1 **Altered cortical development and psychiatric symptom risk in adolescents exposed to**
2 **maternal stress *in utero***
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4
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7
8 **ABSTRACT**
9
10 **Objective:** Maternal exposure to stress during pregnancy is associated with increased risk for
11 cognitive and behavioral sequelae in offspring. Animal research demonstrates exposure to stress
12 during gestation has effects on brain structure. In humans, however, little is known about the
13 enduring effects of *in utero* exposure to maternal stress on brain morphology. We examine whether
14 maternal report of stressful events during pregnancy is associated with brain structure and behavior
15 in adolescents.
16
17 **Method:** We compare gray matter morphometry of typically-developing early adolescents (11-14
18 years of age, mean 12.7) based on presence/absence of maternal report of stressful event(s) during
19 pregnancy: prenatal stress (PS; n=28), no prenatal stress (NS; n=55). The Drug Use Survey Index
20 Revised (DUSI-R) assessed adolescent risk for problematic behaviors. Exclusionary criteria
21 included pre-term birth, low birth weight, and maternal substance use during pregnancy. Groups
22 were equivalent for demographic (age, sex, IQ, SES, race/ethnicity), and birth measures (weight,
23 length).
24
25 **Results:** Compared to NS peers, adolescents in the PS group exhibited increased gray matter
26 volume in bilateral posterior parietal cortex (PPC): bilateral intraparietal sulcus, left superior
27 parietal lobule and inferior parietal lobule. Additionally, the PS group displayed greater risk for
28 psychiatric symptoms and family system dysfunction, as assessed via DUSI-R subscales.
29
30 **Conclusion:** This study provides evidence for the enduring neurodevelopmental effects of
31 exposure to maternal stress while *in utero*, suggesting the dynamic alterations in brain structure
32 that occur during the adolescent critical period may unmask the latent effects of gestational stress
33 on brain morphology and increase subsequent risk for psychiatric symptomatology.
34
35 **INTRODUCTION**
36
37 A large body of animal research has demonstrated negative effects of prenatal stress on the
38 structure of the developing brain in offspring, including preclinical[1–3] and non-human primate
39 studies[4,5]. *In utero* stress exposure has adverse effects on neurodevelopment of the corpus
40 callosum[4], hippocampus[5–7], amygdala[8], rostral anterior cingulate cortex[9], and frontal cortex[10].
41 Corresponding closely with the functional neuroanatomy of these regions, offspring of animals
42 stressed during gestation exhibit deficits in attention[11], as well as an increase in behaviors
43 associated with anxiety[12,13] and depression (e.g., altered circadian rhythms[14] and learned
44 helplessness[15]). Critically, the negative effects of prenatal stress endure throughout the lifespan of
45 the animal[16].
46

47   As in animals, research in humans has demonstrated that maternal exposure to stress during
48   pregnancy is associated with adverse cognitive and behavioral outcomes in childhood,
49   adolescence, and adulthood. These studies operationalize stress in various ways, including major
50   life events[17], natural disasters[18,19], military invasion[20], and maternal psychiatric symptoms, such as
51   depression[21] and anxiety[22,23]. Despite differences in methodologies and specific findings, research
52   reveals a largely consistent picture showing maternal stress experienced during pregnancy is
53   related to aberrant cognitive, behavioral and emotional development in offspring, and is associated
54   with heightened risk for development of psychiatric symptoms and illnesses, including
55   impulsivity[22], attention deficit hyperactivity disorder [24,25], anxiety [21], depression[23], autism
56   spectrum disorder[17,26], and schizophrenia[20,27,28].

58   While effects of maternal stress on cognition and behavior are thoroughly documented, studies
59   have only recently examined impacts on child neurodevelopment. These nascent studies have
60   demonstrated effects of *in utero* stress on white matter organization[29,30], and on gray matter in
61   cortical[31–33] and subcortical[34] structures. For instance, in neonates, prenatal maternal anxiety is
62   associated with reduced cortical thickness in frontal and parietal cortices, an effect modulated by
63   genetic variants implicated in increased vulnerability to psychiatric disorders[35]. Effects of maternal
64   stress during gestation have been observed in older offspring as well. Maternal reports of stress
65   during pregnancy are associated with differences in white matter microstructural organization of
66   the uncinate fasciculus in offspring aged 6-9 years[29]. Further, studies of 6-9 year-olds have shown
67   that greater maternal pregnancy-specific anxiety at 19-weeks gestation is linked to reduced gray
68   matter volume in bilateral prefrontal cortex, temporal and parietal cortices, and cerebellum[31], and
69   greater maternal depressive symptoms are associated with thinner cortices across the brain[32].
70   Finally, maternal first-trimester cortisol (a biological marker of stress) is positively correlated with
71   right amygdalar volume in 7-year old female offspring; further amygdalar volume mediates the
72   relationship between higher maternal cortisol and increased affective symptoms in female
73   offspring[34].

