The Effects of Prenatal Exposure to Neighborhood Crime on Neonatal Functional Connectivity

Supplemental Information

fMRI Processing Pipeline

Resting-state fMRI data were preprocessed through a standard neonatal BOLD preprocessing pipeline using a combination of FSL tools (1) and the 4dfp tool suite (ftp://imaging.wustl.edu/pub/raichlab/4dfp_tools/; 2). BOLD timeseries data were corrected for intensity differences due to interleaved acquisition and debanded. Rigid body motion within BOLD runs was corrected using linear realignment. Images were bias field corrected and normalized to whole brain mode 1000. Time series data were corrected for readout distortion and linearly registered to 711-2N Talairach atlas space as: BOLD→individual T2w or pseudo-T2w→cohort-specific T2w atlas→711-2N Talairach atlas, with linear registrations performed in a single step. Atlas registered BOLD timeseries were mapped to subject-specific surfaces using methods adapted from Marcus et al., 2013 (3) and Marcus et al., 2011 (4). Frame censoring was performed so that only data with at least three consecutive frames with frame displacement (FD) < 0.25 mm were used. Each BOLD run was demeaned, detrended, and regressed for nuisance waveforms including: white matter, ventricular and extra-axial cerebrospinal fluid (CSF), whole brain, and the 24-Friston motion parameters. Data were then bandpass filtered (0.005-0.1 Hz) to remove non-BOLD frequencies and spatially smoothed. This process is also described and validated in Sylvester et al. (*Under Review*).

Timing of Exposure within Pregnancy

The main results of this paper demonstrate that living in a high crime area during pregnancy is associated with altered frontolimbic connectivity within the neonatal brain; however, it is unclear whether the timing of exposure within pregnancy is important. One potential way to answer this question is to examine mothers that moved during pregnancy. Out of the 319 mothers included in the fMRI analysis, 87% (n = 278) had addresses at multiple timepoints. Of those mothers, 74% did not move during pregnancy (n = 207), 25% moved once during pregnancy (n = 69), and less than 1% of mothers moved more than once (n = 2). First, we examined whether mothers moved into areas with significantly different crime rates. We found that mothers who moved once (n=69) did not move into areas with significantly different crime rates, regardless of when they moved during pregnancy. The Skillings-Mack statistic, which is a non-parametric equivalent to a repeated measures ANOVA that accounts for non-balanced groups (5), was 4.2 (p = .24) for the block-group levels of violent crime and was 5.4 (p = .14) for block-group levels of property crime. The sample size of mothers who moved more than once during pregnancy (n=2) was not sufficient for statistical tests. Given that mothers did not move between neighborhoods with significantly different crime rates, the timing of the relationship between neighborhood crime exposure within pregnancy and neonatal brain function could not be assessed.

Additional Adversity Controls

Childhood Lead Levels

There is a known relationship between childhood lead exposure in an area and subsequent levels of violent crime (6). As such, lead may be an important environmental toxin

and confounding variable in the analysis of neighborhood crime and neonatal brain function. The authors sought to address this by including lead levels in the analysis; however, it was not possible to obtain pregnant women's blood lead levels, either directly in the study or by using public health datasets. As a proxy, data on childhood lead levels for children ages 0-5 years at the census-track level was obtained from the Missouri Department of Health and Senior Services (7). Data at the census tract level was downloaded from MOPHIMS Environmental Public Health Tracking Program Lead Level, with a confidentiality suppression if there were between 1-9 elevated or total tests per census tract. A calculated variable representing the percentage of lead tests with an elevated blood lead level > 5 μg/dL (number of elevated blood tests / total number of lead tests) per census tract from 2017-2019 was used in all analyses.

There were 254 mothers living in census tracts with lead data from the Missouri of Public Health, 217 of which had fMRI data. As expected, the percentage of elevated lead tests was related to violent crime levels ($R^2 = .28$, $p < .001$), but not property crime levels ($R^2 < .001$, $p=.62$). The percentage of elevated lead tests was also related to mother's advantage composite scores ($R^2 = .14$, $p < .001$), but not psychosocial stress scores ($R^2 = .002$, $p = .442$). When the percentage of elevated lead levels was added to the model predicting neonatal brain function using violent crime and advantage scores, violent crime continued to predict neonatal brain function connectivity between thalamus-aDMN (*Table S3*). The connectivity between the amygdala-hippocampus missed the threshold for statistical significant ($p = .057$; *Table S3*). The percentage of elevated lead levels was not a significant predictor for the investigated neonatal functional connections (*Table S3*).

