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Citation for published version (APA):

Lautarescu, A., Hadaya, L., Craig, M., Makropoulos, A., Batalle, D., Nosarti, C., Edwards, D., Counsell, S., & Victor, S. (in press). Exploring the relationship between maternal prenatal stress and brain structure in premature neonates. *PLoS One*.

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2 Exploring the relationship between maternal prenatal stress and brain structure in
3 premature neonates

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Abstract

Background: Exposure to maternal stress in utero is associated with a range of adverse outcomes. We previously observed an association between maternal stress and white matter microstructure in a sample of infants born prematurely. In this study, we aimed to investigate the relationship between maternal trait anxiety, stressful life events and brain volumes.

Methods: 221 infants (114 males, 107 females) born prematurely (median gestational age = 30.43 weeks [range 23.57-32.86]) underwent magnetic resonance imaging around term-equivalent age (mean=42.20 weeks, SD=1.60). Brain volumes were extracted for the following regions of interest: frontal lobe, temporal lobe, amygdala, hippocampus, thalamus and normalized to total brain volume. Multiple linear regressions were conducted to investigate the relationship between maternal anxiety/stress and brain volumes, controlling for gestational age at birth, postmenstrual age at scan, socioeconomic status, sex, days on total parenteral nutrition. Additional exploratory Tensor Based Morphometry analyses were performed to obtain voxel-wise brain volume changes from Jacobian determinant maps.

Results and Conclusion: In this large prospective study, we did not find evidence of a relationship between maternal prenatal stress or trait anxiety and brain volumes. This was the case for both the main analysis using a region-of-interest approach, and for the exploratory analysis using Jacobian determinant maps. We discuss these results in the context of conflicting evidence from previous studies and highlight the need for further research on premature infants, particularly including term-born controls.

Keywords: maternal anxiety, prenatal stress, structural MRI, preterm

28 **Introduction**

29

30 Poor maternal mental health during pregnancy represents a global public health problem,
31 affecting 10-35% of pregnant women [1, 2]. Maternal prenatal psychological distress in the
32 form of maternal depression, anxiety, and/or stress has been associated with adverse
33 obstetrical and early behavioural outcomes, and an increased risk of neurodevelopmental and
34 psychiatric disorders [3-7]. The biological basis of these effects is still poorly understood.
35 However, studies by our group and others suggest prenatal maternal stress modulates the
36 neurodevelopment of brain networks that underpin these disorders [8-11].

37 The brain regions that appear to be most vulnerable to maternal prenatal stress, other forms of
38 early adversity, and psychopathology include the regions of the frontal lobe, temporal lobe,
39 and limbic system [12-17]. These areas are connected by the uncinate fasciculus, and we
40 recently reported an association between maternal stressful life events and increased
41 diffusivity in this tract, in a sample of premature neonates [18].

42

43 However, although there is evidence suggesting that maternal prenatal stress affects the
44 development of white matter tracts, evidence for early changes in structural brain
45 development is inconclusive [12]. A small number of studies have examined this relationship
46 in neonates and infants born at term, suggesting no evidence for differences in brain volumes
47 in relation to maternal psychological distress [10, 19, 20]. Several studies have been
48 conducted on older participants (i.e. childhood, adolescence, and adulthood), with the most
49 commonly reported findings being cortical thinning [21, 22, 23, 24], and either reductions
50 [25-27], or increases in regional volumes [28-30].

51

52 While human studies so far have been inconclusive, animal studies have provided some
53 limited evidence that maternal distress is related to early volume changes in the limbic
54 system, particularly the hippocampus, amygdala, and thalamus [31-36].

55

56 We must also consider biological sex as a potential moderator of risk transmission, as several
57 studies have reported volume changes in females, but not males [28, 30, 37]. In utero stress
58 exposure has been associated with higher rates of mood disorders and anxiety [38-40] in
59 females, and behavioural problems [41] and ADHD [6] in males. High maternal cortisol
60 levels at 15 weeks' gestation has been associated with increased right amygdala volumes and
61 more affective problems in female, but not male, offspring [41].

62

63 In summary, although research has reported differences in brain structure in children,
64 adolescents and adults exposed to maternal psychological distress, evidence in infants is
65 inconclusive. To our knowledge, no studies have investigated this relationship in infants born
66 prematurely. Premature birth is associated with changes in brain development [42] and an
67 increased risk of adverse neurodevelopmental and psychiatric outcomes [43, 44]. In order to
68 improve outcomes in these children, it is important to better understand the role that early
69 adverse experiences such as exposure to prenatal stress could have in moderating these
70 associations.