75   The trajectory of cortical maturation from childhood through adulthood identifies adolescence as
76   a critical period in the non-linear development of frontal and parietal cortical gray matter[36–38]. It is
77   important to note that during adolescence gray matter volume is expected to decrease as a result
78   of cortical pruning. Cortical gray matter volume during this developmental period may be a
79   relatively sensitive indicator of earlier neurodevelopmental influences, and previously masked
80   deficits may be revealed by the maturational processes occurring during this time[39]. Understanding
81   how prenatal stress exposure impacts the developmental trajectory of cortical development during
82   the adolescent period may be particularly revealing, as many types of mental health problems
83   emerge in adolescence[40]. Adversity early in life has been shown to set forth a "cascade" of effects
84   in the developing brain[41–43], including those at the molecular, cellular and network levels, which
85   may only manifest during a later developmental period[44–46], such as adolescence.

87   Although the mechanisms by which gestational stress impacts offspring human neurodevelopment
88   and increases risk for psychiatric symptoms have yet to be fully elucidated[47–49], both the animal
89   and human literature demonstrate that prenatal stress affects brain development and can play a
90   contributory etiological role in cognitive and behavioral sequelae. Identifying offspring brain
91   structures affected by prenatal stress exposure and understanding how these structures are altered,

92 as well as the behavioral and psychiatric outcomes of these structural alterations, may allow for
93 identification of youth at elevated risk for poor outcomes.
94
95 The current study examined cortical gray matter volume in two groups of typically developing,
96 early adolescents who differed with regards to whether mothers experienced at least one major
97 stressful life event during their pregnancy. While we did not predict specific neuroanatomical
98 regions to differ *a priori,* we hypothesized that adolescents whose mothers experienced significant
99 stress during their pregnancy would have a neuroanatomical profile suggestive of delayed gray
100 matter development compared to their non-prenatally stressed peers.
101
102 **METHODS**
103
104 Participants were recruited as part of the Adolescent Development Study, a prospective
105 longitudinal investigation of the neural, cognitive and behavioral precursors and consequences of
106 substance use initiation and escalation. Demographic, cognitive, behavioral, and imaging
107 assessments were conducted at baseline and were repeated during two follow-up visits,
108 approximately 18- and 36-months later. The data reported here were collected during the baseline
109 visit. Complete information on the methods of this study are described in detail elsewhere[50].
110 Briefly, 135 substance-naïve 11-13-year-olds and their caregivers were recruited from the
111 Washington D.C. metropolitan region. Primary exclusionary criteria were prior substance use by
112 the adolescent, neurodevelopmental disorder (e.g., autism spectrum disorder, active tic disorder
113 that would interfere with imaging), prior head trauma, left-handedness, and conditions
114 contraindicated in MRI. The Georgetown University Institutional Review Board approved the
115 study, and caregivers and adolescents provided consent and assent prior to all data collection.
116
117 Family/caregiver measures:
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119 ***Pre-/Perinatal questionnaire***. Biological mothers were invited to complete a pre-/perinatal
120 questionnaire collecting information about the pregnancy with, and delivery of, their enrolled
121 adolescent. Mothers were asked to indicate whether any stressful events occurred during their
122 pregnancy with the adolescent participant. Questions concerning stressors were adapted from the
123 second item of a short screening scale for posttraumatic stress disorder (PTSD)[51]. Items from the
124 scale probing PTSD symptom domains (e.g., re-experiencing of traumatic event(s), exaggerated
125 startle response, etc.) were omitted. The following stressful events were queried: relationship
126 conflict (e.g., divorce, break up, infidelity), death of someone close (e.g., partner, parent, another
127 child), severe illness/harm of someone close (e.g., cancer, heart attack, severe car accident), severe
128 financial issues (e.g., major property damage, foreclosure, sudden unemployment), involvement
129 in an accident (e.g., car, fire, other disaster), being physically or emotionally attacked (e.g.,
130 threatened with a weapon, rape), or another terrible event that most people do not experience (with
131 space provided for elaboration). Mothers could indicate that they had experienced no stressful
132 event during pregnancy by selecting the option "nothing like this happened to me while I was
133 pregnant with this child."
134
135 Mothers also indicated their age at time of delivery, incidence of any obstetric complications, and
136 extent of any tobacco, alcohol, or prescription or illicit drug use during the pregnancy. Finally,

