**Supplemental Data**

**Supplemental Methods.**

**Study enrollment.**

**Cohort 1**. Healthy pregnantwomen, ages 18 - 35, were recruited at the Universidade Federal de São Paulo (UNIFESP). Infant-women dyads presenting with any of the following were excluded: maternal diagnosis of schizophrenia or bipolar disorder, history of brain injury with loss of consciousness, history of neurosurgery, intellectual disability, need of neonatal intensive care/treatment, active suicidal ideation, multiparous, or substance use disorder. All pregnancies were deemed low risk by the obstetrical service. All infants were at least 37 weeks’ gestation at birth, newborns had an Apgar index above 7, and none had serious perinatal complications (e.g., extended neonatal ICU stay, congenital anomalies) as determined by a study physician.

**Cohort 2.**Healthy pregnant women, ages 18–45 years, were recruited at Columbia University Irving Medical Center (CUIMC). Women were excluded if they acknowledged smoking or use of recreational drugs, lacked fluency in English or were multiparous, or had major medical complications as determined by the CUIMC obstetrical service. All infants were at least 36 weeks’ gestation at birth, and none had serious perinatal complications (e.g., extended neonatal ICU stay, congenital anomalies) as determined by a study physician.

**Excluded Participants due to Prenatal SSRI Exposure.** A total 16 mother-infant dyads with usable MRI data were excluded from the present analyses due to women using SSRIs during pregnancy.Excluded and included dyads differed in medication use, socioeconomic status, birth type, gestational age, and maternal age at birth (see Table S1). Importantly, no differences in maternal childhood maltreatment were detected.

**Harmonization of SES indicators:** In Cohort 1, SES was indexed using the Brazilian Socioeconomic Scale (ABEP), a widely used and official categorization system for SES stratification in Brazil. In Cohort 2, mothers reported on household income. Data was harmonized by creating a three-level categorical variable. This well-established Brazilian socioeconomic scale ABEP1 was used to define SES classes: low (E and D classes), middle (C and B classes), and high (A class ) groups. The ABEP scale is the conventional and official way to stratify socioeconomic status in Brazil.

|  |
| --- |
| Socio Economic Status (Brazilian Reais R$)\* |
| D-E    (R$ 0-639.78) |
| C2      (R$ 640 -1,446.24) |
| C1      (R$ 1,447-2,409.01) |
| B1-B2 (R$ 2,410-8,695.88) |
| A     (R$ 8,696-20,272.56) |

We thus created three comparable categories to match to Cohort 2 data as displayed bellow:

The three categories included:

|  |
| --- |
| **Socioeconomic class** |
| **1: $0–25,000 or D-E** |
| **2: $25,001–100,000 or C2, C1, B2, B1** |
| **3: $100,001+ or A** |

**Data Acquisition, Preprocessing, and Harmonization.**

Structural and diffusion MRIs were acquired on 3T whole-body scanners (Cohort 1: Philips 3T Achieva scanner; 8-channel head coil; Cohort 2: MR 750; GE Healthcare; 8-channel head coil). In the case of an infant waking up, scans were paused and only resumed when the infant fell back asleep. Although pulse sequence protocols lasted ~45 minutes, MRI sessions took around two hours to accommodate infants waking up. To ensure acquisition of high-quality data, scans were repeated if motion was detected during the scan. MRI analyses were conducted on the single run from each modality with the least amount of head motion.

MR pulse sequences were as follows: **Cohort 1:** for T2-weighted structural images: voxel size 1 × 1 × 1 mm3, dimensions 222 × 256 × 256, FOV 160mm, TR/TE 3000/260 ms, flip angle 90 degrees; and for diffusion MRI: voxel size 1.75 × 1.75 × 1.75 mm3; dimensions 128 x 128 x 70; FOV 224 mm; slices 70, TR/TE 10816/100ms, flip angle 90 degrees, and 1 images without diffusion weighting (b0) and 32 images with diffusion weighting along non-collinear directions (b=1000 s m−2); **Cohort 2:** for T2-weighted structural images: PROPELLER (Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction) sequence, voxel size 0.74 × 0.74 × 1 mm3, dimensions 256 x 256 x 108, FOV 190mm, TR/TE 11832/100 ms, flip angle 142 degrees; and for diffusion MRI: voxel size 0.74 × 0.74 × 2 mm3; dimensions 256 × 256 × 56; FOV 190 mm; slices 50, TR/TE 8000/83.4ms, flip angle 90 degrees, and 3 images without diffusion weighting (b0) and 11 images with diffusion weighting along non-collinear directions (b=600 s m−2).

First, trained researchers (TR, NW), blind to group status, visually examined for all subjects every T2 image and every DWI volume for severe artifacts. The Developing Human Connectome Project (dHCP) pipeline was used to segment T2-weighted images and estimate brain volumes. The dHCP pipeline is a fully automated cortical surface-based processing pipeline developed specifically for segmenting the developing neonatal brain. It was developed and validated with a large (n=465) sample of infants (28 - 45 weeks post-menstrual age at scan) and is one of the most frequently used pipelines for this age group2. Within the dHCP pipeline, images are first rescaled, N4 bias corrected, and brain-extracted with FSL’s bet. The pipeline then utilizes an expectation maximization algorithm called Draw-EM to segment the preprocessed image, using a spatial prior term and an intensity model of the image. The resulting segmentation produces 87 distinct regions which are merged to create tissue labels, as well as white matter and pial surface masks for both hemispheres. Following segmentation white matter, pial, and midthickness surfaces are generated from an extracted white-matter mesh. Finally, the white matter surface is inflated and projected onto a sphere, from which cortical structure measures can be estimated. Of the 87 ROIs estimated, the following ROIs were examined due to their relevance in prior early adversity research: bilateral amygdala, hippocampus, caudate and anterior cingulate cortex (ACC). Total brain volume, as well as gray and white matter volumes were examined to maximize overlap with prior research.3 Of note, total brain volume was not included as a covariate in analyses examining volumetric differences. Our analyses controlled for infant weight at scan, which was highly correlated with total brain volume (*r = .658; p <.001*) and total gray matter volume (*r = .698; p <.001*). Thus, to avoid issues with collinearity we did not include total brain volume in analyses.