71

72 In this study, we investigated the relationship between maternal trait anxiety and stressful life
73 events, and brain volumes in a large sample of infants born prematurely. We have previously
74 shown differences in white matter microstructure in the uncinate fasciculus in this sample
75 [18]. Based on previous literature, we hypothesized that maternal prenatal stress/trait anxiety
76 would be associated with regional volume differences in areas adjacent to the uncinate

77 fasciculus: frontal and temporal lobe volume, amygdala, hippocampus and thalamus. As the
78 direction of effect in the literature is inconsistent (i.e. volumes found to be normal, enlarged,
79 or decreased), we did not hypothesize a direction of effect. Lastly, given the heterogeneity of
80 outcomes associated with maternal stress, as well as the complexity of functional anatomy in
81 the chosen regions of interest (Text in S1 Supplement), we conducted a whole brain analysis
82 using Tensor Based Morphometry.

83

84 **Methods and materials**

85

86 **Participants**

87

88 Participants were mother-infant dyads who took part of the Evaluation of Preterm Imaging

89 Study (ePRIME, [45]). Ethical approval was obtained from the Hammersmith and Queen

90 Charlotte's Research Ethics Committee (09/H0707/98) and informed written consent was

91 obtained from all participants. Participants were recruited between April 2010 and July 2013

92 by screening 3619 admissions to level 1,2 and 3 neonatal units at 14 London Hospitals.

93 Eligibility criteria for the main study included: infant born before 33 weeks gestational age,

94 mother aged over 16 years, not a hospital inpatient, no major congenital malformation, no

95 prior MRI, no care in a centre where preterm MRI was routine, no metallic implants, parents

96 able to speak English, parents not subject to child protection proceedings. The ePrime cohort

97 is representative of the UK NICU population in terms of birth weight, ethnicity, and

98 prevalence of cerebral palsy (6%). Additional information is available in [45].

99

100 Data was available for n=511 infants who were born prematurely (before 33 weeks of

101 gestation) and scanned at term equivalent age. We excluded cases where the postmenstrual

102 age at scan was >45 (n=48), data was not available for all variables of interest (n=160),

103 women disclosed alcohol and/or drug abuse during pregnancy (n=5), or the images showed
104 major focal lesions such as periventricular leukomalacia, haemorrhagic parenchymal
105 infarction, and other ischemic or haemorrhagic lesions (n=40). In cases where a mother had
106 multiple infants enrolled in the study (i.e. twin and triplet pregnancies), only one infant was
107 randomly included in the final analysis. From the remaining sample, segmentation data for
108 the structures of interest were available for n=221 (Table 1), and a voxel-wise exploratory
109 analysis using Tensor Based Morphometry was performed on the same 221 participants. The
110 sample partially overlapped (n=191) with a previous study [18]. Maternal socioeconomic
111 status (SES) values were extracted from the Carstairs index, which takes into consideration
112 variables such as unemployment, car ownership, household overcrowding, and social class
113 [46].

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Table 1. Obstetric and Sociodemographic characteristics (n=221)

Maternal Characteristics	Reported	Values
Stressful life events score	Median (range)	53 (0-270)
Trait anxiety score	Median (range)	36 (20-67)
Maternal age at scan	Mean (SD)	32.94 (5.70)
Maternal SES	Median (range)	17.44 (1.73-60.58)
Maternal education (years)	N (%)	
16 or less		24 (10.8%)
17-19		30 (13.5%)
19+		156 (70.6%)
Still in full-time education		8 (3.6%)
Not reported		3 (1.3%)
Infant Characteristics	Reported	Values
Infant sex	N (%)	
Male		114 (51.5%)
Female		107 (48.4%)
GA at birth (weeks)	Median (range)	30.43 (23.57-32.86)
PMA at scan (weeks)	Mean (SD)	42.20 (1.60)
Birth weight (grams)	Median (range)	1300 (600-2600)
OFC at birth (cm), n=192	Median (range)	29.00 (21.80-36)
Number of days on TPN	Median (range)	6 (0-59)
Number of days on ventilation	Median (range)	0 (0-33)

130 Mean and SD are reported for normally distributed data; median and range are reported for
 131 non normally distributed data. GA=gestational age, OFC=Orbitofrontal circumference,
 132 PMA=postmenstrual age, SD=standard deviation, SES=socioeconomic status, TPN=Total
 133 Parenteral Nutrition, Maternal education = age at leaving formal education. No missing data
 134 unless otherwise specified in table.

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138

139 **Trait anxiety**

140

141 The State Trait Anxiety Inventory (STAI, [47]) which measures levels of anxiety right now

142 (i.e. state) and in general (i.e. trait), was administered at the time of the MRI scan. The

143 analysis was restricted to trait anxiety, as it measures a relatively stable tendency to be prone
144 to experiencing anxiety and thus extends to the period before birth.

145

146 For trait anxiety, missing values were imputed for cases in which a maximum of 10% of
147 questions were missing. We imputed missing values by calculating the average response for
148 the questions that were answered. Missing values were imputed for n=23 (n=18 missing 1/20
149 answers and n=5 missing 2/20 answers).