137 outcomes after pregnancy were reported for both the mother (post-partum depression(PPD)) and
138 child (birth weight and length).
139
140 ***Family socioeconomic status index (SES).*** An SES Index was calculated by averaging the mean
141 of two standard scores (mean household income bracket before taxes and mean cumulative
142 parental education), and re-standardizing these to obtain a z-score distribution with a 0-centered
143 mean and a standard deviation of 1 for the sample analyzed (n=83) (method adapted from[52]).
144
145 <u>Adolescent measures:</u>
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147 ***Risk measure.*** Adolescents completed the Drug Use Survey Index Revised (DUSI-R), a 159-item
148 survey that measures current use of drugs and alcohol, risk for future problematic use, as well as
149 experiences and behaviors known to precede and co-occur with substance use[53,54]. Although non-
150 diagnostic in nature, previous research has shown the DUSI-R to be psychometrically valid for
151 identifying adolescents at risk for adverse outcomes, including disrupted psychosocial
152 development, psychiatric symptomatology, and antisocial behavior[55–60]. Survey questions are *yes-*
153 *no* items categorized into ten domains: psychiatric symptoms, family system, behavior patterns,
154 health status, leisure and recreation, social competence, school performance, peer relationships,
155 substance use, and work performance. For each domain a problem density index was tabulated[59].
156 Higher scores suggest greater problems within a particular domain. Given limited variability and
157 null responses (by design) in two of the subscales (work performance and substance use), the
158 present analysis examines the other 8 DUSI subscales.
159
160 ***Intelligence and physical development.*** Full-scale intelligence was estimated via the Kaufman
161 Brief Intelligence Test, 2nd edition (KBIT-2)[61]. In order to determine physical growth
162 characteristics in the adolescent groups, pubertal development and body mass index (BMI z-score)
163 were assessed. Participants completed the Scale of Physical Development[62], a self-report
164 questionnaire highly correlated with Tanner stage[63]. The questionnaire evaluates the degree to
165 which particular physical maturational changes have occurred, including changes in skin/voice,
166 breast development and facial hair. Possible scores range from 1 (prepubertal) to 4 (postpubertal).
167 BMI (kg/m^2) was calculated using height measured via stadiometer (SECA 216 wall-mount
168 mechanical measuring rod; triplicate measures within 0.5 cm, averaged) and weight measured via
169 digital scale (Health-O-Meter Professional 394KLX). BMI norms for age and sex were used to
170 determine z-scores and percentiles[64]. These three measures were collected during the baseline visit
171 except in the case of one adolescent, whose IQ was assessed during the 1.5-year follow-up visit.
172
173 **MRI acquisition and analysis**
174
175 ***MRI data acquisition.*** During the baseline visit, high-resolution structural images were acquired
176 on a Siemens TIM Trio 3 T scanner with a 12-channel head coil using a T1-weighted magnetization
177 prepared rapid acquisition gradient echo (MPRAGE) sequence. A total of 176 sagittal slices were
178 collected using the following parameters: TR/TE/TI = 920/2.52/900 ms, flip angle = 9°, slice

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179   thickness = 1.0 mm, FOV = 250 × 250 mm^2 and a matrix of 256 × 256 for an effective spatial
180   resolution of 0.97 × 0.97 × 1.0 mm^3.
181
182   ***Quality control for MPRAGEs.*** Quality of structural scans for inclusion in a Voxel-Based
183   Morphometry (VBM) analysis was determined through visual inspection conducted by three
184   independent raters blind to participant group status (PS vs NS). Structural scans were scored on a
185   0 - 5 point scale for degree of artifacts that may affect the tissue classification algorithm (i.e., gross
186   quality problems including phase wrap, ringing, and ghosting), where 0 indicates a scan free from
187   visible artifact and 5 represents a scan of the poorest quality due to prominence of the relevant
188   artifact. For each of the 3 raters, a weighted summary score was calculated. Summary rating scores
189   were found to have good to excellent agreement between raters (intraclass correlation
190   coefficient=.914, 95% confidence interval=.834-.950 [SPSS 24 based on mean rating (k=3),
191   absolute agreement, 2-way mixed-effects model])[65]. The average weighted score of the 3 raters
192   was assigned to each of the structural scans. Scans with the highest scores, indicating extremely
193   poor quality, were flagged and after review by two of the authors (VLD and JVM) were confirmed
194   to be unsuitable for VBM analysis.
195
196   ***MRI data preprocessing and analyses.*** Preprocessing for VBM was performed in SPM 8
197   (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The *New Segment* option with default
198   parameters identified different tissue types, generating native space tissue segmentation and
199   DARTEL imported gray and white matter tissue maps. The DARTEL toolbox was used to create
200   a study-specific whole-brain template (i.e., semi-optimized), and this template was registered to
201   MNI space (affine transform) and modulated by the determinant of the Jacobian transform to
202   preserve tissue volume and create images corresponding to gray matter volume (GMV). The GMV
203   images were smoothed using a 12mm FWHM Gaussian kernel to reduce noise, compensate for
204   spatial noise introduced during normalization, and improve validity of parametric statistics used[66].
205   To account for inter-individual differences in brain size, measures of GMV were normalized by
206   total intracranial volume (ICV).
207
208   **Statistical analysis**
209
210   ***Inclusion Criteria for Analyses.*** Given the potential impact of preterm birth[67], low birth weight[68–
211   70], and exposure to alcohol and other substances *in utero*[71,72] on fetal and postnatal brain
212   development and behavior, analyses were restricted to adolescents whose imaging data met quality
213   control criteria and were born at term (defined as >37 weeks) with normal birth weight (≥2500
214   grams, or 88.18 oz.) and no maternal report of tobacco, alcohol, regular prescription medication,
215   or illicit drug use during pregnancy with the enrolled adolescent. Further, adolescent participants
216   who reported substance use at baseline were excluded from analysis, given the effects of early
217   substance initiation on adolescent neurodevelopment[73,74]. Finally, participants were excluded for
218   poor image quality.
219
220   A total of 128 mothers completed the questionnaire. Based on the inclusion criteria detailed above,
221   45 participants were excluded from analyses. For details of participants remaining at each stage of
222   data filtering, see Table S1, available online. Of the remaining 83 participants with complete pre-
223   /perinatal history, 55 (66%) mothers reported having experienced no stressful event during
224   pregnancy, and 28 (34%) reported having experienced at least one stressful life event during

