	631 (80.0%)/158 (20.0%)	
CTQ, *n* = 665	35.75 ± 13.25	61.90 ± 24.24	$t_{663} = 17.15$, $p < .001$
Available/missing	340 (31.3%)/747 (68.7%)	325 (41.2%)/464 (58.8%)	

Continuous variables are presented as mean ± SD, while categorical variables are presented as *n* or *n* (%). Descriptive statistics for age, sex, PTSD severity, MDD diagnosis, depression severity, and CTQ scores by PTSD diagnosis. The statistics reported in the final column represent unadjusted group differences (*t* tests for continuous variables, χ^2 tests for categorical variables) and do not account for the covariates (age, sex, total surface area) or random effects of site included in the primary linear mixed-effects models.

CTQ, Childhood Trauma Questionnaire; MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

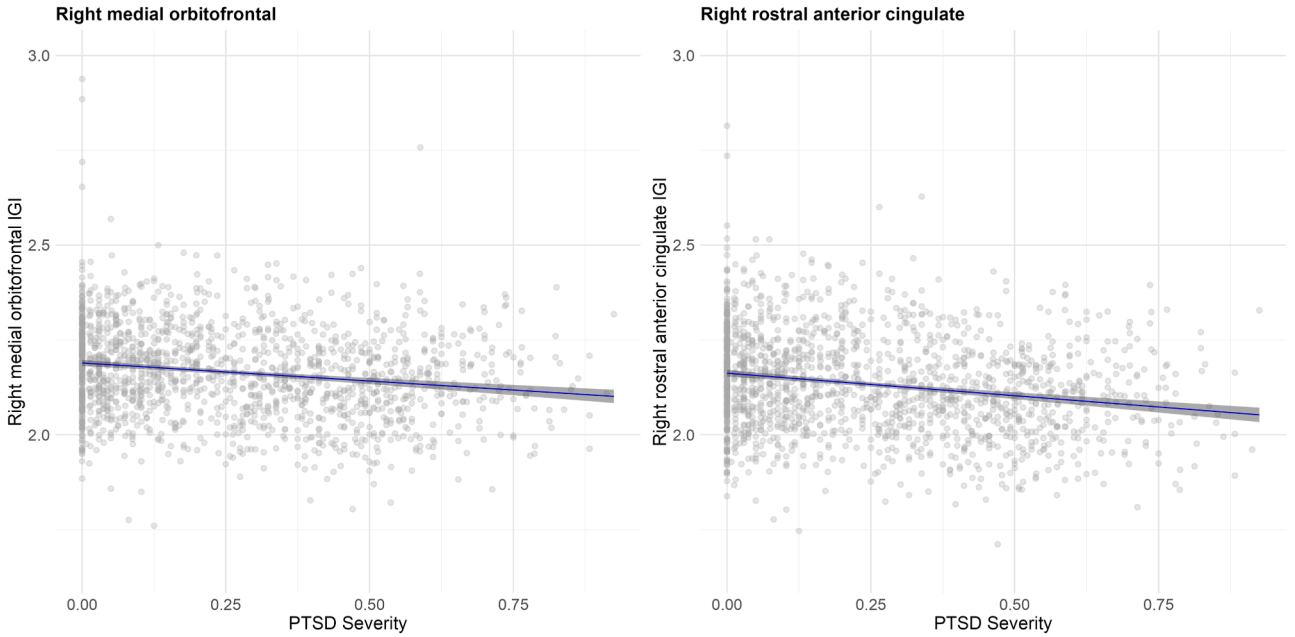

Figure 3. Posttraumatic stress disorder (PTSD) severity by local gyrification index (lGI) for significant regions. PTSD severity by right medial orbitofrontal gyrus (left) lGI and right rostral anterior cingulate gyrus (right) lGI. The fitted line is in blue with gray 95% confidence bands, and the data points are plotted in the background.

females had greater lGI for most regions (see Table S11) including the left mOFC ($\beta = 0.051$, $t_{1633} = 9.24$, $p_{FDR} < .001$) and the left supramarginal cortex ($\beta = 0.087$, $t_{1555} = 8.78$, $p_{FDR} < .001$).

Sex × PTSD Severity

The interaction between PTSD severity and sex (model 8) had a trend-level association with greater lGI of the right caudal middle frontal cortex ($\beta = 0.123$, $t_{1719} = 3.37$, $p_{FDR} = .053$, $p_{unc} < .001$). Simple slopes analysis revealed that the association between PTSD severity and right caudal middle frontal lGI was negative for males ($\beta = -0.08$, $p \leq .001$) but trended positive for females ($\beta = 0.05$, $p \leq .08$). As PTSD severity increased, right caudal middle frontal lGI increased for females but decreased for males.