150

151 **Stressful life events**

152

153 Stressful life events were assessed using a questionnaire adapted from the Avon Longitudinal
154 Study of Parents and Children [48], which included yes/no answers to a list of potentially
155 stressful life events the participant may have experienced in the year prior to the study visit
156 (e.g. “Arguments with your partner increased”). Events were ranked according to severity
157 [18] based on the Social Readjustment Rating Scale [49] and summed to form a final score
158 that accounts for the number and severity of events experienced (Table J in S1 Supplement).

159 There were no missing data for this variable.

160

161

162 **MR imaging**

163

164 Magnetic resonance imaging data were acquired using an 8-channel phased array head coil,
165 on a Philips 3T (Philips Medical Systems, Best, The Netherlands) MR system located on the
166 intensive care unit. Imaging data was acquired as follows: Three-dimensional magnetization
167 prepared rapid acquisition gradient echo (repetition time: 17 ms; echo time: 4.6 ms; flip
168 angle: 13°; slice thickness: 0.8 mm; in-plane resolution: 0.82 × 0.82 mm²), T2-weighted
169 turbo spin echo (repetition time: 8670 ms; echo time: 160 ms; flip angle: 90°; slice thickness:
170 2 mm; in-plane resolution: 0.86 × 0.86 mm²), and single shot echo planar DTI (repetition

171 time: 7536 ms; echo time: 49 ms; flip angle: 90°; slice thickness: 2 mm; in-plane resolution:
172 2 x 2 mm², 32 noncollinear gradient directions, b value of 750 s/mm², 1 non-diffusion-
173 weighted image, b = 0).

174

175 An experienced paediatrician supervised all scanning sessions. To enable a successful scan,
176 the majority of infants included in this study were sedated with oral chloral hydrate (25-50
177 mg/kg) and monitored throughout the scan using pulse oximetry, temperature monitors and
178 electrocardiography. Ear protection was used for all infants, in the form of earplugs molded
179 from a silicone-based putty (President Putty; Coltene Whaledent, Mahwah, NJ) and neonatal
180 earmuffs (MiniMuffs; Natus Medical Inc., San Carlos, CA).

181

182 **Segmentations**

183

184 Images were analysed using an automated processing pipeline optimised for neonates.

185 Following motion correction, bias correction and brain extraction, T2w images were
186 segmented using the Draw-EM algorithm, an open-source software optimised for neonatal
187 brain segmentation [50]. Analysing MR images from infants, and especially preterm infants,
188 poses unique challenges, such as motion, lower contrast-to-noise ratio, and partial volume
189 effects; for a discussion of how these were addressed, see [50].

190 Based on previous literature and considerations of multiple comparisons issues, the following
191 volumes were chosen as variables of interest: amygdala, hippocampus, thalamus, frontal lobe
192 and temporal lobe (Table A in S1 Supplement). To account for inter-individual differences in
193 brain size, all brain volumes included in the analysis were normalized to total brain volume
194 (i.e. dividing each regional volume by total brain volume).

195

196 **Tensor-Based Morphometry**

197

198

199 **Template construction**

200

201 A multivariate study-specific template was built using images from a subset of 161
202 participants. In order to reduce computational load, a smaller subset of 161 images meeting
203 inclusion criteria (i.e. PMA at scan <45 weeks, no major lesions, and of good quality) were
204 used to build the population template for this study. Using the Advanced Normalization
205 Tools (ANTs) software to build the template [51], we applied field bias correction and used
206 the Developing Human Connectome Project 40 weeks' gestational age T2-weighted [52] and
207 T2 tissue labels templates [50] as the target volumes for the template construction inputs.
208 Iteration limit was set to the default (4 iterations).

209

210 **Registration and log-Jacobian determinants**

211

212 Images were registered to the study-specific template using the multimodal Symmetric
213 Normalisation (SyN) algorithm from the ANTs software (n=221) [53]. To improve image
214 registration, two input modalities were used: T2-weighted images and T2-based tissue type
215 segmentation [50]. T2-weighted deformation tensor fields (i.e. warps) from non-linear
216 transformations of the registration process were used to compute a logarithm transformation
217 of Jacobian determinant maps (i.e. deformation tensor field gradients), which reflect volume
218 changes from the template at the voxel-level [54]. Jacobian determinants reflect the degree of
219 transformation (i.e. the expanding or contracting) an image voxel has undergone in order to
220 fit into the template space; therefore, providing information on the relative volumes of brain
221 structures. Smoothing with a 4mm full-width half-maximum Gaussian filter was applied to
222 the log-Jacobian determinants, in order to increase the signal-to-noise ratio. We re-sampled
223 the smoothed log-Jacobian maps from the original isotropic voxel size of 0.5 cm³ to 1 cm³

224 before running statistical analyses in order to help with computation and memory
225 constraints.