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225 pregnancy (Table 2). Given the large number of respondents reporting no exposure to stressful
226 events, groups were dichotomized into those whose mothers had not experienced stress during
227 pregnancy (No-Stress group, *NS*; n = 55) and those who had experienced at least one event
228 (Prenatal Stress group, *PS*; n = 28).

230 Seven mothers (NS = 4; PS = 3) reported presence of obstetric complications during pregnancy
231 with the enrolled adolescent (Table 1). The mean birth weight for these 7 participants was 7.8
232 pounds (range: 6.9-8.8 pounds). Given that complications were reported in both groups, and
233 infants were all full-term and born with normal birth weight[75], these adolescents were included in
234 analyses. Finally, 5 mothers (NS = 2; PS = 3) reported having been diagnosed with PPD after birth
235 of the enrolled adolescent. As no additional details concerning PPD diagnosis were collected and
236 the number of diagnosed mothers was small and distributed across both groups, we included these
237 participants in analyses.

239 *Analyses.* Dependent variable distributions were examined prior to analyses to confirm the data
240 were free from outliers and that the assumption of normality was satisfied. The distribution of each
241 of the eight DUSI-R subscales was non-normal (Shapiro-Wilk < .001, df = 82, for all subscales).
242 Because standard transformations failed to normalize distributions, non-parametric statistical test
243 were used for DUSI-R variables. Data analysis was conducted using SPSS Version 24.0.

245 PS and NS groups were compared on adolescent, prenatal, and demographic characteristics using
246 Independent Samples Student's *t*-test, Mann-Whitney U-test, and Chi-square test of independence,
247 as noted. Additionally, groups were compared on the 8 DUSI subscales using the Mann-Whitney
248 U-test with Bonferroni adjusted alpha levels of $p < .00625$ per test (.05/8) to correct for multiple
249 comparisons.

251 *Imaging.* Statistical modeling compared PS and NS groups. Given that the distribution of males
252 and females approximated a significant difference (p = .051) (Table 1), and because cortical
253 thinning trajectories show sex differences[36–38], sex was included as a covariate of no interest in
254 imaging analyses. Clusters were defined using an uncorrected threshold of p < 0.001, k = 10.
255 Corrections for multiple comparisons were made using non-stationary cluster correction
256 (p < 0.05)[76,77].

258 **RESULTS**

260 *Group characteristics.* Groups were similar in demographic (SES, race, and sex) and adolescent
261 characteristics (age at MRI, IQ, pubertal development score, BMI, total intracranial volume, total
262 GMV) (Table 1). Critically, groups were similar in neonatal characteristics (birth weight and
263 length), allowing the inference that groups were similar in both neonatal head circumference[78] and
264 brain size[79]. Further, mothers were similar in age at delivery, and groups were similar in elapsed
265 duration between the child's birth and pre-/perinatal survey data collection. By design, the PS and
266 NS groups differed regarding maternal experience of stress during pregnancy. Table 2 summarizes
267 the stressful events reported by PS group mothers. Within the PS group, 6 mothers reported having
268 experienced more than one event, (5 reported 2 events, 1 reported 3) (see Table S2).