Whereas a number of regions and networks have been associated to early childhood adversity4, fewer studies have examined which regions and connectivity that could be impacted by intergenerational transmission of adversity in neonates. Further, many of the commonly implicated regions (e.g., anterior insula, ventral medial PFC) and networks (e.g., salience network) may not be reliably examined in this age groups as the existing neonatal atlases may not feature such subregions and may be poorly defined at this developmental period5.”

dMRI images were first visually inspected to identify bad volumes, which were removed prior to any processing. Definite guidelines for infant data processing are not yet available. Overall, 98.27% (±4.03) of volumes were retained in analyses (cohort 1, 99.20% ±42.26; cohort 2, 96.24% ±5.93). Only 2 infants had volume retention rates under 80% (2 subjects from cohort 1, each had 7 volumes censored = 78.79% of volumes retained). Importantly, there were no differences between child maltreatment groups in percentage of volumes retained (CM+ = 98.19±3.21; CM- = 98.32±4.43; *F*(2, 12) = 0.21, *p* < .886. Images were then processed using the following MRtrix pipeline6. Preprocessing included denoising, de-Gibbs ringing, and motion/eddy current correction with eddy\_cuda9.17. Brain extraction was performed with FSL’s BET8 on the mean b=0 image, and bias correction for the whole image was performed with ANTS N4ITK9. Images were resampled to 0.875 mm isotropic to improve tensor fitting. We then estimated fiber orientation distributions (FOD) from the preprocessed data using multi-shell multi-tissue constrained spherical deconvolution, and log-domain intensity normalizing. Probabilistic tractography was performed by taking the second-order integration over the FODs (iFOD2). We used the anatomically constrained tractography (ACT10) framework to generate a target streamline count of 5 million. The 5TT (five-tissue-type) image used during this step is created from the dHCP segmentation. Streamline counts were the connectivity metric chosen as our outcome variable. A prior macaque study suggests the validity of streamline counts as an indicator of fiber connection strength, with the number of streamlines significantly correlating with tract-tracing strength in the macaque brain11.

Tractograms were then filtered using the SIFT12 algorithm down to 1 million streamlines. To generate connectivity matrices, we made a node image. To create the node image, we first used ANTS to warp the dHCP segmentation2 to the UNC AAL13 atlas and further parcellate the frontal, occipital, and parietal lobes. As the AAL atlas has a finer parcellation in those regions, we further subdivide the large dHCP regions with the AAL labels, generating an additional 56 regions, details are published elsewhere5. This resulted in a total of 143 ROIs (87 ROIs from the original dHCP plus 56 new ROIs). Streamline counts were then defined as the number of SIFT-filtered streamlines that pass between a given pair of ROIs. With 143 ROIs, this resulted in 10153 connections per subject.

To further ensure that the connections examined in our analyses were robustly measured and estimated, only connections for which 90% of sample showed a value of 10 or more streamline counts were included in our analyses. This was done as a visual examination revealed that for some of our tracts of interest (e.g., bilateral subcortical connectivity: right amygdala to left hippocampus), many subjects had 0 estimated fiber counts, raising questions about whether these tracts were robustly developed in neonates. Although this threshold is admittedly arbitrary, to date no threshold specific to neonatal probabilistic tractography exists. A total of 30 connections met both our inclusion criteria: (1) 90% of sample showed a value of 10 or more streamline counts for said connection, and (2) connection being part of frontostriatal or frontoparietal circuity. We tested lower alternative thresholds (80% and 70% of sample) and did not find any differences in the connections included/excluded.

Finally, once volumetric estimates and streamline counts were generated, ComBat was used to account for differences between scanning sites (scanner model and head coil). ComBat is a harmonization tool originally developed for the removal of batch-effect in genomics, which has become a standard tool in multi-site MR research due to its success in removing unwanted variation introduced by MR scanners while preserving biological variability14,15. To ensure no systematic differences attributable to site, scanner, or pulse sequence remained in the data, site differences in connectivity, volumetric, and principal component data were tested. Analyses (Table S3) revealed only one white connectivity variable (L ACC-R mid ORB) differed between the cohorts (Cohort 1 showed slightly higher connectivity), however this difference was no longer significant when we controlled for multiple comparisons.

**CBCL.**

Mothers reported on children’s behaviors through follow-up assessments using the Child Behavior Checklist (CBCL). The somatic complaints, attention problems, aggressive behaviors, internalizing problems, and externalizing problems T- scores from the parent-report CBCL were included in analyses. Children were 3-7 years old at the time of the assessment, thus both the preschool (1.5-5 years16) and school-age (6-18 years17) versions of the CBCL were used. Bivariate partial correlations examined associations between brain components and the CBCL T-scores, controlling for child’s age at the CBCL assessment and are presented in the main text. Fully adjusted models, controlling for all the study covariates (maternal age, pre-pregnancy BMI, prenatal medication use, infant sex, weight at scan, gestational age at delivery, birth type, SES, study site, prenatal maternal distress and alcohol, substance, and tobacco use) also yielded a significant relationship between intra-hemispheric fronto-limbic connectivity and somatic complaints on the CBCL for male offspring (rmale = 0.773, pmale = .015, nmale = 13; Table 3). This association was not significant for female offspring (rfemale = -0.120, pfemale = .726, nfemale = 17) or when analyses combined both sexes. No other significant associations emerged.

**Supplemental Analyses.**

An alternative prenatal maternal distress variable was created to test whether considering depressive and anxiety symptomatology instead of disorders impacted study results. Weighted linear regressions (including the study covariates detailed in the hypothesis testing section of the manuscript) were re-run with a new alternative prenatal maternal distress variable that only included mothers with a depression and/or anxiety diagnosis on the MINI (Cohort 1). Results did not change for intra-hemispheric fronto-limbic connectivity; the sex X CTQ interaction remained significant, and the male-specific effect was consistent and remained significant (*b*= 1.02 & *p*= .005, compared to *b*= 0.96 & *p*= .008 with the original prenatal distress variable). However, the main effect of CTQ on right ACC– left PFC connectivity was mitigated and no longer statistically significant (*b*= -0.37 & *p=* 0.11, compared to *b*= -0.47 & *p*= 0.044 with the original variable). Of note, the main effect on right ACC– left PFC connectivity was similarly mitigated in the models that did not control for perinatal distress and alcohol/substance, suggesting that this higher threshold for perinatal maternal distress may miss subthreshold distress.