226

227 **Statistical analysis**

228

229 **Main analysis**

230

231

232 Statistical analysis was performed using R [55], with the main packages being psych [56],

233 ggplot2 [57], and hmisc [58]. A minimal dataset and the analysis code including a

234 comprehensive list of packages are available in the Supplement (Text in S1 Supplement, S3

235 Dataset).

236

237 We assessed potential covariates using bivariate Spearman's correlations (Table B in S1

238 Supplement). Birth weight was excluded as a covariate from the main analysis as it was

239 highly correlated with gestational age ($r=.74$, $p<.001$). The number of days on ventilation was

240 also excluded as a covariate in the main analysis as it was highly correlated with the number

241 of days on total parenteral nutrition ($r=.60$, $p=.001$), both measures provide information on

242 the health status of the infant, and the distribution of days on total parenteral nutrition was

243 less skewed. Maternal education and number of complications were not correlated with any

244 of the variables of interest and thus were excluded in the main analysis. The regression

245 models used were the same as those used in [18].

246

247 Multiple linear regressions were conducted to investigate the relationship between maternal

248 trait anxiety/stress and brain volumes in premature infants. Our models contained the

249 following predictors: stressful life events, trait anxiety, GA, PMA, SES, biological sex, days

250 on total parenteral nutrition. The models were run separately for each dependent variable

251 (frontal lobe grey matter, temporal lobe grey matter, thalamus, amygdala, hippocampus).

252 Correction for multiple comparisons was performed using False Discovery Rate (FDR), and
253 all p values reported below are uncorrected. Unless otherwise specified, all regression
254 models met assumptions for multiple regression (i.e. normality, linearity, homogeneity of
255 variance, uncorrelated predictors, no influential outliers, independence of residuals, [59],
256 Table C in S1 Supplement). One outlier was removed from all regressions due to violating
257 assumptions of normality (days TPN = 59).

258

259 **Exploratory analysis of Tensor Based Morphometry**

260

261

262 Voxel-wise statistical analyses were performed using FSL's randomise nonparametric
263 permutation testing [60]. A general linear model tested for relationships between log-
264 Jacobian values at the voxel level and the outcome variables of interest (maternal prenatal
265 stress and trait anxiety). We included gestational age at birth, postmenstrual age at scan,
266 socioeconomic status, sex and days on total parenteral nutrition as covariates in our model.
267 We ran 10,000 permutations of the data and used 3D Threshold-Free Cluster Enhancement
268 (TFCE) and Family Wise Error (FWE) to correct for multiple comparisons [61]. Voxels with
269 FWE-corrected P-values at a threshold of $P < 0.05$ were considered to be significant.

270

271 **Results**

272

273 **Segmentations**

274

275

276

277 **Frontal grey matter volume**

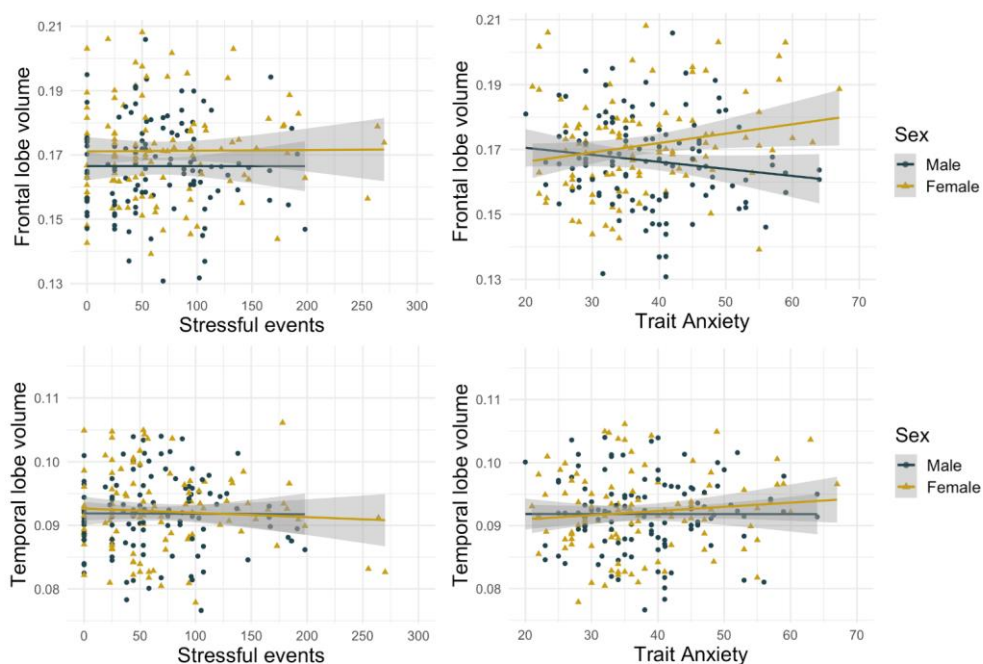
278 The model performed better than expected by chance ($p < .001$) and accounted for 42% of
279 variance in frontal lobe volume (predicted by PMA, with $B = .0058$ and SES, with $B = .00015$).