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271   *Table 1. Adolescent and maternal/perinatal characteristics*

	All Participants N = 83	**Prenatal Stress (PS)** N = 28	**No Stress (NS)** N = 55	**p**
Adolescent characteristics				
Age at scan, Mean (SD)	12.7 (.7)	12.5 (.6)	12.8(.7)	.061
Sex				.051
Males, n (%)	38 (46%)	17 (61%)	21 (38%)	
Females, n (%)	45 (54%)	11(39%)	34 (62%)	
Pubertal development Mean (SD)				
Girls and boys	2.27 (.72)	2.32 (.73)	2.25 (.72)	.693
Girls	*2.56 (.69)*	*2.93 (.64)*	2.44 (.68)	.042*
Boys	*1.97 (.54)*	*1.93 (.49)*	*2.0 (.59)*	.69
BMI z-score (SD)	.40 (.96)	.36 (1.1)	42 (.86)	.762
Percentile (SD)ᵃ	*61.3 (27.5)*	*59.2(31.8)*	62.4(25.3)	.859
Race (%)				.739
Caucasian	*57%*	*53.5%*	*58.18%*	
African American	*30%*	*32%*	*29.1%*	
Hispanic/Latino	*6%*	*3.5%*	*7.27%*	
Other	*7%*	*11%*	*5.45%*	
Intelligence (K-BIT), Mean (SD)	108.6 (15.7)	107.1 (16.9)	109.4 (15.1)	.529
Maternal/perinatal characteristics				
Maternal Age at delivery, mean (SD)	30.9 (6.1)	31.5 (7.5)	30.6 (5.3)	.532
Elapsed time, birth and maternal survey completion Mean (SD)	13.3 (1.2)	13.1 (1.1)	13.4 (1.3)	.287
SES index z-score (SD) N = 80		n = 27 -.237 (1.06)	n = 53 .120 (.955)	.131
Parental education (years, mean (SD)) Household income (median)	*16.0 (2.7)* $100,000 - $149,999	*16.48 (2.7)* $50,000 - $74,999	*16.48 (2.6)* $100,000 - $149,999	
Birth weight (ounces) Mean (SD) N=79	122.8 (14.2)	n = 27 124.5 (15.1)	n = 52 121.9 (13.8)	.455
Birth length, (inches) Mean (SD) N = 58	19.7 (3.9)	n = 23 19.0 (6.1)	n = 35 20.2 (.9)	.261

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Obstetric anomaly *(n)*
  Description
	7
	  Gestational diabetes (n=4)
	Bleeding during 1st trimester (n=1)
	Breach/emergency C-section (n=1)
	Unspecified (n=1)
		3
		Gestational diabetes (n=2)
		Breach/emergency C-section (n=1)
			4
			Gestational Diabetes (n=2)
			Bleeding during 1st trimester (n=1)
			Unspecified (n=1)
				--

PPD diagnosis *(n)* *PPD therapy*	5 *Medication (n = 2)* *Therapy (n = 3)*	3 *Medication (Sertraline (SSRI))(n=1)* *Therapy (n=2)*	2 *Medication (unknown) (n=1)* *Therapy (n=1)*	--

272 *Notes: SES = socioeconomic status, BMI = body mass index, PPD = postpartum depression,*
273 *SSRI = selective serotonin reuptake inhibitor*

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275 *Table 2. Summary of reported stressful events occurring during pregnancy in PS group.*

Event description	# reports
Relationship conflict (e.g., divorce, break up, infidelity)	10
Death of someone close (e.g., partner, parent, other child)	5
Severe illness/harm of someone close (e.g., cancer, heart attack, severe car accident)	4
Severe financial issues (e.g., major property damage, foreclosure, sudden unemployment)	2
Involvement in an accident (e.g., car, fire, other disaster)	3
Being physically or emotionally attacked (e.g., threatened with a weapon, rape)	4
Other terrible experience that most people never go through.	7
Total stressful events reported	**35**

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278 ***Gray matter volume analysis.*** Whole brain non-stationary cluster corrected analysis revealed
279 significantly greater GMV for the PS group compared to the NS group in bilateral parietal cortex
280 (Table 3, Figure 1). Specifically, clusters in the right intraparietal sulcus (IPS: 40, -45, 55) (p_{corr} =
281 .019), the left IPS (-32, -43, 55) (p_{corr} = .004), the left inferior parietal lobule (supramarginal gyrus)
282 (IPL: -56, -23, 34) (p_{corr} = .035), and the left superior parietal lobule (SPL: -19, -44, 49) (p_{corr} =
283 0.048) showed greater volume for the contrast PS > NS (see Figures S2, S3). No significant results
284 were found for the reverse contrast, NS > PS.