Table S1. Comparison of Demographic Variables Between Excluded and Included Subjects

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Included dyads** | **Excluded dyads** | **Test Statistic (df)** | ***p* value** |
| **(n = 92)** | **(n = 16)** |
| **Infant sex** |  |  | *Χ2* (1) = 0.235 | 0.628 |
| **Male** | n=40; 38% | n=8; 7% |  |  |
| **Female** | n=52; 48% | n=8; 7% |  |  |
| **Infant weight at scan (grams)** | 3798.054 ± 662.332 | 4004.473 ± 890.896 | *F* (1,105) = 1.128 | 0.291 |
| **Infant gestational age at scan (weeks)** | 40.054 ± 1.637 | 38.705 ± 1.003 | *F* (1,105) = 10.152 | 0.002 |
| **Postmenstrual age at scan (weeks)** | 42.494 ± 2.553 | 43.520 ± 2.966 | *F* (1,105) = 2.086 | 0.687 |
| **Maternal age** | 29.038 ± 6.014 | 32.800 ± 4.411 | *F* (1,105) = 5.374 | 0.152 |
| **Birth type** |  |  | *Χ2* (2) = 2.692 | 0.260 |
| **C-section** | n=34, 31% | n=5, 5% |  |  |
| **Vaginal delivery** | n=55, 51% | n=7, 6% |  |  |
| **Other (forceps, induced, etc.)** | n=3, 3% | n=4, 4% |  |  |
| **Socioeconomic class** |  |  | *Χ2* (2) = 34.569 | 0.001 |
| **1: $0–25,000 or D-E** | n=24, 22% | n=1, 1% |  |  |
| **2: $25,001–100,000 or C2, C1, B2, B1** | n=58, 54% | n=3, 3% |  |  |
| **3: $100,001+ or A** | n=10, 9% | n=12, 11% |  |  |
| **Maternal prenatal BMI** | 25.719 ± 5.438 | 23.406 ± 5.0424 | *F* (1,105) = 2.511 | 0.116 |
| **Prenatal medication use1** |  |  | *Χ2* (1) = 40.880 | 0.000 |
| **Yes** | n=18, 17% | n=16, 15% |  |  |
| **No** | n=74, 68% | n=0, 0% |  |  |
| **Prenatal alcohol, substance, and tobacco use** |  |  | *Χ2* (1) = 0.248 | 0.618 |
| **Yes** | n=18, 17% | n=4, 4% |  |  |
| **No** | n=74, 68% | n=12, 11% |  |  |
| **Prenatal maternal distress** |  |  | *Χ2* (1) = 0.315 | 0.574 |
| **Yes** | n=28, 26% | n=6, 6% |  |  |
| **No** | n=64, 59% | n=10, 9% |  |  |
| **Childhood Maltreatment** |  |  | *Χ2* (1) = 0.044 | 0.834 |
| **Yes** | n=32, 30% | n=6, 6% |  |  |
| **No** | n=60, 55% | n=10, 9% |  |  |

Notes: BMI = body mass index. 1All prenatal SSRI users were excluded from study, medications included allergy medications and such.

Table S2. Impact of Alternative Prenatal Distress Measure on Reported Effects

|  |  |  |  |
| --- | --- | --- | --- |
| **Component** | **Main effect CM** | **Main effect Sex** | **Sex X CM Interaction** |
| *b* [95% CI] | *b* [95% CI] | *b* [95% CI] |
| **Models controlling for original prenatal distress measure** | | | | |
| Volumetric | 0.15 [-0.23, 0.53] | -0.72 [-1.08, -0.35]\*\*\* | -0.35 [-1.07, 0.36] |
| Interhemispheric fronto-limbic connectivity | 0.35 [-0.16, 0.87] | -0.40 [-0.90, 0.09] | -1.14 [-2.06, -0.21]\* |
| Right ACC connectivity | -0.47 [-0.92, -0.01]\* | -0.07 [-0.51, 0.36] | 0.16 [-0.68, 1.01] |
| Left ACC connectivity | 0.19 [-0.29, 0.67] | 0.07 [-0.39, 0.53] | 0.29 [-0.60, 1.18] |
| Subcortical connectivity | -0.07 [-0.49, 0.36] | 0.44 [0.04, 0.85] | -0.30 [-1.09, 0.49] |
| **Models controlling for alternative prenatal distress measure** | | | | |
| Volumetric | 0.10 [-0.27, 0.47] | -0.75 [-1.11, -0.39]\*\*\* | -0.36 [-1.07, 0.35] |
| Interhemispheric fronto-limbic connectivity | 0.40 [-0.10, 0.90] | -0.38 [-0.86, 0.10] | -1.14 [-2.06, -0.22]\* |
| Right ACC connectivity | -0.37 [-0.82, 0.08] | 0.00 [-0.43, 0.43] | 0.18 [-0.67, 1.03] |
| Left ACC connectivity | 0.18 [-0.28, 0.64] | 0.04 [-0.40, 0.48] | 0.24 [-0.64, 1.12] |
| Subcortical connectivity | -0.09 [-0.50, 0.32] | 0.39 [0.00, 0.78] | -0.37 [-1.15, 0.41] |

Table S3. Site differences in connectivity, volumetric, and principal component data