280 There was no association between frontal grey matter volume and either stressful life events
281 ($B=.000018$, $t=1.27$, $p=.204$) or trait anxiety ($B=-.000024$, $t=-.304$, $p=.761$, Table D in S1
282 Supplement). An alternative model removing these two variables performed better ($R^2=.42$,
283 $AIC=-1338.38$) than the original model ($R^2=.41$, $AIC=-1336.09$), suggesting that the best fit
284 for a model predicting frontal grey matter volume is one without stressful life events or trait
285 anxiety.

286 Further exploring this relationship with direct Spearman correlations (in the absence of
287 covariates) showed no evidence for a relationship (Fig 1) between frontal grey matter volume
288 and stressful life events ($r=.04$, $p=.593$) or trait anxiety ($r=.006$, $p=.929$).

289

290 **Fig 1. Scatterplots for correlations between maternal trait anxiety/stress and volumes**
291 **for the frontal and temporal lobes.** See Fig A in S1 Supplement for partial regression
292 scatterplots.



293

294

295 **Temporal grey matter volume**

296 The model did not meet assumptions of homogeneity of variance, and thus we report the
297 heteroscedasticity corrected covariance matrix (Table F in S1 Supplement). The model
298 accounted for 45% of variance in temporal grey matter volume (predicted by PMA, with
299 $B=.0025$ and SES, with $B=.000051$). There was no relationship with stressful life events
300 ($B=.0000027$, $t=.495$, $p=.621$) or trait anxiety ($B=.0000047$, $t=.140$, $p=.889$) (Table E in S1
301 Supplement).

302 An alternative model removing these two variables performed better ($R^2=.46$, $AIC=-.1735.3$)
303 than the original model ($R^2=.46$, $AIC=-1731.5$), suggesting that the best fit for a model
304 predicting temporal grey matter volume is one without stressful life events or trait anxiety.
305 Further exploring this relationship with direct Spearman correlations (in the absence of
306 covariates) showed no evidence for a relationship (Fig 1) between temporal grey matter
307 volume and stressful life events ($r=.04$, $p=.667$) or trait anxiety ($r=.05$, $p=.440$).

308

309

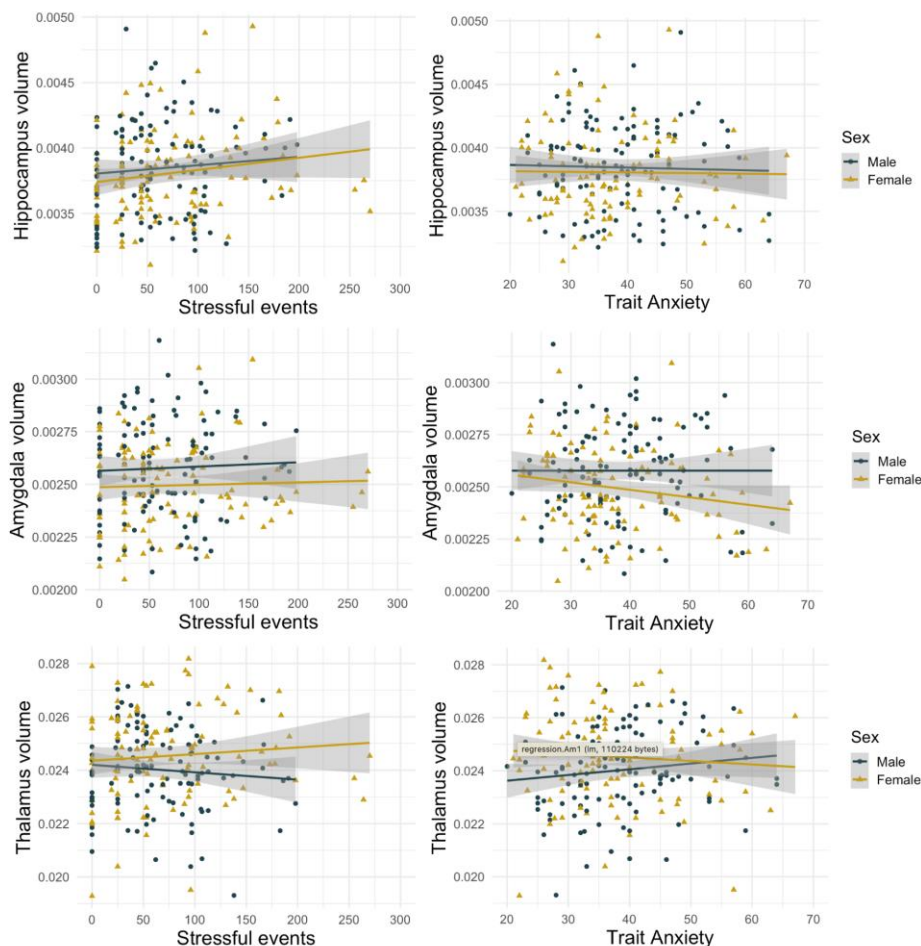
310

311 **Hippocampal volume**

312 Hippocampal volume was not accurately predicted by the model ($R^2=.06$, $F(8,211)=1.58$,
313 $p=.131$), with the only significant predictor being socioeconomic status ($B=-.0000040$, $t=-$
314 2.08 , $p=.039$). As the model showed deviations from linearity (Text in S1 Supplement), we
315 repeated the analysis removing 3 outliers (stressful life event scores >250). The new model
316 did not adequately predict hippocampal volume either ($R^2=.07$, $F(8,208)=2.17$, $p=.031$), but
317 stressful life events was a significant predictor ($B=.0000012$, $t=2.57$, $p=.011$), alongside
318 socioeconomic status ($B=-.0000045$, $t=-2.36$, $p=.019$) (Table G in S1 Supplement). This