Age

While controlling for PTSD diagnosis, age (model 1) was associated with lower lGI for most regions including the right precentral cortex ($t_{1776} = -15.91$, $p_{FDR} < .001$) and right caudal middle frontal cortex ($t_{1733} = -15.64$, $p_{FDR} < .001$) but greater lGI of the right parahippocampal cortex ($t_{1516} = 2.97$, $p_{FDR} = .0038$) (see Table S12). While controlling for PTSD severity, age (model 2) was associated with lower lGI for most

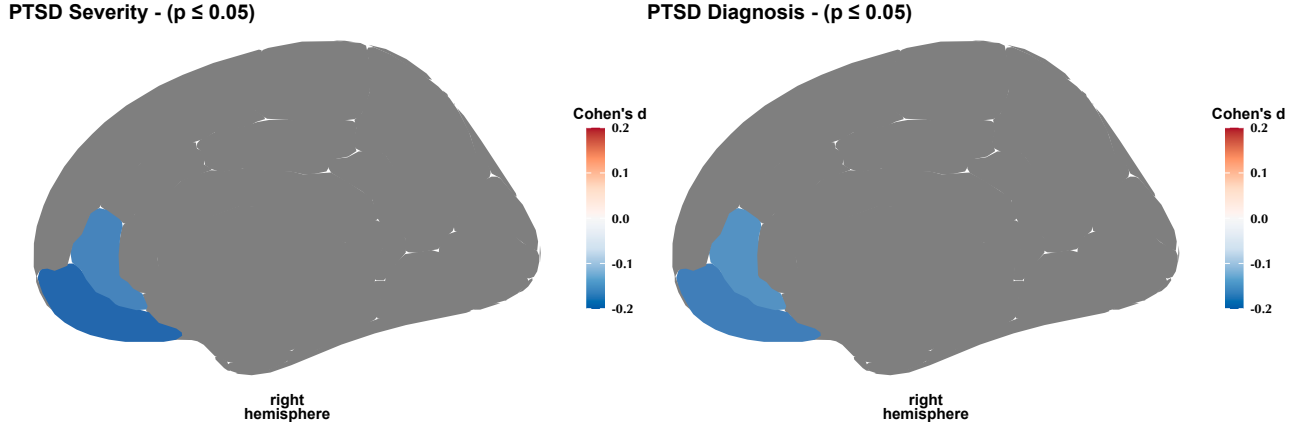

Figure 4. Effect size plotted for posttraumatic stress disorder (PTSD) diagnosis and severity. Right medial view of false discovery rate–corrected $p < .05$ thresholded Cohen's *d* plot for PTSD severity (left) and PTSD diagnosis (right).

regions including the right precentral cortex ($t_{1650} = -15.54$, $p_{FDR} < .001$) and right caudal middle frontal cortex ($t_{1616} = -15.23$, $p_{FDR} < .001$) but greater lGI of the right parahippocampal cortex ($t_{1448} = 2.66$, $p_{FDR} = .0074$) (see Table S13).

Age × PTSD Interactions

The PTSD severity × age interaction (model 9) was associated with lower lGI of the left rostral middle frontal cortex ($t_{1733} = -3.57$, $p_{FDR} = .015$) and the right rostral middle frontal cortex ($t_{1721} = -3.51$, $p_{FDR} = .015$). Using the Johnson-Neyman technique, PTSD severity significantly predicted left rostral middle frontal cortex lGI when age was outside the interval of 23.6 to 43.3 years, and PTSD severity significantly predicted right rostral middle frontal cortex lGI when age was outside the interval of 14.4 to 38.0 years. Gyrification was reduced with advancing age, and this association was stronger with greater PTSD severity (see Figure S4). The range of observed values of age was 8 to 95 years.

Sensitivity Analyses

Sensitivity analyses confirmed that the associations between PTSD (diagnosis and severity) and lower lGI in the right mOFC were robust to alcohol exclusion, scanner field strength, and diagnostic instrument ($p < .05$) (see Tables S14 and S15). Associations in the right rostral ACC remained significant for PTSD severity across all subsets, although the association with diagnosis was statistically attenuated in alcohol-restricted samples.

DISCUSSION

Leveraging data from the ENIGMA-PGC PTSD consortium, we tested the relationship between PTSD and the degree of cortical folding. PTSD diagnosis and severity were associated with hypogyrification of regions within the right ventromedial prefrontal cortex (vmPFC), the right rostral ACC, and the right mOFC (see Figure 4). Having comorbid MDD and PTSD was associated with lower lGI in the left inferior and middle temporal cortices compared with having a PTSD diagnosis alone. We also observed an interaction between PTSD severity and age, where gyrification reduction with advancing age was more pronounced in individuals with higher PTSD severity. Lastly, female participants exhibited significantly greater lGI across most brain regions examined. These findings provide novel evidence that the morphology of the cortex, beyond its overall size, is associated with PTSD diagnosis and symptom severity.