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Brain variables** | **Cohort 1** *m* *(SD)* | **Cohort 2** *m* *(SD****)*** | ***p*** | ***p- FDR corrected*** |
| L hippo-L amy | 64.064 (52.042) | 69.147 (60.761) | 0.700 | 0.860 |
| R hippo-L amy | 75.456 (47.049) | 92.708 (69.005) | 0.231 | 0.837 |
| L hippo- L ant FUSI | 552.982 (273.202) | 544.616 (270.077) | 0.892 | 0.903 |
| L amy-L ant FUSI | 105.752 (55.585) | 111.104 (80.879) | 0.749 | 0.860 |
| R hippo-R ant FUSI | 684.535 (344.624) | 786.489 (342.299) | 0.194 | 0.837 |
| R amy- R ant FUSI | 122.934 (78.034) | 154.044 (95.574) | 0.134 | 0.837 |
| R ACC-R sup ORB | 314.808 (116.265) | 321.882 (152.047) | 0.826 | 0.900 |
| R ACC-R mid ORB | 311.615 (114.655) | 300.997 (161.824) | 0.753 | 0.860 |
| R ACC-R inf ORB | 267.041 (124.832) | 289.339 (141.289) | 0.472 | 0.837 |
| R ACC-R med ORB | 694.396 (211.798) | 754.433 (230.872) | 0.243 | 0.837 |
| R ACC-R dor SFG | 1282.235 (488.861) | 1254.537 (671.748) | 0.844 | 0.900 |
| R ACC-R med SFG | 2010.704 (536.377) | 2084.070 (717.641) | 0.628 | 0.837 |
| L ACC-L sup ORB | 382.808 (139.439) | 342.905 (147.987) | 0.230 | 0.837 |
| L ACC-L mid ORB | 232.19 (100.154) | 220.043 (108.719) | 0.615 | 0.837 |
| L ACC-L inf ORB | 248.748 (131.928) | 229.272 (164.073) | 0.580 | 0.837 |
| L ACC-L med ORB | 375.585 (180.027) | 402.952 (210.525) | 0.550 | 0.837 |
| L ACC-L dor SFG | 1227.774 (387.187) | 1194.427 (469.223) | 0.741 | 0.860 |
| L ACC-L med SFG | 1475.263 (640.105) | 1681.701 (814.345) | 0.237 | 0.837 |
| R ACC-L sup ORB | 44.844 (31.052) | 50.175 (32.316) | 0.463 | 0.837 |
| R ACC-L mid ORB | 47.490 (31.673) | 52.107 (33.777) | 0.540 | 0.837 |
| R ACC-L inf ORB | 39.709 (30.603) | 45.868 (33.982) | 0.412 | 0.837 |
| R ACC-L med ORB | 36.580 (32.321) | 52.763 (45.308) | 0.092 | 0.837 |
| R ACC-L dor SFG | 126.234 (69.841) | 124.206 (75.206) | 0.903 | 0.903 |
| R ACC-L med SFG | 98.317 (49.280) | 105.139 (57.240) | 0.584 | 0.837 |
| L ACC-R sup ORB | 29.776 (18.782) | 25.712 (21.199) | 0.384 | 0.837 |
| L ACC-R mid ORB | 35.707 (21.157) | 23.277 (24.360) | 0.023 | 0.837 |
| L ACC-R inf ORB | 27.249 (20.928) | 22.115 (27.958) | 0.385 | 0.837 |
| L ACC-R med ORB | 38.288 (25.932) | 41.310 (26.018) | 0.609 | 0.837 |
| L ACC-R dor SFG | 73.605 (39.742) | 74.944 (45.415) | 0.893 | 0.903 |
| L ACC-R med SFG | 46.521 (29.523) | 49.978 (31.263) | 0.621 | 0.837 |
| L hippo Vol | 778.268 (115.379) | 764.077 (103.665) | 0.562 | 0.837 |
| R hippo Vol | 862.979 (142.855) | 877.669 (124.446) | 0.621 | 0.837 |
| L amy Vol | 481.543 (59.794) | 490.504 (68.841) | 0.551 | 0.837 |
| R amy Vol | 539.149 (69.881) | 532.852 (79.256) | 0.717 | 0.860 |
| L ACC Vol | 2775.476 (464.008) | 2577.752 (566.078) | 0.109 | 0.837 |
| R ACC Vol | 2960.699 (449.782) | 2924.674 (397.800) | 0.703 | 0.860 |
| L caudate Vol | 1987.936 (251.321) | 1915.148 (261.126) | 0.218 | 0.837 |
| R caudate Vol | 1922.123 (260.962) | 1843.151 (235.585) | 0.158 | 0.837 |
| cortical GM Vol | 171673.792 (24937.995) | 168336.813 (21484.009) | 0.517 | 0.837 |
| subcortical GM Vol | 29735.885 (2700.898) | 28985.422 (3065.546) | 0.266 | 0.837 |
| GM Vol | 201416.311 (27213.631) | 197313.130 (24245.158) | 0.475 | 0.837 |
| WM Vol | 157298.051 (15498.627) | 153485.713 (17169.065) | 0.316 | 0.837 |
| TIV | 396686.943 (43720.000) | 387387.064 (43060.401) | 0.346 | 0.837 |
| Principal Component 1 | 0.074 (1.002) | -0.154 (0.996) | 0.317 | 0.837 |
| Principal Component 2 | 0.019 (0.901) | -0.040 (1.196) | 0.813 | 0.900 |
| Principal Component 3 | -0.085 (0.831) | 0.175 (1.281) | 0.325 | 0.837 |
| Principal Component 4 | 0.097 (0.969) | -0.202 (1.049) | 0.202 | 0.837 |
| Principal Component 5 | -0.099 (1.011) | 0.204 (0.962) | 0.176 | 0.837 |

Notes. L= left, R= right, GM= gray matter, Vol = volume, TIV = total intracranial volume.