319 result did not survive correction for multiple comparisons and visual inspection of the plot
 320 suggests no relationship between the variables. An alternative model excluding trait anxiety
 321 and stressful life events performed worse ($R^2=.05$, $p=.111$), with a higher AIC of -2840.17
 322 compared with $-.2842.99$. Further exploring this relationship with direct Spearman
 323 correlations (in the absence of covariates), suggested a positive correlation between
 324 hippocampal volume and stressful life events ($r=.16$, $p=.020$), but not trait anxiety ($r=-.004$,
 325 $p=.959$)(Fig 2).

326 **Fig 2. Scatterplots for correlations between maternal trait anxiety/stress and volumes**
 327 **for the hippocampus, amygdala, and thalamus.** See Fig B in S1 Supplement for partial
 328 regression scatterplots.



329

330 Amygdala volume

331 For amygdala volume, the model performed better than expected by chance and accounted
 332 for 27% of variance in outcome measures (predicted by PMA, with $B=-.000064$ and SES,

333 with $B=-.0000023$). There was no relationship with stressful life events ($B=-.000000028$, $t=-$
334 $.114$, $p=.909$) or trait anxiety ($B=-.0000013$, $t=-1.000$, $p=.319$)(Table H in S1 Supplement).
335 An alternative model removing these two variables performed better ($R^2=.27$, $AIC=-3123.95$)
336 than the original model ($R^2=.27$, $AIC=-3121.05$). Direct Spearman correlations showed no
337 evidence for a relationship between amygdala volume and stressful life events ($r=.02$,
338 $p=.770$) or trait anxiety ($r=-.05$, $p=.505$)(Fig 2). As the model showed deviations from
339 linearity (Text in S1 Supplement), we repeated the analysis removing 3 outliers (stressful life
340 event scores >250). The new model revealed similar results (Table H in S1 Supplement).

341 **Thalamus volume**

342 **Thalamus volume**
343
344 Thalamus volume was not accurately predicted by the model ($R^2=.08$, $F(8,210)=2.40$,
345 $p=.017$). There was no significant relationship between thalamus volume and stressful events
346 ($B=-.00000021$, $t=-.10$, $p=.920$) or trait anxiety ($B=-0.00000067$, $t=-.05$, $p=.953$) (Table I in
347 S1 Supplement). Direct Spearman correlations showed that there was no relationship between
348 thalamus volume and stressful life events ($r=-.03$, $p=.684$) or trait anxiety ($r=.03$, $p=.713$)(Fig
349 2).

350

351

352

353 **Exploratory analysis subdividing the sample by sex**

354

355 As visual inspection of scatterplots suggested that the relationship between maternal trait
356 anxiety/stress and brain volumes may be influenced by infant sex, we repeated our analysis
357 subdividing the sample into males and females. There were no significant relationships
358 between maternal trait anxiety/stressful events and infant volume in frontal lobe, temporal
359 lobe, amygdala, thalamus (Text in S1 Supplement).

360 In our female sample, hippocampal volume was not accurately predicted by the model
361 ($R^2=.12$, $F(7,95)=1.79$, $p=.097$), but the only significant predictor was stressful life events
362 ($B=.0000017$, $t=2.65$, $p=.009$). This did not survive correction for multiple comparisons. The
363 relationship between hippocampal volume and stressful life events was not observed in
364 males.

365

366 **Voxel wise Tensor Based Morphometry results**

367

368 In order to explore whether maternal stress or trait anxiety were associated with neonatal
369 brain volumes at the voxel-level, we conducted Tensor Based Morphometry analyses to
370 obtain Jacobian determinant maps which reflect relative voxel-wise volume changes. Tensor
371 Based Morphometry did not reveal any significant relationships between the smoothed log-
372 Jacobian determinants and maternal prenatal stress or trait anxiety at the FWE $p<0.05$
373 threshold. The T-statistic maps (Fig 3) show the test statistic at the voxel level before
374 corrections for multiple comparisons were applied. The whole-brain t-stat maps show
375 generally low t-stat values indicating poor associations between maternal trait anxiety (Fig
376 3a), or stressful life events (Fig 3b) and log-Jacobian determinants. Nifti files for the t-stat
377 maps are available in the S2 File.