Direct Exposure to Crime

Prior studies examining the relationships between crime exposure and brain function in children and adolescents have used survey measures of crime exposure (8–12). Unfortunately, this study did not contain a comparable survey measure of crime exposure time-locked to pregnancy. Mothers completed the Stress and Adversity Inventory (STRAIN) during pregnancy; however, this survey assesses lifetime exposures (13). Despite this limitation, we assessed two variables from the STRAIN as additional controls. The first is a measure that addresses difficulties in the crime/legal domain and the second is a measure that assesses instances of physical danger. The legal/crime domain of the STRAIN was not related to either violent or property crime exposure during pregnancy ($p = .90$ and $p = .87$, respectively). The physical danger domain of the STRAIN was related to property crime exposure ($p = .03$), but not violent crime exposure ($p = .14$). When the STRAIN physical danger domain was added to the model predicting neonatal brain function using property crime and advantage scores, property crime continued to predict neonatal brain function connectivity between the thalamus-aDMN (*Table S4*). The STRAIN physical danger domain was not a significant predictor for the investigated neonatal functional connections (*Table S4*).

Full Term Analysis

Given differences in preterm and full term brain development, including in thalamocortical areas, we investigated whether our results replicated in full-term infants born between 36-41 weeks (mean = 38.5) gestational age (14–18). For this analysis, the sample consisted of 271 infants, 55% of whom were male (n=150), who had an MRI scan between 38- and 45-weeks gestational age (mean = 41.3). The results were largely unchanged when focusing

the analyses on full-term infants. Violent crime was related to functional connectivity between the Amygdala-aDMN (β = -.21, p = .001), Thalamus-aDMN (β = -.22, p < .001), and Thalamus-aFPN (β = -.16, p = .01), but was not significantly related to Amygdala-Hippocampus (β = -.11, p = .076). When controlling for other forms of adversity, violent crime only contributed significant variance to the Thalamus-aDMN (β = -.16, p = .02), with Amygdala-Hippocampus (β= -.14, p = .058) and Amygdala-DMN (β = -.13, p = .059) missing the threshold for statistical significance. Property crime was related to Thalamus-aDMN, after controlling for adversity (β=-.15, p=.008).

Analysis Excluding Marijuana Use

Given the potential confound of marijuana use during pregnancy, we investigated whether our results replicated when excluding mothers who self-reported marijuana use and/or had exposure significant enough to result in a positive urine drug screen. For this analysis, the sample consisted of 239 infants, 56% of whom were male (n=133), who had an MRI scan between 37- and 45-weeks gestational age (mean = 41.2). The results were mostly unchanged when excluding subjects with marijuana use. In line with the results of the manuscript, property crime was related to Thalamus-aDMN, after controlling for adversity (β = -.15, p = .008). Violent crime was related to functional connectivity between the Amygdala-Hippocampus (β = -.17, p = .01), Thalamus-aDMN (β = -.22, p = .001), and Thalamus-aFPN (β = -.21, p = .002), but not the Amygdala-aDMN (β = -.11, p = .10). When controlling for adversity, violent crime contributed additional variance to the Amygdala-Hippocampus and Thalamus-aDMN over and above other forms of adversity (β = -.19, p = .02 and β = -.16, p = .03), as in the main analyses.

Types of Crime Exposure

We tested whether the relationships between property crime and brain function were significantly different from the relationships between violent crime and brain function. Specifically, we used the Z-test described in Paternoster et al. 1998 (equation #4) to test the differences between standardized beta values for the models relating crime to brain function, controlling for adversity (19). We tested whether violent crime (β = -.16, SE = .07) was more related to amygdala-hippocampus connectivity than property crime (β = -.06, SE = .06), when we controlled for covariates and adversity in both models. This difference was non-significant with a Z value of 1.09 and a p-value of .27.