Table S4. Component loadings

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Individual brain variables** | **Principal components** | | | | |
| **1: Volumetric** | **2: Intra-hemispheric fronto-limbic connectivity** | **3: R ACC – L PFC connectivity** | **4: L ACC – R PFC connectivity** | **5: Subcortical connectivity** |
| L hippo-L amy | - | - | - | - | - |
| R hippo-L amy | - | - | - | - | - |
| L hippo- L ant FUSI | - | - | - | - | 0.60 |
| L amy-L ant FUSI | - | - | - | - | - |
| R hippo-R ant FUSI | - | - | - | - | 0.58 |
| R amy- R ant FUSI | - | - | - | - | 0.66 |
| R ACC-R sup ORB | - | - | - | - | - |
| R ACC-R mid ORB | - | 0.69 | - | - | - |
| R ACC-R inf ORB | - | 0.79 | - | - | - |
| R ACC-R med ORB | - | - | - | - | - |
| R ACC-R dor SFG | - | 0.69 | - | - | - |
| R ACC-R med SFG | - | - | - | - | - |
| L ACC-L sup ORB | - | - | - | - | - |
| L ACC-L mid ORB | - | 0.85 | - | - | - |
| L ACC-L inf ORB | - | 0.85 | - | - | - |
| L ACC-L med ORB | - | - | - | - | - |
| L ACC-L dor SFG | - | - | - | - | - |
| L ACC-L med SFG | - | - | - | - | - |
| R ACC-L sup ORB | - | - | 0.74 | - | - |
| R ACC-L mid ORB | - | - | 0.71 | - | - |
| R ACC-L inf ORB | - | - | 0.66 | - | - |
| R ACC-L med ORB | - | - | 0.77 | - | - |
| R ACC-L dor SFG | - | - | 0.60 | - | - |
| R ACC-L med SFG | - | - | 0.72 | - | - |
| L ACC-R sup ORB | - | - | - | 0.81 | - |
| L ACC-R mid ORB | - | - | - | 0.76 | - |
| L ACC-R inf ORB | - | - | - | 0.52 | - |
| L ACC-R med ORB | - | - | - | 0.57 | - |
| L ACC-R dor SFG | - | - | - | - | - |
| L ACC-R med SFG | - | - | - | 0.54 | - |
| L hippo Vol | 0.66 | - | - | - | - |
| R hippo Vol | 0.66 | - | - | - | - |
| L amy Vol | 0.56 | - | - | - | - |
| R amy Vol | 0.64 | - | - | - | - |
| L ACC Vol | 0.63 | - | - | - | - |
| R ACC Vol | 0.81 | - | - | - | - |
| L caudate Vol | 0.77 | - | - | - | - |
| R caudate Vol | 0.76 | - | - | - | - |
| cortical GM Vol | 0.93 | - | - | - | - |
| subcortical GM Vol | 0.89 | - | - | - | - |
| GM Vol | 0.94 | - | - | - | - |
| WM Vol | 0.87 | - | - | - | - |
| TIV | 0.97 | - | - | - | - |

Notes. Component loadings were thresholded at 0.5 to maximize interpretability. L= left, R= right, GM= gray matter, Vol = volume, TIV = total intracranial volume.

Table S5. Associations between maternal childhood maltreatment and individual measures of newborn brain volume and white matter connectivity

|  |  |  |  |
| --- | --- | --- | --- |
| **Individual brain variables** | **Males** | **Females** | **Sex X CM Interaction** |
| *β* [95% CI] | *β* [95% CI] | *β* [95% CI] |
| TIV | 17930.42 [-4878.91,40739.76] | 2246.07 [-19167.5,23659.64] | -15684.35 [-45862.53,14493.83] |
| Gray Matter | -3817.02 [-7779.61,145.57] | -786.02 [-4446.22,2874.18] | 3031.00 [-2163.54,8225.54] |
| Cortical GM | -3616.58 [-7630.78,397.63] | -727.30 [-4435.17,2980.57] | 2889.27 [-2372.92,8151.47] |
| Subcortical GM | -204.04 [-1108.42,700.33] | -62.75 [-898.11,772.60] | 141.29 [-1044.24,1326.82] |
| White Matter | 2132.42 [-2330.38,6595.23] | 562.81 [-3559.43,4685.05] | -1569.62 [-7419.88,4280.65] |
| L hippocampus | 37.86 [-29.31,105.02] | -14.18 [-76.22,47.86] | -52.04 [-140.08,36.01] |
| R hippocampus | 38.38 [-40.32,117.08] | -11.73 [-84.42,60.97] | -50.11 [-153.28,53.06] |
| L Amygdala | 12.30 [-22.42,47.02] | 2.95 [-29.12,35.01] | -9.36 [-54.87,36.16] |
| R Amygdala | 8.95 [-33.91,51.81] | -19.37 [-58.96,20.22] | -28.32 [-84.51,27.87] |
| L ACC | -280.91 [-517.96,-43.87]\*\* | -56.93 [-275.88,162.03] | 223.98 [-86.76,534.72] |
| R ACC | -300.70 [-473.59,-127.81]\* | -89.53 [-249.22,70.17] | 211.17 [-15.46,437.81] |
| L Caudate | 18.56 [-113.36,150.47] | 23.39 [-98.46,145.24] | 4.83 [-168.1,177.76] |
| R Caudate | 52.5 [-72.47,177.46] | -40.32 [-155.75,75.11] | -92.82 [-256.63,71] |
| L hippo-L Amy | 19.93 [-14.71,54.58] | 0.11 [-32.62,32.83] | -19.83 [-66,26.35] |
| R hippo-R Amy | 2.29 [-29.53,34.1] | -22.65 [-52.7,7.4] | -24.94 [-67.35,17.47] |
| L hippo-L ant FUS | 133.78 [-47.93,315.48] | -39.04 [-210.67,132.59] | -172.81 [-415.02,69.39] |
| L Amy-L ant FUS | 59.47 [14.35,104.59]\* | -22.62 [-65.23,20] | -82.09 [-142.23,-21.95]\*\* |
| R hippo-R ant FUS | 18.48 [-198.29,235.26] | 147.79 [-56.96,352.54] | 129.31 [-159.63,418.25] |
| R Amy-R ant FUS | -25.88 [-77.55,25.8] | 11.11 [-37.69,59.92] | 36.99 [-31.89,105.87] |
| R ACC-L dor SFG | -31.72 [-75.36,11.92] | 3.82 [-37.4,45.04] | 35.54 [-22.63,93.71] |
| L ACC-L dor SFG | -47.35 [-322.86,228.17] | 31.38 [-228.86,291.61] | 78.73 [-288.52,445.97] |
| R ACC-R dor SFG | 499.12 [105.03,893.21]\* | -63.02 [-435.25,309.22] | -562.13 [-1087.43,-36.84]\* |
| L ACC-R dor SFG | 25.75 [-0.15,51.65] | -0.79 [-25.25,23.68] | -26.53 [-61.06,7.99] |
| R ACC-L sup ORB | -18.99 [-39.03,1.04] | -4.99 [-23.91,13.94] | 14.00 [-12.7,40.71] |
| L ACC-L sup ORB | 8.62 [-81.97,99.22] | -18.50 [-104.07,67.07] | -27.13 [-147.88,93.63] |
| R ACC-R sup ORB | 36.26 [-47,119.52] | -110.92 [-189.57,-32.28]\* | -147.19 [-258.17,-36.21]\* |
| L ACC-R sup ORB | -8.21 [-20.93,4.51] | -1.13 [-13.14,10.89] | 7.08 [-9.87,24.04] |
| R ACC-L mid ORB | -4.29 [-25.09,16.5] | -7.81 [-27.45,11.83] | -3.52 [-31.23,24.2] |
| L ACC-L mid ORB | 67.41 [-4.39,139.21] | -6.02 [-73.83,61.8] | -73.43 [-169.13,22.28] |
| R ACC-R mid ORB | 108.20 [17.03,199.36]\* | -22.43 [-108.53,63.68] | -130.62 [-252.14,-9.11]\* |
| L ACC-R mid ORB | 1.99 [-13,16.98] | 8.75 [-5.41,22.91] | 6.76 [-13.22,26.74] |
| R ACC-L inf ORB | -3.07 [-23.58,17.45] | -12.65 [-32.02,6.73] | -9.58 [-36.92,17.77] |
| L ACC-L inf ORB | 130.67 [30.53,230.81]\* | -30.86 [-125.45,63.72] | -161.53 [-295.01,-28.05]\* |
| R ACC-R inf ORB | 19.39 [-61.02,99.79] | -16.69 [-92.64,59.25] | -36.08 [-143.26,71.09] |
| L ACC-R inf ORB | 12.69 [-3.16,28.54] | 16.32 [1.35,31.29]\* | 3.63 [-17.5,24.76] |
| R ACC-L med SFG | -7.02 [-40.13,26.1] | -24.13 [-55.41,7.14] | -17.12 [-61.25,27.02] |
| L ACC-L med SFG | 342.27 [-84.28,768.82] | -123.55 [-526.44,279.34] | -465.82 [-1034.37,102.73] |
| R ACC-R med SFG | -266.97 [-631.01,97.07] | 43.03 [-300.83,386.88] | -31.00 [-175.24,795.23] |
| L ACC-R med SFG | 14.70 [-4.96,34.36] | 9.15 [-9.42,27.72] | -5.55 [-31.75,20.65] |
| R ACC-L med ORB | -2.98 [-27.06,21.11] | -14.44 [-37.19,8.31] | -11.46 [-43.56,20.64] |
| L ACC-L med ORB | 7.98 [-100.29,116.25] | -66.16 [-168.43,36.1] | -74.14 [-218.46,70.18] |
| R ACC-R med ORB | -121.16 [-256.39,14.06] | -90.73 [-218.46,36.99] | 30.43 [-149.81,210.67] |
| L ACC-R med ORB | 0.00 [-17.99,17.99] | 7.41 [-9.58,24.41] | 7.41 [-16.57,31.39] |