The vmPFC is a hub for mentalizing (57), self-referential thought (58), decision making (59,60), and interoception (61), connecting episodic memory with affective processes (61). In PTSD, intrusive memories (62) are often triggered by heightened arousal to trauma-resembling contexts (63), highlighting the importance of contextual control in conditioned fear responses (64,65). In rodent models, vmPFC-amygdala interconnectivity modulates fear extinction (66). In humans, lower vmPFC activation is associated with higher PTSD severity (67), decreased amygdala connectivity (68), and hypoactivation during extinction recall. Considered together, individuals with PTSD exhibit altered processing of contextual information distinguishing danger from safety (65,69). Thus, reduced vmPFC gyrification is consistent with diminished inhibitory control over the amygdala and impaired contextual processing.

Gray matter reduction of the ACC (70) and vmPFC (70,71) has been found in patients with PTSD compared with trauma-exposed control participants. Cortical thickness of the vmPFC has been associated with extinction retention (72), and larger cortical thickness of the right subgenual ACC subregion has been directly correlated with an improvement in PTSD symptoms after a 6- to 9-month follow-up (73). In North Korean refugees, greater mPFC thickness was observed only in trauma-exposed control participants and was associated with lower anxiety and depression, suggesting a link between mPFC morphology and resilience (74). Cortical gyrification is strongly associated with volume and surface area (38,75). Frontal gyrification is linked to working memory, mental flexibility (31), and fluid intelligence (76), whereas the vmPFC is implicated in impulsivity and self-control (77–79). Thus, lower right vmPFC gyrification in PTSD supports published findings and may explain the reduced capacity to regulate intrusive thoughts and negative mood.

Two previous studies examined gyrification in PTSD. Chu *et al.* (43) reported decreased left lateral OFC lGI, while Gharehgazlou *et al.* (44) found altered lGI in parietal and occipital lobes, with positive severity associations in the dorsolateral PFC and lateral OFC. While our study found nonsignificant results for those regions, it had a much larger sample size ($N = 1876$), a sociodemographically more diverse sample, and an inclusive sample (i.e., female participants, many trauma types, and trauma-exposed control participants), resulting in greater statistical power and more robust findings. The Cohen's d effect sizes that we calculated for the right mOFC were $d_{PTSD\ Diagnosis} = -0.18$ and $d_{PTSD\ Severity} = -0.2$ and for the right rostral ACC were $d_{Diagnosis} = -0.16$ and $d_{Severity} = -0.17$. While these associations are statistically robust, the small effect sizes indicate that they are unlikely to be sufficient for individual-level clinical diagnosis. Rather, these findings contribute to understanding group-level neurobiological correlates of PTSD. Future studies integrating gyrification measures with other neuroimaging modalities and clinical measures may help determine whether cortical folding patterns can contribute to clinically useful multivariate predictive models.

Notably, the effects of PTSD on gyrification appeared to be specific to the disorder. We found no significant effects of CTQ scores, but PTSD remained significantly associated with lower lGI of the right mOFC and right rostral ACC. This dissociation suggests that the observed hypogyrification is linked to the pathophysiology of PTSD rather than being a general neurodevelopmental consequence of childhood trauma. However, given the cross-sectional design, we cannot definitively determine causality. While these alterations may be a consequence of the disorder, it is possible that lower lGI represents a preexisting vulnerability that predates trauma exposure and impairs resilience, thereby increasing the risk of developing PTSD.

MDD, which is highly comorbid with PTSD (52,80–82), is associated with lower cortical gyrification of the bilateral OFC (83,84), left ACC (83), and insula (83,84), while hypergyrification is observed in the right precentral and supramarginal regions (85). In our analysis, the comorbid PTSD-MDD group showed

significantly lower lGI in the left inferior and medial temporal cortices compared with the PTSD-only group ($p < .001$). Notably, when we contrasted the PTSD-only group and the control group, PTSD-only was associated with greater left middle temporal lGI ($p = .036$). While this hypergyrification finding was less statistically robust and warrants replication, it suggests that comorbidity is not simply an additive effect. Instead, PTSD may exhibit a distinct morphological profile compared with the combined burden of PTSD and MDD. A morphometry meta-analysis and structural comparison study found no regional volume differences when comparing PTSD and MDD (86,87), highlighting that interactive effects of cortical morphology are complex and necessitate further investigation.

Further analyses showed significant interactions between PTSD and age. Specifically, lGI of the bilateral rostral middle frontal cortex decreased with age, and the rate of decline was steeper as PTSD severity increased. This suggests that PTSD may exacerbate age effects on the rostral middle frontal cortex, a region previously implicated in PTSD via cortical complexity (88) and volume/thickness reductions (89–92). This interpretation is consistent with work linking PTSD to advanced biological aging in DNA methylation (27,28), cardiovascular health (93), and predicted brain age (29,30). These findings support the hypothesis that PTSD accelerates brain aging effects in the rostral middle frontal cortices. However, we must interpret this interaction with caution given the cross-sectional design. While similar associations between trauma and accelerated senescence have been reported in traumatic brain injury (TBI) (94,95), it is possible that this interaction is influenced by unmeasured comorbidities. For example, TBI is highly prevalent in military populations and shares overlapping features with PTSD. Therefore, the interaction could alternatively reflect the cumulative burden of TBI and PTSD in older veterans or a preexisting vulnerability [e.g., reduced cognitive reserve resulting from genetic factors (96)] that becomes more pronounced with age rather than an acceleration of the aging process itself.