Differentiation of Subcortical ROIs

Given that subcortical structures in neonates are small and in close proximity to one another, we wanted to ensure that our observed association between violent crime exposure during pregnancy and amygdala-hippocampus connectivity was not due to overlapping BOLD signal between the two structures. We compared functional connectivity between the hippocampus and the rest of the brain (subcortical structures and cortical networks) with functional connectivity between the amygdala and the rest of the brain. In this analysis, we found that the hippocampus-brain connectivity was largely distinct from the amygdala-brain connectivity (*Table S5*). The only associations that did not significantly differ between the thalamus and amygdala were with the Temporal Network, Posterior Fronto-parietal Network, and the Cerebellum (*Table S5*), none of which were investigated in the neighborhood crime analysis. These results indicate that amygdala and hippocampus are separable in neonatal resting-state functional MRI analyses. Comparisons are also displayed in *Figure S4*.

Supplemental References

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Figure S1. Neonatal Functional Brain Networks

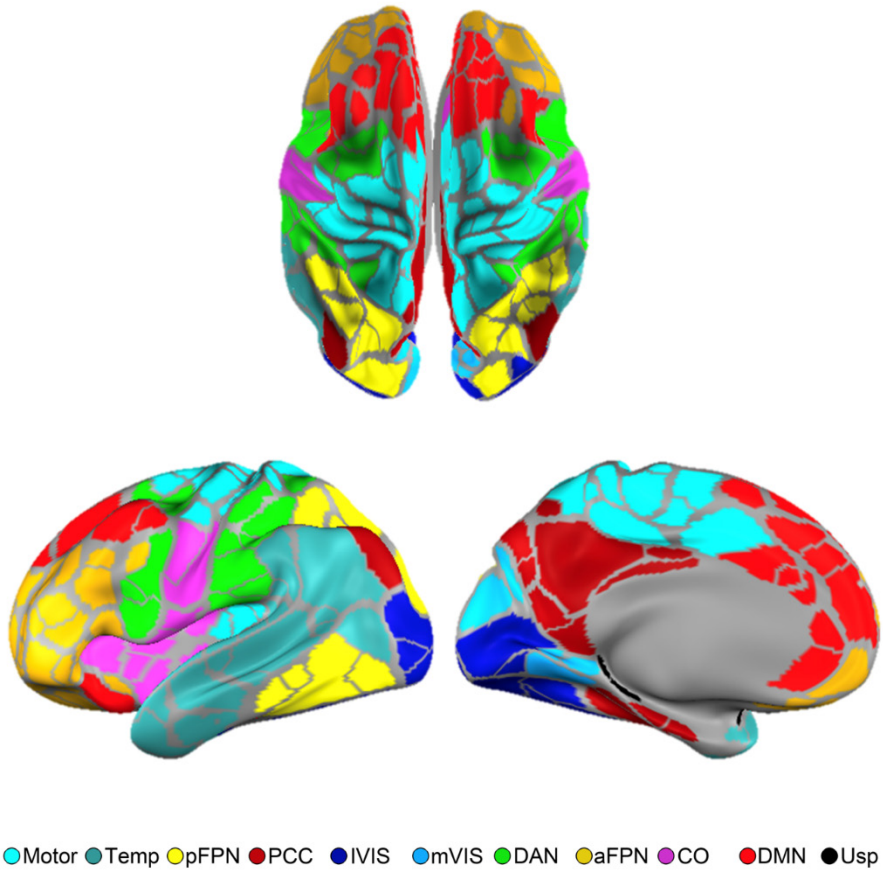


Figure S1 displays the neonatal brain network solution containing 11 neonatal networks based on InfoMap, a community detection algorithm. Abbreviations: Temp – Temporal Network; pFPN – Posterior Frontal Parietal Network; PCC – Posterior Cingulate Cortex Network; lVIS – Lateral Visual Network; mVIS – Medial Visual Network; DAN – Dorsal Attention Network; aFPN – Anterior Frontal Parietal Network; CO – Cingulo-opercular Network; DMN – Default Mode Network; Usp – Unspecified. The PCC and DMN are referred to as the posterior DMN and anterior DMN, respectively, in the manuscript.