Notes. CM= Childhood maltreatment, β- standardized coefficient, CI- confidence interval, TIV- total intracranial volume, GM- gray matter, L- left, R- right, ACC- anterior cingulate cortex. \*\*\* p < .001, \*\* p < .01, \*p < .05.

Table S6. Comparison of Study Variables Between the Two Cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Cohort 1** | **Cohort 2** | **Test Statistic (df)** | ***p* value** |
| **(n = 29)** | **(n = 63)** |
| **Infant sex** |  |  | *Χ2* (1) = 0.031 | 0.859 |
| **Male** | n=13; 14% | n=27; 29% |  |  |
| **Female** | n=16; 17% | n=36; 10% |  |  |
| **Infant weight at scan (grams)** | 3466.207 ± 570.306 | 3953.272 ± 648.924 | *F* (1,90) = 11.990 | 0.001 |
| **Infant gestational age at birth (weeks)** | 39.598 ± 1.282 | 39.364 ± 1.218 | *F* (1,90) = 0.756 | 0.387 |
| **Postmenstrual age at scan (weeks)** | 41.667 ± 1.520 | 42.850 ± 2.821 | *F* (1,90) = 4.205 | 0.043 |
| **Maternal age** | 27.721 ± 6.075 | 29.653 ± 5.934 | *F* (1,90) = 2.063 | 0.154 |
| **Birth type** |  |  | *Χ2* (2) = 2.241 | 0.326 |
| **C-section** | n=13; 14% | n=21; 24% |  |  |
| **Vaginal delivery** | n=16; 17% | n=39; 42% |  |  |
| **Other (forceps, induced, etc)** | n=0; 0% | n=3; 3% |  |  |
| **Socioeconomic class** |  |  | *Χ2* (2) = 8.484 | 0.014 |
| **1: $0–25,000 or D-E** | n=5; 5% | n=19; 21% |  |  |
| **2: $25,001–100,000 or C2, C1, B2, B1** | n=24; 26% | n=34; 37% |  |  |
| **3: $100,001+ or A** | n=0; 0% | n=10;11% |  |  |
| **Group** |  |  | *Χ2* (1) = .002 | 0.967 |
| **CM+** | n=10; 11% | n=22; 24% |  |  |
| **CM-** | n=18; 21% | n=41; 45% |  |  |
| **Maternal prenatal BMI** | 23.657 ± 3.502 | 26.635 ± 5.900 | *F* (1,90) = 6.146 | 0.015 |
| **Prenatal medication use1** |  |  | *Χ2* (1) = 6.990 | 0.008 |
| **Yes** | n=1; 1% | n=17; 18% |  |  |
| **No** | n=29; 30% | n=46; 50% |  |  |
| **Prenatal alcohol, substance, and tobacco use** |  |  | *Χ2* (1) = 3.540 | 0.060 |
| **Yes** | n=9; 10% | n=9; 10% |  |  |
| **No** | n=20; 22% | n=54; 58% |  |  |
| **Prenatal maternal distress** |  |  | *Χ2* (1) = 0.162 | 0.687 |
| **Yes** | n=8; 9% | n=20; 22% |  |  |
| **No** | n=21; 23% | n=42; 47% |  |  |
| **CBCL somatic complaints** | 59.429 ± 8.848 | 53.517 ± 5.145 | *F* (1,34) = 5.523 | 0.025 |
| **CBCL attention problems** | 56.143 ± 9.703 | 53.379 ± 5.454 | *F* (1,34) = 1.048 | 0.313 |
| **CBCL aggressive behaviors** | 62.429 ± 9.449 | 52.793 ± 4.387 | *F* (1,34) = 16.566 | 0.001 |
| **CBCL internalizing problems** | 64.143 ± 10.961 | 47.241 ± 9.527 | *F* (1,34) = 16.789 | 0.001 |
| **Child externalizing problems** | 60.857 ± 9.974 | 47.448 ± 9.372 | *F* (1,34) = 11.280 | 0.002 |

Notes: CM = childhood maltreatment, BMI = body mass index. 1All prenatal SSRI users were excluded from study, medications included allergy medications and such.