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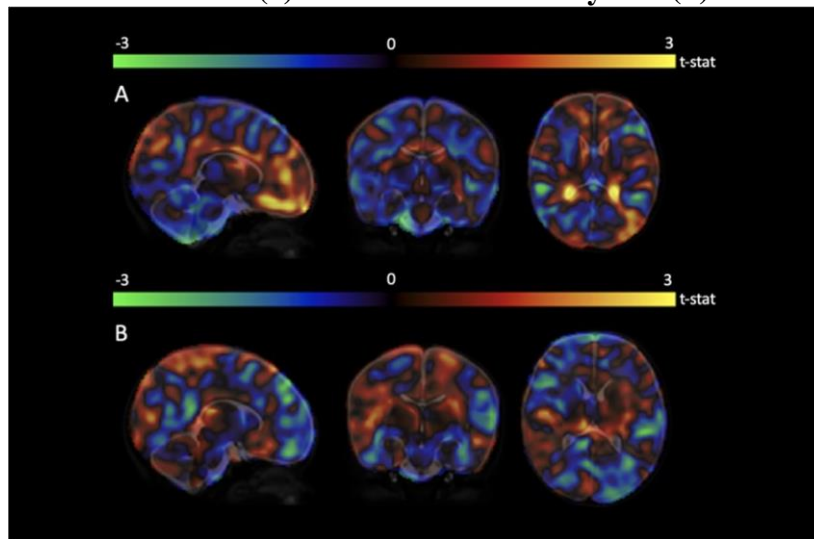
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386 **Fig 3. T-statistic maps showing the relationships between voxel-wise log-Jacobian**
387 **determinants and (a) maternal trait anxiety and (b) stressful life events.**



388

389 **Discussion**

390

391 In this study, we did not find evidence for a relationship between maternal stress (i.e.
392 stressful life events and trait anxiety) and grey matter volumes in a large sample of infants
393 born prematurely. These results were consistent across 2 methodologies, using both a whole-
394 brain voxel-wise approach, as well as a region of interest analysis (i.e. hippocampus,
395 amygdala, thalamus, frontal lobe, and temporal lobe).

396

397 Interpretation of these findings raises important questions for a field that, to date, has been
398 complicated by inconsistencies between studies along multiple dimensions. These include
399 differences in the samples studied (e.g. age, gender), imaging protocols, definitions of stress,
400 and sample size [12, 62]. Our findings are in line with [10] who reported no difference in
401 right amygdala volume in a large sample of neonates (n=157) exposed to maternal depression
402 in the second trimester of pregnancy. Similarly, [20] reported no difference in hippocampal
403 volume at birth, but suggested that the hippocampal volume exhibits slower growth in
404 response to exposure to maternal trait anxiety in utero, with smaller volumes being observed

405 at 6 months of age. In a study of exposure to selective serotonin reuptake inhibitors,
406 differences in volume were reported in the right amygdala and right insula [19], but the
407 authors reported no differences in limbic system volumes between untreated depression and
408 controls. Further, [27], in a study of young adults, reported no association between maternal
409 prenatal stress and hippocampal volume, which was instead associated with postnatal anxiety.
410 Studies that have reported associations with maternal distress, primarily regarding cortical
411 thinning in regions of the frontal and temporal lobes [21-24] have been conducted on children
412 rather than infants. Overall, at present, there seems to be no consistent evidence that maternal
413 prenatal stress is associated with neonatal brain volumes, in line with our findings.

414

415 This is in stark contrast to the diffusion MRI literature, where studies have consistently
416 reported alterations in limbic and prefrontal microstructure in neonates and infants exposed to
417 maternal psychological distress in utero [9-11, 18, 63]. Further, given that diffusion MRI
418 studies have reported also collecting T2-weighted images, we need to consider whether the
419 lack of studies reporting structural MRI analyses may be driven by the failure to report non-
420 significant findings (i.e. the “file-drawer” problem, [64]). In a recent study published on an
421 overlapping sample [18], we showed differences in white matter microstructure in the
422 uncinate fasciculus in relation to maternal stressful life events. Interestingly, a few of the
423 studies which failed to observe differences in brain structure in relation to maternal
424 psychological distress, reported alterations in white matter microstructure. For example, [10],
425 observed lower fractional anisotropy in the right amygdala of neonates exposed to maternal
426 depression, with no evidence for differences in amygdala volume. Converging evidence
427 suggests that maternal prenatal stress can alter the developing connectome, with differences
428 being most commonly reported in fronto-limbic brain networks (using fMRI and dMRI), with
429 limited evidence for differences in brain structure [62]. Further studies conducted on term-

430 born and preterm infants and reporting on both structural and diffusion MRI are required in
431 order to clarify whether white matter is especially vulnerable to maternal prenatal stress. This
432 is of particular importance given that white matter injury is the most common neuropathology
433 in infants born prematurely [65-67] and white matter may therefore be more vulnerable to
434 additional stressors.