Finally, exploratory analyses revealed widespread sexual dimorphism. Females exhibited significantly greater lGI across most cortical regions, including the left medial orbitofrontal and left supramarginal cortices. While previous studies reported mixed findings, such as higher gyrification in males that attenuates after correcting for brain volume (31), our results demonstrate greater female gyrification even after strictly controlling for total cortical surface area. This supports longitudinal work suggesting that males experience steeper age-related prefrontal gyrification declines (97), potentially resulting in higher comparative lGI in females during adulthood. Additionally, recent work in older adults reported higher gyrification in females within frontal regions, although higher gyrification was observed in males in the right supramarginal gyrus (98). This heterogeneity highlights that sex is an important modulator of cortical morphology that likely interacts with age and brain volume. Therefore, biological sex should be treated as a fundamental covariate in future gyrification research.

Limitations and Strengths

Limitations of the current study include the lack of comprehensive data on medication, substance use beyond alcohol, and PTSD chronicity. Furthermore, our pragmatic harmonization of symptom scores enables comparison across cohorts but assumes a linear relationship between raw scores and severity that may vary across instruments. Regarding statistical modeling, while the random intercept approach mitigates baseline site differences, it simplifies factors such as scanner type and population into a single variable. We utilized this structure rather than random slopes to ensure stability, given small sample sizes at specific sites (99). Consequently, the model assumes that the magnitude of the PTSD effect is constant across sites and may not detect nuanced site $\times$ diagnosis interactions. However, sensitivity analyses excluding 1.5T scanner data and restricting the sample to CAPS assessments confirmed that primary findings were robust to these major sources of methodological variance (see Table S15). Finally, regarding the small effect sizes, unmeasured sources of variance in large-scale analyses, such as genetics and environmental exposures, inflate the error term. This suggests that our estimates likely represent a conservative lower bound of the true biological effect. Despite these limitations, this study represents the largest mega-analysis of gyrification in PTSD to date. The clinical demography is highly diverse with respect to age, sex, trauma type, and cultural background. This diversity, combined with the use of data from multiple scanners, significantly enhances the generalizability of these findings compared with previous single-site studies with homogeneous samples.

Conclusions

These findings provide novel evidence that the morphology of the cortex, beyond its overall size, is associated with PTSD diagnosis and symptom severity. Lower lGI, which is associated with impaired signaling efficiency, was observed in the PTSD group compared with the control group for the vmPFC, a region that has been strongly implicated in associative fear learning and extinction. It is possible that PTSD may accelerate the typical age-associated decline in lGI of the rostral middle frontal cortices.