Table S7. Comparison of Study Variables Between Male and Female Offspring

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Males** | **Females** | **Test Statistic (df)** | ***p* value** |
| **(n = 40)** | **(n = 52)** |
| **Infant weight at scan (grams)** | 3896.997 ± 717.529 | 3723.846 ± 614.357 | *F* (1,90) = 1.532 | 0.219 |
| **Infant gestational age at birth (weeks)** | 39.399 ± 1.258 | 39.461 ± 1.110 | *F* (1,90) = 0.062 | 0.806 |
| **Postmenstrual age at scan (weeks)** | 42.62 ± 3.472 | 42.399 ± 1.555 | *F* (1,90) = 1.163 | 0.687 |
| **Maternal age** | 29.287 ± 6.068 | 28.842 ± 6.024 | *F* (1,90) = 0.121 | 0.728 |
| **Birth type** |  |  | *Χ2* (2) = 1.992 | 0.369 |
| **C-section** | n=18; 20% | n=16; 18% |  |  |
| **Vaginal delivery** | n=21; 23% | n=34; 36% |  |  |
| **Other (forceps, induced, etc)** | n=1; 1% | n=2; 2% |  |  |
| **Socioeconomic class** |  |  | *Χ2* (2) = 0.208 | 0.901 |
| **1: $0–25,000 or D-E** | n=10; 11% | n=14; 15% |  |  |
| **2: $25,001–100,000 or C2, C1, B2, B1** | n=25; 28% | n=33; 36% |  |  |
| **3: $100,001+ or A** | n=5; 5% | n=5; 5% |  |  |
| **Group** |  |  | *Χ2* (1) = .230 | 0.631 |
| **CM+** | n=15; 16% | n=17; 18% |  |  |
| **CM-** | n=25; 28% | n=35; 38% |  |  |
| **Cohort** |  |  | *Χ2* (1) = .031 | 0.859 |
| **Cohort 1** | n=27; 29% | n=36; 39% |  |  |
| **Cohort 2** | n=13; 14% | n=16; 18% |  |  |
| **Maternal prenatal BMI** | 25.777 ± 5.118 | 25.673 ± 5.726 | *F* (1,90) = 0.008 | 0.929 |
| **Prenatal medication use1** |  |  | *Χ2* (1) = 0.387 | 0.534 |
| **Yes** | n=9; 10% | n=9; 10% |  |  |
| **No** | n=31; 33% | n=43; 47% |  |  |
| **Prenatal alcohol, substance, and tobacco use** |  |  | *Χ2* (1) = 0.009 | 0.927 |
| **Yes** | n=8; 9% | n=10; 11% |  |  |
| **No** | n=32; 35% | n=42; 45% |  |  |
| **Prenatal maternal distress** |  |  | *Χ2* (1) = 0.3.64 | 0.056 |
| **Yes** | n=8; 9% | n=20; 21% |  |  |
| **No** | n=32; 35% | n=32; 35% |  |  |
| **Volumetric component** | 0.453 ± 1.103 | -0.353 ± 0.75 | *F* (1,90) = 16.812 | 0.001 |
| **Interhemispheric fronto-limbic connectivity** | 0.134 ± 1.067 | -0.105 ± 0.942 | *F* (1,90) = 1.252 | 0.226 |
| **Right ACC connectivity** | -0.065 ± 0.986 | 0.051 ± 1.018 | *F* (1,90) = 0.293 | 0.590 |
| **Left ACC connectivity** | 0.033 ± 1.088 | -0.026 ± 0.936 | *F* (1,90) = 0.073 | 0.787 |
| **Subcortical connectivity** | -0.187 ± 1.012 | 0.146 ± 0.976 | *F* (1,90) = 2.459 | 0.120 |
| **CBCL somatic complaints** | 51.938 ± 3.838 | 56.850 ± 7.155 | *F* (1,34) = 6.111 | 0.019 |
| **CBCL attention problems** | 51.063 ± 1.806 | 56.200 ± 7.804 | *F* (1,34) = 6.614 | 0.0.15 |
| **CBCL aggressive behaviors** | 53.813 ± 4.505 | 55.350 ± 8.184 | *F* (1,34) = 0.453 | 0.505 |
| **CBCL internalizing problems** | 47.688 ± 8.897 | 52.800 ± 13.481 | *F* (1,34) = 1.702 | 0.201 |
| **Child externalizing problems** | 49.500 ± 7.563 | 50.500 ± 12.984 | *F* (1,34) = 0.074 | 0.787 |

Notes: CM = childhood maltreatment, BMI = body mass index. 1All prenatal SSRI users were excluded from study, medications included allergy medications and such.