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291   *Table 3. Summary of results for contrast PS > NS, with sex as covariate of no interest.*
292   *Coordinates are reported in MNI space. Results were thresholded at p<0.001, k =10 voxels.*
293   *Cluster-level non-stationary corrected p-values are reported.*

Region	Cluster size	x	y	Z	Corrected p-value
R Intraparietal sulcus	2093	40	-45	55	.019
L Intraparietal sulcus	1703	-32	-43	55	.029
L supramarginal gyrus	1463	-56	-23	34	.035
L superior parietal lobule	297	-19	-44	49	.048

294
295
296   *Table 4. Outcome measures*

	All participants	Prenatal Stress (PS)	No Stress (NS)	p
N	83	28	55	
Mean Total ICV, Cubic Liters (SD)	1.50 (.12)	1.52 (.10)	1.49 (.13)	.315
Mean Total GMV, Cubic Liters (SD)	0.72 (0.06)	0.73 (0.05)	0.72 (0.06)	.27
DUSI-R Subscales[a] Median (range)				
	82	28	54	
Psychiatric symptoms	20 (0-75)	30 (0-75)	15 (0-70)	.001[*b]
Family system	7 (0-71)	14 (0-71)	7 (0-42)	.006[*b]
Behavior patterns	15 (0-65)	17 (0-65)	10 (0-65)	.108
Health status	20 (0-50)	20 (0-50)	10 (0-50)	.033
Leisure & Recreation	16 (0-58)	16 (0-58)	12 (0-58)	.016
School performance	15 (0-60)	17 (0-60)	10 (0-45)	.010
Social competence	14 (0-64)	21 (0-64)	14 (0-57)	.046
Peer relationships	7 (0-42)	14 (0-42)	7 (0-42)	.033

297   *Note: ICV = intracranial volume, GMV = gray matter volume, DUSI-R = Drug Use Survey*
298   *Inventory, Revised*
299   *a. Mann-Whitney U-test used to examine group differences.*
300   *b. Significant at Bonferroni adjusted alpha level of p < .00625.*
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304   *Figure 1. VBM analysis results for PS > NS using sex as a covariate of no interest; p < 0.05,*
305   *non-stationary cluster corrected. Anatomical orientation showing posterior (A), superior (B),*
306   *coronal (C) and cutaway (D) views of four PPC clusters (L = left, R = right).*
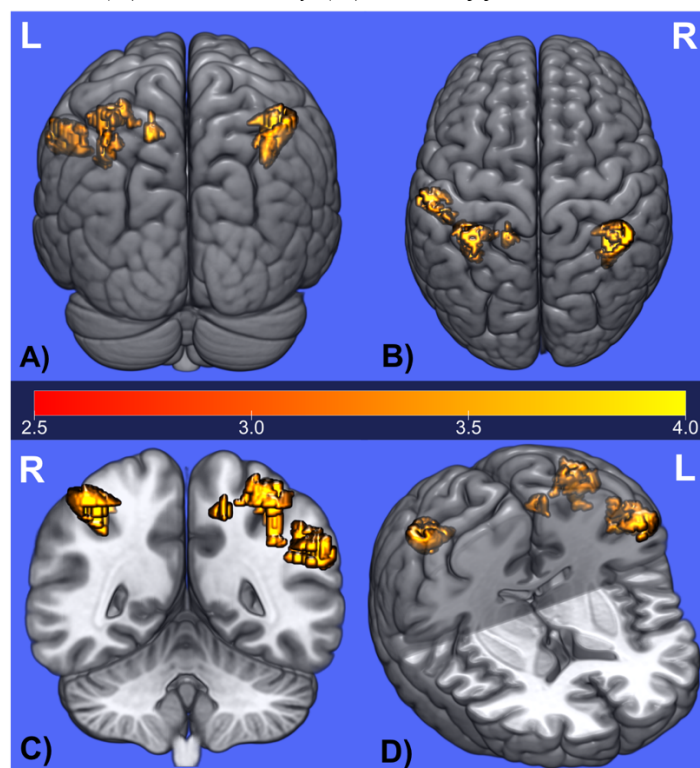
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310   **Risk measure.** The two groups differed significantly on two of the eight DUSI-R subscales at the
311   Bonferroni adjusted alpha-level of p < .00625 (Table 5, Figure 2). First, the PS group scored
312   significantly higher on the DUSI psychiatric symptoms subscale (U(81)= 416.5,z=-3.339 p=.001),
313   indicating a greater risk among the stress-exposed group for mental health symptomatology.
314   Second, the PS group showed significantly higher scores for the family system subscale compared
315   to the NS group (U(81) =486.5, z=-2.738, p=.006), indicating greater interfamilial
316   dysfunction/conflict, less parental supervision, and/or less marital agility.
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318   **Exploratory Analysis**
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320   To obtain a better understanding of the specific behavioral domains problematic for PS
321   adolescents compared to their NS peers, we examined DUSI-R-derived subscales created
322   specifically for use in screening for 4 psychiatric disorders in individuals under age 18[80]. The
323   subscales, which probe features of ADHD, anxiety, depression and conduct disorder, cull
324   questions from across the 10 original DUSI domains. These scales have been shown to be useful
325   in identifying individuals who may require further evaluation for current psychiatric
326   symptomatology, as well as those at risk for development of psychiatric disorder up to 8-10 years
327   after their DUSI assessment[80].
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329 Scores were non-normally distributed and standard transformations were unsuccessful; we
330 therefore compared the two groups using a one-tailed Mann-Whitney U-test, correcting for
331 multiple comparisons using Bonferroni adjusted alpha levels of p < .0125 per test (.05/4). For all
332 four DUSI-derived scales, PS adolescents showed higher scores, indictive of greater problems, and
333 uncorrected values were significant for ADHD, anxiety, and depression. After corrections for
334 multiple comparisons, only the ADHD scale remained significantly greater in PS adolescents,
335 suggestive of greater risk for attentional dysfunction (U(81)= 506.5, z= -2.468, p=.007) (see Table
336 S3).
337
338 **DISCUSSSION**
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340 To our knowledge, ours is the first study to examine the effects of exposure to maternal stress
341 during gestation on brain morphology in typically-developing early adolescents. Compared to
342 adolescents whose mothers report no exposure to a significant stressor during pregnancy,
343 adolescents whose mothers experienced at least one stressful event showed increased GMV in
344 PPC, and displayed greater risk for psychiatric symptoms and family system difficulties.
345 Illuminating those effects of prenatal stress that may not manifest until adolescence is critical,
346 given that latent deficits in structure may be revealed during this period of dramatic brain
347 development,[39] and moreover, altered developmental trajectories during this period may be
348 associated with increased risk for negative outcomes[40,81], including psychiatric symptomatology.
349
350 *Our central finding identified a relationship between maternal exposure to stress during*
351 *pregnancy and GMV in early adolescence.* The PS group exhibited increased GMV compared to
352 the NS group in bilateral PPC: bilateral IPS, and left SPL and IPL. There were no regions for
353 which NS adolescents showed increased GMV relative to the PS group. Changes in GMV from
354 childhood through adulthood exhibit a heterochronic pattern, with different regions of cortex
355 showing distinct developmental trajectories. Parietal gray matter increases during preadolescence,
356 reaching maximum volume at 10.2 years for females and 11.8 years for males, and declining
357 thereafter[36-38]. Given that groups were similar in chronological age (mean 12.5 years) and the
358 potential influence of sex was controlled for, we would expect participants to be at similar stages
359 in cortical development; that is, post-peak gray matter volume in PPC, with cortical pruning
360 resulting in developmentally-appropriate cortical thinning[36-38,82,83].
361
362 Our finding aligns with studies demonstrating a relationship between exposure to maternal distress
363 during gestation and enduring effects on childhood brain morphology, including, importantly, in
364 parietal cortex[31-33]. One notable difference between findings in the current study and findings of
365 previous studies is the age of the children at the time of MRI scanning. While the present study
366 examined early adolescents (11-14 years), previous studies examined children ages 6-9 or younger,
367 a time in which normative development is characterized by increases in gray matter volume[36-38].
368 Thus, our results are in accord with previous research when considering this nonlinear
369 developmental trajectory of the cortex. Our findings among early adolescents, taken together with
370 the findings reported in the literature on early childhood, lead us to speculate that children exposed
371 to the effects of stress *in utero* may show a temporal shift in peak gray matter volume, including a
372 potentially altered trajectory of parietal cortical development, though this remains to be formally
373 tested via longitudinal analyses.