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REFERENCES

1. Burgess AW, Holmstrom LL (1974): Rape trauma syndrome. Am J Psychiatry 131:981–986.
2. Koren D, Norman D, Cohen A, Berman J, Klein EM (2005): Increased PTSD risk with combat-related injury: A matched comparison study of injured and uninjured soldiers experiencing the same combat events. Am J Psychiatry 162:276–282.
3. Madakasira S, O'Brien KF (1987): Acute posttraumatic stress disorder in victims of a natural disaster. J Nerv Ment Dis 175:286–290.
4. American Psychiatric Association (2013): Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC: American Psychiatric Association.
5. Van Wyk M: The relationship between PTSD, hypervigilance and disordered sleep. University of Cape Town, Faculty of Humanities, Department of Psychology. Available at: http://hdl.handle.net/11427/13992. Accessed June 15, 2024.
6. Brewin CR (2015): Re-experiencing traumatic events in PTSD: New avenues in research on intrusive memories and flashbacks. Eur J Psychotraumatol 6:27180.
7. Foa EB, Hearst-Ikeda D (1996): Emotional dissociation in response to trauma. In: Michelson LK, Ray WJ, editors. Handbook of Dissociation. Boston: Springer, 207–224.
8. Kilpatrick DG, Resnick HS, Milanak ME, Miller MW, Keyes KM, Friedman MJ (2013): National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. J Trauma Stress 26:537–547.
9. Shin LM, Rauch SL, Pitman RK (2006): Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci 1071:67–79.
10. Morey RA, Gold AL, LaBar KS, Beall SK, Brown VM, Haswell CC, *et al.* (2012): Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Arch Gen Psychiatry 69:1169–1178.
11. Thomaes K, Dorrepaal E, Draijer N, De Ruiter MB, Van Balkom AJ, Smit JH, Veltman DJ (2010): Reduced anterior cingulate and orbitofrontal volumes in child abuse–related complex PTSD. J Clin Psychiatry 71:1636–1644.
12. Cisler JM, Steele JS, Lenow JK, Smitherman S, Everett B, Messias E, Kilts CD (2014): Functional reorganization of neural networks during repeated exposure to the traumatic memory in posttraumatic stress disorder: An exploratory fMRI study. J Psychiatr Res 48:47–55.
13. Hu H, Sun Y, Su S, Wang Y, Qiu Y, Yang X, *et al.* (2018): Cortical surface area reduction in identification of subjects at high risk for post-traumatic stress disorder: A pilot study. Aust N Z J Psychiatry 52:1084–1091.
14. Santhanam P, Wilson SH, Mulatya C, Oakes TR, Weaver LK (2019): Age-accelerated reduction in cortical surface area in United States service members and veterans with mild traumatic brain injury and post-traumatic stress disorder. J Neurotrauma 36:2922–2929.
15. Wrocklage KM, Averill LA, Cobb Scott J, Averill CL, Schweinsburg B, Trejo M, *et al.* (2017): Cortical thickness reduction in combat exposed U.S. veterans with and without PTSD. Eur Neuropsychopharmacol 27:515–525.
16. Yang J, Huggins AA, Sun D, Baird CL, Haswell CC, Frijling JL, *et al.* (2024): Examining the association between posttraumatic stress disorder and disruptions in cortical networks identified using data-driven methods. Neuropsychopharmacology 49:609–619.
17. Logue MW, Van Rooij SJH, Dennis EL, Davis SL, Hayes JP, Stevens JS, *et al.* (2018): Smaller hippocampal volume in posttraumatic stress disorder: A multisite ENIGMA-PGC study: Subcortical volumetry results from posttraumatic stress disorder consortia. Biol Psychiatry 83:244–253.
18. Wang X, Xie H, Chen T, Cotton AS, Salminen LE, Logue MW, *et al.* (2021): Cortical volume abnormalities in posttraumatic stress disorder: An ENIGMA-Psychiatric Genomics Consortium PTSD workgroup mega-analysis. Mol Psychiatry 26:4331–4343.
19. Tallinen T, Chung JY, Biggins JS, Mahadevan L (2014): Gyrification from constrained cortical expansion. Proc Natl Acad Sci U S A 111:12667–12672.
20. Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K (1995): The ontogeny of human gyrification. Cereb Cortex 5:56–63.
21. Klein D, Rotarska-Jagiela A, Genc E, Sritharan S, Mohr H, Roux F, *et al.* (2014): Adolescent brain maturation and cortical folding: Evidence for reductions in gyrification. PLoS one 9:e84914.
22. Marzola P, Melzer T, Pavesi E, Gil-Mohapel J, Brocardo PS (2023): Exploring the role of neuroplasticity in development, aging, and neurodegeneration. Brain Sci 13:1610.
23. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW (1999): In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci 2:859–861.
24. Peverill M, Rosen ML, Lurie LA, Sambrook KA, Sheridan MA, McLaughlin KA (2023): Childhood trauma and brain structure in children and adolescents. Dev Cogn Neurosci 59:101180.
25. Gold AL, Sheridan MA, Peverill M, Busso DS, Lambert HK, Alves S, *et al.* (2016): Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing. J Child Psychol Psychiatry 57:1154–1164.
26. Madan CR (2021): Age-related decrements in cortical gyrification: Evidence from an accelerated longitudinal dataset. Eur J Neurosci 53:1661–1671.
27. Katrinli S, King AP, Duval ER, Smith AK, Rajaram N, Liberzon I, Rauch SAM (2023): DNA methylation GrimAge acceleration in US military veterans with PTSD. Neuropsychopharmacology 48:773–780.
28. Wolf EJ, Logue MW, Hayes JP, Sadeh N, Schichman SA, Stone A, *et al.* (2016): Accelerated DNA methylation age: Associations with PTSD and neural integrity. Psychoneuroendocrinology 63:155–162.
29. Clausen AN, Fercho KA, Monsour M, Disner S, Salminen L, Haswell CC, *et al.* (2022): Assessment of brain age in posttraumatic stress disorder: Findings from the ENIGMA PTSD and brain age working groups. Brain Behav 12:e2413.
30. Niu X, Liang H, Zhang F (2018): Brain age prediction for post-traumatic stress disorder patients with convolutional neural networks: A multi-modal neuroimaging study. In: 2018 Conference on Cognitive Computational Neuroscience. Brentwood: Cognitive Computational Neuroscience. Available at: https://ccneuro.org/2018/Papers/ViewPapers.asp?PaperNum=1121. Accessed August 16, 2024.
31. Gautam P, Anstey KJ, Wen W, Sachdev PS, Cherbuin N (2015): Cortical gyrification and its relationships with cortical volume, cortical thickness, and cognitive performance in healthy mid-life adults. Behav Brain Res 287:331–339.
32. Toro R, Burnod Y (2005): A morphogenetic model for the development of cortical convolutions. Cereb Cortex 15:1900–1913.
33. Zilles K, Palomero-Gallagher N, Amunts K (2013): Development of cortical folding during evolution and ontogeny. Trends Neurosci 36:275–284.
34. Deng F, Jiang X, Zhu D, Zhang T, Li K, Guo L, Liu T (2014): A functional model of cortical gyri and sulci. Brain Struct Funct 219:1473–1491.
35. Zhang S, Liu H, Huang H, Zhao Y, Jiang X, Bowers B, *et al.* (2019): Deep learning models unveiled functional difference between cortical gyri and sulci. IEEE Trans Biomed Eng 66:1297–1308.
36. Lefèvre J, Mangin JF (2010): A reaction-diffusion model of human brain development. PLoS Comput Biol 6:e1000749.
37. Van Essen DCV (1997): A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 385:313–318.
38. Xu G, Knutsen AK, Dikranian K, Kroenke CD, Bayly PV, Taber LA (2010): Axons pull on the brain, but tension does not drive cortical folding. J Biomech Eng 132:071013.
39. Gregory MD, Kippenhan JS, Dickinson D, Carrasco J, Mattay VS, Weinberger DR, Berman KF (2016): Regional variations in brain gyrification are associated with general cognitive ability in humans. Curr Biol 26:1301–1305.
40. Miskovich TA, Pedersen WS, Belleau EL, Shollenbarger S, Lisdahl KM, Larson CL (2016): Cortical gyrification patterns associated with trait anxiety. PLoS one 11:e0149434.
41. Molent C, Maggioni E, Cecchetto F, Garzitto M, Piccin S, Bonivento C, *et al.* (2018): Reduced cortical thickness and increased