Table S8. Comparison of Study Variables Between Offspring with and without CBCL assessments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **With CBCL** | **Without CBCL** | **Test Statistic (df)** | ***p* value** |
| **(n = 36)** | **(n = 56)** |
| **Infant weight at scan (grams)** | 3976.69 ± 747.95 | 3681.13 ± 577.36 | *F* (1,90) = 4.502 | 0.0371 |
| **Infant gestational age at birth (weeks)** | 39.55 ± 1.18 | 39.36 ± 1.17 | *F* (1,90) = 0.601 | 0. 440 |
| **Postmenstrual age at scan (weeks)** | 42.84 ± 1.63 | 42.27 ± 2.99 | *F* (1,90) = 1.077 | 0. 302 |
| **Maternal age** | 28.24 ± 5.43 | 29.53 ± 6.35 | *F* (1,90) = 0.989 | 0.323 |
| **Baby sex** |  |  | *Χ2* (2) = 0.022 | 0.881 |
| **Male** | n=16; 17% | n=24; 26% |  |  |
| **Female** | n=20; 22% | n=32; 35% |  |  |
| **Birth type** |  |  | *Χ2* (2) = 1.167 | 0.558 |
| **C-section** | n=11; 12% | n=23; 25% |  |  |
| **Vaginal delivery** | n=24; 26% | n=31; 34% |  |  |
| **Other (forceps, induced, etc)** | n=1; 1% | n=2; 2% |  |  |
| **Socioeconomic class** |  |  | *Χ2* (2) = 2.675 | 0.262 |
| **1: $0–25,000 or D-E** | n=12; 13% | n=12; 13% |  |  |
| **2: $25,001–100,000 or C2, C1, B2, B1** | n=19; 21% | n=39; 43% |  |  |
| **3: $100,001+ or A** | n=5; 5% | n=5; 5% |  |  |
| **Group** |  |  | *Χ2* (1) = 0.440 | 0.507 |
| **CM+** | n=14; 15% | n=18; 20% |  |  |
| **CM-** | n=22; 24% | n=38; 41% |  |  |
| **Cohort** |  |  | *Χ2* (1) = 3.996 | 0.046 |
| **Cohort 1** | n=29; 31% | n=34; 37% |  |  |
| **Cohort 2** | n=7; 8% | n=22; 24% |  |  |
| **Maternal prenatal BMI** | 24.15 ± 3.85 | 28.12 ± 6.58 | *F* (1,90) = 13.205 | 0.001 |
| **Prenatal medication use1** |  |  | *Χ2* (1) = 2.535 | 0.111 |
| **Yes** | n=10; 11% | n=8; 9% |  |  |
| **No** | n=26; 28% | n=48; 52% |  |  |
| **Prenatal alcohol, substance, and tobacco use** |  |  | *Χ2* (1) = 1.211 | 0.271 |
| **Yes** | n=5; 5% | n=13; 14% |  |  |
| **No** | n=31; 34% | n=43; 47% |  |  |
| **Prenatal maternal distress** |  |  | *Χ2* (1) = 0.235 | 0.628 |
| **Yes** | n=12; 13% | n=16; 17% |  |  |
| **No** | n=24; 26% | n=40; 44% |  |  |

**Figure S1. Scree plot**

![A picture containing chart

Description automatically generated]()

Scree plot shows percent of the variance (eigenvalue) across connectivity and volumetric measures explained by components. Five components explaining 55% of the variance were selected.

**Figure S2.**



An overall effect of CM was detected in right ACC– left PFC connectivity (shown in red), such that infants in the CM+ group showed lower values in connectivity relative to infants in the CM- group (*b*=-0.47, *p*=0.044, [95%CI -0.92 – -0.01]). Interestingly, in a model without prenatal distress and alcohol, substance, and tobacco use, the effect of CM was no longer significant. Further analysis suggests that this may be a result of opposing mediational processes. Specifically, the direct effect of CM on right ACC – left PFC connectivity (shown in blue), while the indirect effect through prenatal maternal distress is marginally positive (shown in blue); thus, when prenatal maternal distress is not included in the model the opposing processes lead to a diminished overall effect.

References Cited

1. Dutra-Thome L, Koller SH, McWhirter EH, McWhirter B. Application of the Future Expectation Scale for Adolescents (FESA) in Brazil/Aplicacao da Escala de Expectativas Futuras para Adolescentes (FESA) no Brasil. *Psicologia: Reflexao & Critica* 2015; **28**: 331+.

2. Makropoulos A, Robinson EC, Schuh A, et al. The developing human connectome project: A minimal processing pipeline for neonatal cortical surface reconstruction. *Neuroimage* 2018; **173**: 88-112.

3. Moog NK, Entringer S, Rasmussen JM, et al. Intergenerational Effect of Maternal Exposure to Childhood Maltreatment on Newborn Brain Anatomy. *Biol Psychiatry* 2018; **83**(2): 120-7.

4. McLaughlin KA, Weissman D, Bitrán D. Childhood Adversity and Neural Development: A Systematic Review. *Annu Rev Dev Psychol* 2019; **1**: 277-312.

5. Wang Y, Hinds W, Duarte CS, et al. Intra-session test-retest reliability of functional connectivity in infants. *bioRxiv* 2020: 2020.06.25.169524.

6. Tournier JD, Smith R, Raffelt D, et al. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *Neuroimage* 2019; **202**: 116137.

7. Andersson JL, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage* 2003; **20**(2): 870-88.

8. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002; **17**(3): 143-55.

9. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med Imaging* 2010; **29**(6): 1310-20.

10. Smith RE, Tournier JD, Calamante F, Connelly A. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. *Neuroimage* 2012; **62**(3): 1924-38.

11. van den Heuvel MP, de Reus MA, Feldman Barrett L, et al. Comparison of diffusion tractography and tract-tracing measures of connectivity strength in rhesus macaque connectome. *Hum Brain Mapp* 2015; **36**(8): 3064-75.

12. Smith RE, Tournier JD, Calamante F, Connelly A. SIFT: Spherical-deconvolution informed filtering of tractograms. *Neuroimage* 2013; **67**: 298-312.

13. Shi F, Yap P-T, Wu G, et al. Infant brain atlases from neonates to 1- and 2-year-olds. *PLoS One* 2011; **6**(4): e18746-e.

14. Johnson WE, Li C, Rabinovic A. Adjusting batch effects in microarray expression data using empirical Bayes methods. *Biostatistics* 2007; **8**(1): 118-27.

15. Fortin J-P, Parker D, Tunç B, et al. Harmonization of multi-site diffusion tensor imaging data. *Neuroimage* 2017; **161**: 149-70.

16. Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms and profiles: Burlington, VT: University of Vermont, Research center for children, youth …; 2000.

17. Achenbach TM, Rescorla L. Manual for the ASEBA school-age forms & profiles: An integrated system of multi-informant assessment: Aseba Burlington, VT:; 2001.