435

436 The current study also raised the possibility that the relationship between maternal distress
437 and early brain development may be at least partly influenced by sex differences in the
438 vulnerability to maternal stress in utero. Maternal stressful life events were associated with
439 increased hippocampal volume in the whole sample and in females, but not males; however,
440 these findings were not found to be statistically significant after correction for multiple
441 comparisons.

442

443 It is important to highlight that our sample consisted of preterm infants, a population known
444 to have regional brain volume abnormalities [42] and adverse neuropsychiatric and
445 developmental outcomes [44, 68]. We caution against generalizing these findings to infants
446 born at term, and suggest that further studies with term-born controls are needed to further
447 clarify the role that early adverse experiences such as maternal stress may have in moderating
448 the association between preterm birth and adverse outcomes in this vulnerable population.

449

450 Although in this study we have examined mean bilateral volumes, several studies of children
451 have reported unilateral differences in volume, such as increased left amygdala volume in
452 girls exposed to pregnancy-specific anxiety, but not boys [37] and greater right amygdala
453 volume in girls exposed to maternal depression, but not boys [30]. Although our analysis was
454 based on mean volumes, the whole-brain analysis did not suggest lateralized differences in

455 volume associated with maternal stress or trait anxiety. Further, other studies that have
456 reported differences in volumes in areas such as the frontal lobe, reported these in very
457 specific areas, such as the mid-dorsolateral frontal cortex [27] or left medial temporal lobe
458 [26]. This may mean that any changes associated with maternal prenatal stress may be more
459 subtle, and thus not affect the overall volume of the frontal or temporal lobes. However, our
460 findings using a voxel-wise whole-brain analysis did not suggest any volume differences
461 associated with maternal stress.

462

463 Our findings are not in line with those of [26], who reported decreased amygdala volume, or
464 [28], who reported increased amygdala volume in girls. However, both of these studies were
465 conducted on adult samples, and measures of maternal stress were acquired retrospectively.
466 The biological basis of these potential sex differences is unclear, but may include sex
467 differences in placental functioning, fetal exposure to adrenal hormones and testosterone, as
468 well as various epigenetic mechanisms [69].

469

470 Further, there is some evidence to suggest that the child's development may be more
471 susceptible to maternal pregnancy-specific anxiety, rather than generalized anxiety or stress,
472 as well as that the timing of stress exposure is an important factor to consider [20]. A study
473 [25] suggested that pregnancy anxiety is associated with differences in gray-matter volume at
474 age 6-9, and later reported that neither state anxiety nor depression explained any additional
475 variance in developmental outcomes after accounting for pregnancy-specific anxiety [70].
476 Future studies should include measures of pregnancy-specific anxiety and assess stress
477 exposure during early, mid, and late gestation.

478

479 Although not one of the measures of interest in this study, socio-economic status (which was
480 entered into the regression models as a covariate) was consistently associated with
481 differences in brain volume in our sample of infants born prematurely. Based on these
482 findings, we recommend that future studies should investigate the relationship between
483 socioeconomic status and early brain development, particularly given that low SES is known
484 to be associated with adverse mental health, underreporting of mental health concerns, as
485 well as lack of access to mental health services [71].

486

487 It is important to note that although this study was based on subjective self-report measures,
488 the reliability of maternal recall for pregnancy and birth related events appears to be high
489 [72-74], false positive reports of adverse life events are rare [75], and self-reported trait
490 anxiety scores are relatively stable in the perinatal period [76] (See Text in S1 Supplement
491 for further discussion). Future studies should consider including both subjective and
492 laboratory-based measures of stress or anxiety, such as autonomic function, or blood cortisol.

493

494 In conclusion, based on our previous findings in an overlapping sample [18], we expected an
495 association between maternal stress and brain volumes in areas adjacent to the uncinate
496 fasciculus tract. To our knowledge, the current study is the first one to examine this
497 relationship in premature infants. In our sample, there is no credible evidence that maternal
498 prenatal stressful life events or trait anxiety influence volumes in the hippocampus,
499 amygdala, thalamus, frontal grey matter or temporal grey matter volume in preterm infants.
500 Our findings are strengthened by an exploratory voxel-wise analysis, and in line with
501 previous literature. Our findings are of particular interest in the context of having reported
502 differences in white matter microstructure in an overlapping sample, using the same
503 statistical methods [18]. It is important to highlight the proximity of our findings to birth, as

504 this minimises the potential confounding influences within the postnatal environment on
505 brain development, which has been a limitation of most prior human studies. We hope that
506 these findings can contribute to a more balanced view of the literature and inform further
507 research into maternal stress and early brain development.

508

509 **Acknowledgements**

510

511 We would like to acknowledge the contributions of our participants and their families,
512 without whom this work would not have been possible. We would also like to thank the staff
513 involved in data collection.

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800

801 **Supporting Information**

802 **S1 Supplement.** Supporting information.

803 **S2 File.** T-stat maps

804 **S3 Dataset.** De-identified research dataset.

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