11

374 We also found PS adolescents showed greater problematic behavior on the DUSI-R psychiatric
375 symptoms subscale. Further, in exploratory analyses, the PS group had higher scores on the
376 anxiety, depression, and ADHD subscales, though only the latter remained significant after
377 corrections for multiple comparisons. These results are consistent with a robust literature showing
378 an association between maternal stress during pregnancy and offspring cognitive and behavioral
379 difficulties, including anxiety[21,84], depression[23], and schizophrenia[27,28]. Most relevant to the
380 current study is evidence of an association between maternal stress exposure and impulsivity[22] and
381 ADHD[22,24,84,85]. Population cohort studies have demonstrated associations between maternal
382 stressful life events such as those measured here and increased risk for ADHD in offspring. Boys
383 born to mothers who experienced bereavement during pregnancy are at significantly increased risk
384 for ADHD[86]. Similarly, maternal-rated ADHD symptoms in 2-year-olds is associated with
385 exposure to stressful life events during pregnancy[87].

387 Results from studies examining the relationship of ADHD and ADHD features to cortical
388 development are consistent with the proposition advanced here that increased GMV in attentional
389 processing regions is suggestive of a developmental lag in cortical development among PS
390 adolescents. Youth with ADHD have been shown to exhibit the same region-specific pattern of
391 brain development as TD youth, but that pattern is temporally delayed[82,88,89]; further, TD youth
392 with ADHD features demonstrate a similar pattern shift, and increased ADHD features are
393 associated with a more pronounced temporal shift. Among adults with childhood-diagnosed
394 ADHD, only those who no longer meet ADHD diagnostic criteria exhibit normalization of cortical
395 thickness in right parietal cortex, a key attentional region[88].