gyrification in generalized anxiety disorder: A 3 T MRI study. Psychol Med 48:2001–2010.
42. Wallace GL, Robustelli B, Dankner N, Kenworthy L, Giedd JN, Martin A (2013): Increased gyrification, but comparable surface area in adolescents with autism spectrum disorders. Brain 136:1956–1967.
43. Chu C, Xie B, Qiu M, Liu K, Tan L, Wu Y, *et al.* (2017): Cortical folding in post-traumatic stress disorder after motor vehicle accidents: Regional differences in gyrification. Psychiatry Clin Neurosci 71:247–253.
44. Gharehgazlou A, Richardson JD, Jetly R, Dunkley BT (2021): Cortical gyrification morphology in PTSD: A neurobiological risk factor for severity? Neurobiol Stress 14:100299.
45. Bernstein DP, Fink L, Handelsman L, Foote J (2011): Childhood trauma questionnaire. Available at: https://doi.apa.org/doi/10.1037/t02080-000. Accessed June 16, 2024.
46. Schaer M, Cuadra MB, Tamarit L, Lazeyras F, Eliez S, Thiran JP (2008): A surface-based approach to quantify local cortical gyrification. IEEE Trans Med Imaging 27:161–170.
47. FreeSurfer: FreeSurfer 5.3 QA Tools—Free Surfer Wiki. Available at: https://surfer.nmr.mgh.harvard.edu/fswiki/QATools. Accessed June 16, 2024.
48. Worker A, Berthert P, Lawrence AJ, Kia SM, Arango C, Dinga R, *et al.* (2023): Extreme deviations from the normative model reveal cortical heterogeneity and associations with negative symptom severity in first-episode psychosis from the OPTiMiSE and GAP studies. Transl Psychiatry 13:373.
49. Bates D, Mächler M, Bolker B, Walker S (2015): Fitting linear mixed-effects models using lme4. J Stat Soft 67:1–48.
50. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc B 57:289–300.
51. Powers A, Fani N, Cross D, Ressler KJ, Bradley B (2016): Childhood trauma, PTSD, and psychosis: Findings from a highly traumatized, minority sample. Child Abuse Negl 58:111–118.
52. Spinhoven P, Penninx BW, Van Hemert AM, De Rooij M, Elzinga BM (2014): Comorbidity of PTSD in anxiety and depressive disorders: Prevalence and shared risk factors. Child Abuse Negl 38:1320–1330.
53. Farhood LF, Fares S, Sabbagh R, Hamady C (2016): PTSD and depression construct: Prevalence and predictors of co-occurrence in a South Lebanese civilian sample. Eur J Psychotraumatol 7:31509.
54. Johnson PO, Fay LC (1950): The Johnson-Neyman technique, its theory and application. Psychometrika 15:349–367.
55. Long JA: Interactions: Comprehensive, user-friendly toolkit for probing interactions. Available at: https://cran.r-project.org/package=interactions. Accessed August 15, 2024.
56. Ingesson-Hammarberg S, Molander O, Hammarberg A (2024): Clinical cutoffs of the Alcohol Use Disorder Identification Test for identification of DSM-5 alcohol use disorder: A psychometric evaluation in treatment-seeking patients. Drug Alcohol Depend 256:111115.
57. Denny BT, Kober H, Wager TD, Ochsner KN (2012): A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. J Cogn Neurosci 24:1742–1752.
58. Jenkins AC, Macrae CN, Mitchell JP (2008): Repetition suppression of ventromedial prefrontal activity during judgments of self and others. Proc Natl Acad Sci U S A 105:4507–4512.
59. Clark L, Bechara A, Damasio H, Aitken MRF, Sahakian BJ, Robbins TW (2008): Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. Brain 131:1311–1322.
60. Spaniol J, Di Muro F, Ciaramelli E (2019): Differential impact of ventromedial prefrontal cortex damage on "hot" and "cold" decisions under risk. Cogn Affect Behav Neurosci 19:477–489.
61. Roy M, Shohamy D, Wager TD (2012): Ventromedial prefrontal-subcortical systems and the generation of affective meaning. Trends Cogn Sci 16:147–156.
62. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, *et al.* (2018): The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess 30:383–395.
63. Andrewes DG, Jenkins LM (2019): The role of the amygdala and the ventromedial prefrontal cortex in emotional regulation: Implications for post-traumatic stress disorder. Neuropsychol Rev 29:220–243.
64. Pearson DG, Ross FDC, Webster VL (2012): The importance of context: Evidence that contextual representations increase intrusive memories. J Behav Ther Exp Psychiatry 43:573–580.
65. Maren S, Phan KL, Liberzon I (2013): The contextual brain: Implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci 14:417–428.
66. Quirk GJ, Likhtik E, Pelletier JG, Paré D (2003): Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. J Neurosci 23:8800–8807.
67. Powers A, Hinojosa CA, Stevens JS, Harvey B, Pas P, Rothbaum BO, *et al.* (2022): Right inferior frontal gyrus and ventromedial prefrontal activation during response inhibition is implicated in the development of PTSD symptoms. Eur J Psychotraumatol 13:2059993.
68. Stevens JS, Jovanovic T, Fani N, Ely TD, Glover EM, Bradley B, Ressler KJ (2013): Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. J Psychiatr Res 47:1469–1478.
69. Liberzon I, Abelson JL (2016): Context processing and the neurobiology of post-traumatic stress disorder. Neuron 92:14–30.
70. Kühn S, Gallinat J (2013): Gray matter correlates of posttraumatic stress disorder: A quantitative meta-analysis. Biol Psychiatry 73:70–74.
71. Morey RA, Haswell CC, Hooper SR, De Bellis MD (2016): Amygdala, hippocampus, and ventral medial prefrontal cortex volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. Neuropsychopharmacology 41:791–801.
72. Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL (2005): Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proc Natl Acad Sci U S A 102:10706–10711.
73. Dickie EW, Brunet A, Akerib V, Armony JL (2013): Anterior cingulate cortical thickness is a stable predictor of recovery from post-traumatic stress disorder. Psychol Med 43:645–653.
74. Jeong H, Lee YJ, Kim N, Jeon S, Jun JY, Yoo SY, *et al.* (2021): Increased medial prefrontal cortical thickness and resilience to traumatic experiences in North Korean refugees. Sci Rep 11:14910.
75. Toro R, Perron M, Pike B, Richer L, Veillette S, Pausova Z, Paus T (2008): Brain size and folding of the human cerebral cortex. Cereb Cortex 18:2352–2357.
76. Tadayon E, Pascual-Leone A, Santarnecchi E (2020): Differential contribution of cortical thickness, surface area, and gyrification to fluid and crystallized intelligence. Cereb Cortex 30:215–225.
77. Jimura K, Chushak MS, Braver TS (2013): Impulsivity and self-control during intertemporal decision making linked to the neural dynamics of reward value representation. J Neurosci 33:344–357.
78. Wang M, Chen Z, Zhang S, Xu T, Zhang R, Suo T, Feng T (2019): High self-control reduces risk preference: The role of connectivity between right orbitofrontal cortex and right anterior cingulate cortex. Front Neurosci 13:194.
79. Hare TA, Camerer CF, Rangel A (2009): Self-control in decision-making involves modulation of the vmPFC valuation system. Science 324:646–648.
80. Thabet AAM, Abed Y, Vostanis P (2004): Comorbidity of PTSD and depression among refugee children during war conflict. J Child Psychol Psychiatry 45:533–542.
81. Nickerson A, Schick M, Schnyder U, Bryant RA, Morina N (2017): Comorbidity of posttraumatic stress disorder and depression in tortured, treatment-seeking refugees. J Trauma Stress 30:409–415.
82. Kar N, Bastia BK (2006): Post-traumatic stress disorder, depression and generalised anxiety disorder in adolescents after a natural disaster: A study of comorbidity. Clin Pract Epidemiol Ment Health 2:17.
83. Zhang Y, Yu C, Zhou Y, Li K, Li C, Jiang T (2009): Decreased gyrification in major depressive disorder. NeuroReport 20:378–380.
84. Kang Y, Kang W, Kim A, Tae WS, Ham BJ, Han KM (2023): Decreased cortical gyrification in major depressive disorder. Psychol Med 53:7512–7524.