397 Consistent with its diverse structural and functional connectivity patterns, the PPC is a component
398 of multiple brain networks, and PPC subregions are hubs in both dorsal and ventral fronto-parietal
399 attention networks[90–92]. The connections between PPC regions with other structures is key, as input
400 provided by PPC could have an impact on downstream structures, particularly frontal regions.
401 Interestingly, many of the regions that previous studies report as having what may be interpreted
402 as delayed development [21,31,33] are connected to PPC, including frontal cortex, and meta-analytic
403 research has shown hypoactivation in the frontoparietal network in children with ADHD[93].
404 Although the PS group in the current study scored higher in ADHD-type features, they also
405 demonstrated increased depressive and anxious symptoms relative to the NS group. Thus,
406 problems with ADHD-type features may more broadly reflect difficulties in executive function,
407 which could be suggestive of a non-specific risk for psychiatric features, given that deficits in
408 executive function are attested in many disorders (e.g., depression, anxiety, and schizophrenia).

410 The findings reported here must be interpreted within the context of limitations of the current
411 study. First, along with increased psychiatric symptoms, the PS group showed significantly higher
412 scores on the family system subscale of the DUSI-R, a 14-item subscale querying parental
413 involvement/supervision, parent-imposed boundaries/rules, occurrence of frequent or intense
414 arguments between the adolescent and his/her parents or others in the home, as well as questions
415 concerning regular or problematic substance use by or arrest of an immediate family member. We
416 are unable to disentangle the contribution of prenatal maternal stressful life events from that of
417 current dynamics within the child's family since many of the factors in our measure of prenatal
418 stress could foreshadow difficulties in postnatal familial dynamics. Second, the questionnaire-
419 based measure of prenatal stress has limitations. Retrospective assessment of traumatic events

420 may include biases[94]. However, measures such as the one used here have been shown to be
421 accurate and reliable[95–97], and the two groups were similar regarding elapsed time between the
422 adolescents' birth and questionnaire completion. Also, the questionnaire did not include an
423 assessment of the mothers' perception of how stressful the event was. The subjective distress
424 associated with an event rather than the objective event itself has been associated with level of
425 trauma among first-responders in a natural disaster[98]. However, among pregnant women it has
426 been shown that objective events (even in the absence of maternal report of subjective distress
427 during the event) are associated with sequelae among offspring[18,99]. Additionally, the
428 questionnaire did not inquire about the timing of the stressful event during pregnancy, though it is
429 unclear whether gestational stress experienced earlier[100,101] or later[31] is more impactful, and it has
430 been suggested timing of the stressor is not a critical factor in offspring outcomes[102].
431
432 Strengths of the present analysis include the rich characterization of the two, relatively large groups
433 of typically developing adolescents analyzed, including descriptors related to prenatal, postnatal,
434 maternal and adolescent variables. Existing studies asking similar research questions have been
435 correlational, have had smaller total sample sizes, and did not possess the rich characterization of
436 participants presented in the current study[31,32]. Importantly, the chronological age range of the
437 adolescents studied here was narrow and thus more readily allows for consideration of group
438 differences during this period of dynamic alterations in gray matter. Additionally, factors known
439 to be related to GMV, including age, IQ[103], pubertal development,[36] BMI[104], and sex[36,37], were
440 either controlled for or were similar between groups in the current study.
441
442 Given the normative development of parietal cortex, increased GMV in the PS group is potentially
443 suggestive of a developmental lag in cortical maturation compared to their similarly aged NS peers.
444 Our results add to the growing literature demonstrating the enduring effects of maternal stress
445 exposure on brain morphology and the possibility of increased risk for psychiatric symptoms. It is
446 plausible that delayed development in PPC may impact structures that rely on PPC input, creating
447 a feedforward effect, resulting in differential input to other developing structures, especially the
448 prefrontal cortex, which shows a protracted course of development[83,105]. Adolescence is a key
449 period in brain and psychosocial development, during which the risk for emergence of
450 neuropsychiatric disorders is heightened[40] and realized[106,107]. The groups studied here differed
451 neither for proxies for estimated brain size at birth, nor for ICV and total GMV at the time of MRI
452 scans, suggesting that despite overall similarities in brain structure both at birth and in early
453 adolescence, region-specific differences in brain development resulting from *in utero* stress
454 exposure are evident in adolescence, a key neurodevelopmental period. It is therefore critical to
455 understand the factors that contribute to differences in the course of brain development during
456 adolescence, and how these differences potentially increase risk for the development of psychiatric
457 symptoms. Understanding the enduring impact of maternal prenatal stress exposure on adolescent
458 brain and behavior provides an opportunity to target those youth at increased risk for problems and
459 identify factors that can help them attain positive functional outcomes. Furthermore, these results
460 highlight the importance of providing pregnant women with sufficient social support to help
461 mitigate the effects of external stressors.
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