85. Peng D, Shi F, Li G, Fralick D, Shen T, Qiu M, *et al.* (2015): Surface vulnerability of cerebral cortex to major depressive disorder. PLoS one 10:e0120704.
86. Serra-Blasco M, Radua J, Soriano-Mas C, Gómez-Benlloch A, Porta-Casteràs D, Carulla-Roig M, *et al.* (2021): Structural brain correlates in major depression, anxiety disorders and post-traumatic stress disorder: A voxel-based morphometry meta-analysis. Neurosci Biobehav Rev 129:269–281.
87. Kroes MCW, Rugg MD, Whalley MG, Brewin CR (2011): Structural brain abnormalities common to posttraumatic stress disorder and depression. J Psychiatry Neurosci 36:256–265.
88. Kritikos M, Clouston SAP, Huang C, Pellecchia AC, Mejia-Santiago S, Carr MA, *et al.* (2021): Cortical complexity in world trade center responders with chronic posttraumatic stress disorder. Transl Psychiatry 11:597.
89. Eckart C, Stoppel C, Kaufmann J, Tempelmann C, Hinrichs H, Elbert T, *et al.* (2011): Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. J Psychiatry Neurosci 36:176–186.
90. Roy O, Levasseur-Moreau J, Renauld E, Hébert LJ, Leblond J, Bilodeau M, Fecteau S (2022): Whole-brain morphometry in Canadian soldiers with posttraumatic stress disorder. Ann N Y Acad Sci 1509:37–49.
91. Qi S, Mu YF, Cui LB, Zhang J, Guo F, Tan QR, *et al.* (2018): Anomalous gray matter structural networks in recent onset posttraumatic stress disorder. Brain Imaging Behav 12:390–401.
92. Clausen AN, Clarke E, Phillips RD, Haswell C, Morey RA (2020): Combat exposure, posttraumatic stress disorder, and head injuries differentially relate to alterations in cortical thickness in military Veterans. Neuropsychopharmacology 45:491–498.
93. Wolf EJ, Schnurr PP (2016): Posttraumatic stress disorder-related cardiovascular disease and accelerated cellular aging. Psychiatr Ann 46:527–532.
94. Amgalan A, Maher AS, Ghosh S, Chui HC, Bogdan P, Irimia A (2022): Brain age estimation reveals older adults' accelerated senescence after traumatic brain injury. GeroScience 44:2509–2525.
95. Dennis EL, Vervoordt S, Adamson MM, Houshang A, Bigler ED, Caeyenberghs K, *et al.* (2024): Accelerated aging after traumatic brain injury: An ENIGMA multi-cohort mega-analysis. Ann Neurol 96:365–377.
96. Pietzuch M, King AE, Ward DD, Vickers JC (2019): The influence of genetic factors and cognitive reserve on structural and functional resting-state brain networks in aging and Alzheimer's disease. Front Aging Neurosci 11:30.
97. Mutlu AK, Schneider M, Debbané M, Badoud D, Eliez S, Schaer M (2013): Sex differences in thickness, and folding developments throughout the cortex. NeuroImage 82:200–207.
98. Cui D, Wang D, Jin J, Liu X, Wang Y, Cao W, *et al.* (2023): Age- and sex-related differences in cortical morphology and their relationships with cognitive performance in healthy middle-aged and older adults. Quant Imaging Med Surg 13:1083–1099.
99. Sun D, Rakesh G, Haswell CC, Logue M, Baird CL, O'Leary EN, *et al.* (2022): A comparison of methods to harmonize cortical thickness measurements across scanners and sites. Neuroimage 261:119509.
100. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM (1995): The development of a Clinician-Administered PTSD Scale. J Trauma Stress 8:75–90.
101. Davidson JRT, Book SW, Colket JT, Tupler LA, Roth S, David D, *et al.* (1997): Assessment of a new self-rating scale for post-traumatic stress disorder. Psychol Med 27:153–160.
102. Falsetti SA, Resnick HS, Resick PA, Kilpatrick DG (1993): The Modified PTSD Symptom Scale: A brief self-report measure of posttraumatic stress disorder. Behav Ther 16:161–162.
103. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP: PTSD Checklist for DSM-5 (PCL-5). Available at: https://www.ptsd.va.gov/. Accessed June 15, 2024.
104. Weathers FW, Reyes G, Elhai JD, Ford D (2008): Posttraumatic stress disorder checklist. In: Encyclopedia of Psychological Trauma. Hoboken, NJ: John Wiley & Sons, 491–494.
105. Briere J (1996): Trauma symptom checklist for children. Psychological Assessment Resources. Available at: https://www.researchgate.net/publication/267726306_Trauma_Symptom_Checklist_for_Children_TSCC. Accessed July 3, 2024.
106. First MB, Gibbon M (2004): The Clinical Interview for DSM-IV Axis I disorders (SCID-I) and the Clinical Interview for DSM-IV Axis II disorders (SCID-II). In: Comprehensive Handbook of Psychological Assessment. Chichester, UK: John Wiley & Sons, Inc., 134–143
107. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al.* (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59(suppl 20):22–33; quiz 34–57.
108. Silverman WK, Saavedra LM, Pina AA (2001): Test-retest reliability of anxiety symptoms and diagnoses with the Anxiety Disorders Interview Schedule for DSM-IV: Child and Parent versions. J Am Acad Child Adolesc Psychiatry 40:937–944.