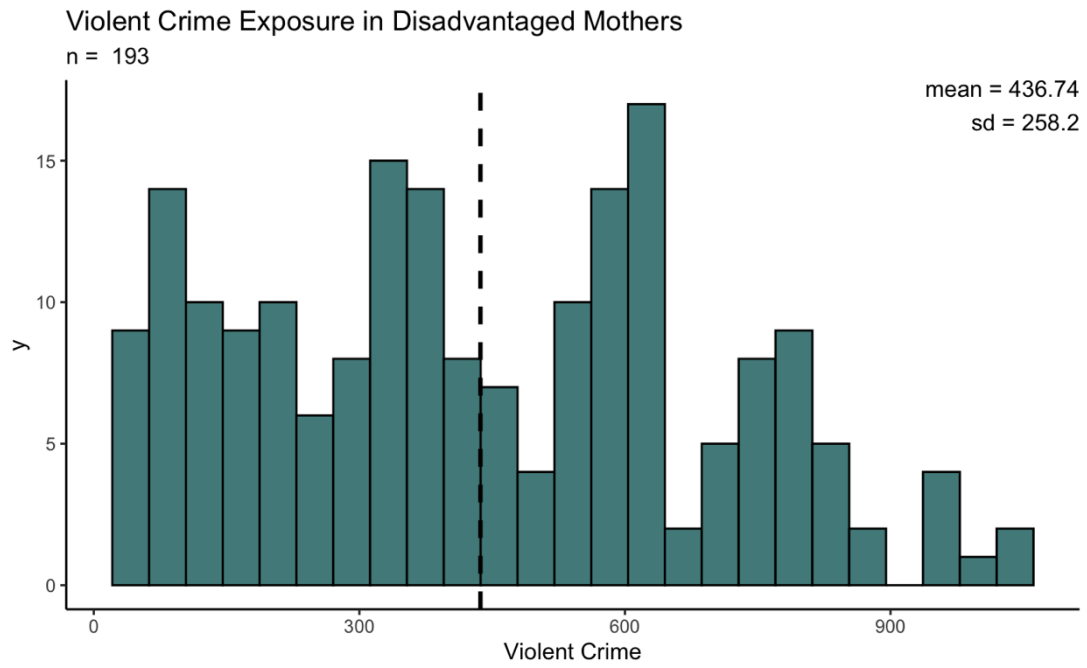
Table S1. Crime-fc Screening Correlations

	Violent Crime		Property Crime	
fMRI Regions of Interest	r	p	r	p
aFPN_vs_aFPN	0.10	0.19	0.11	0.31
CO_vs_aFPN	0.03	0.68	-0.09	0.36
CO_vs_CO	-0.08	0.34	0.05	0.62
DMN_vs_aFPN	0.07	0.35	0.08	0.41
DMN_vs_CO	-0.03	0.69	-0.06	0.54
DMN_vs_DMN	-0.04	0.68	-0.02	0.95
Thal_vs_aFPN	-0.17	0.02	-0.10	0.31
Thal_vs_CO	-0.02	0.77	0.02	0.95
Thal_vs_DMN	-0.24	0.00	-0.20	0.01
Thal_vs_Thal	-0.13	0.05	-0.02	0.95
Hipp_vs_aFPN	-0.04	0.68	-0.09	0.36
Hipp_vs_CO	0.03	0.68	0.01	0.97
Hipp_vs_DMN	-0.09	0.24	-0.09	0.36
Hipp_vs_Thal	-0.03	0.68	0.00	0.97
Hipp_vs_Hipp	-0.01	0.91	0.03	0.95
Amyg_vs_aFPN	-0.10	0.20	-0.10	0.31
Amyg_vs_CO	-0.04	0.68	0.00	0.97
Amyg_vs_DMN	-0.19	0.01	-0.11	0.31
Amyg_vs_Thal	-0.14	0.05	-0.03	0.95
Amyg_vs_Hipp	-0.13	0.05	-0.07	0.54
Amyg_vs_Amyg	-0.15	0.04	0.00	0.97
Motor_vs_Motor	-0.06	0.44	-0.02	0.95
DMN_vs_Motor	-0.05	0.59	-0.05	0.62

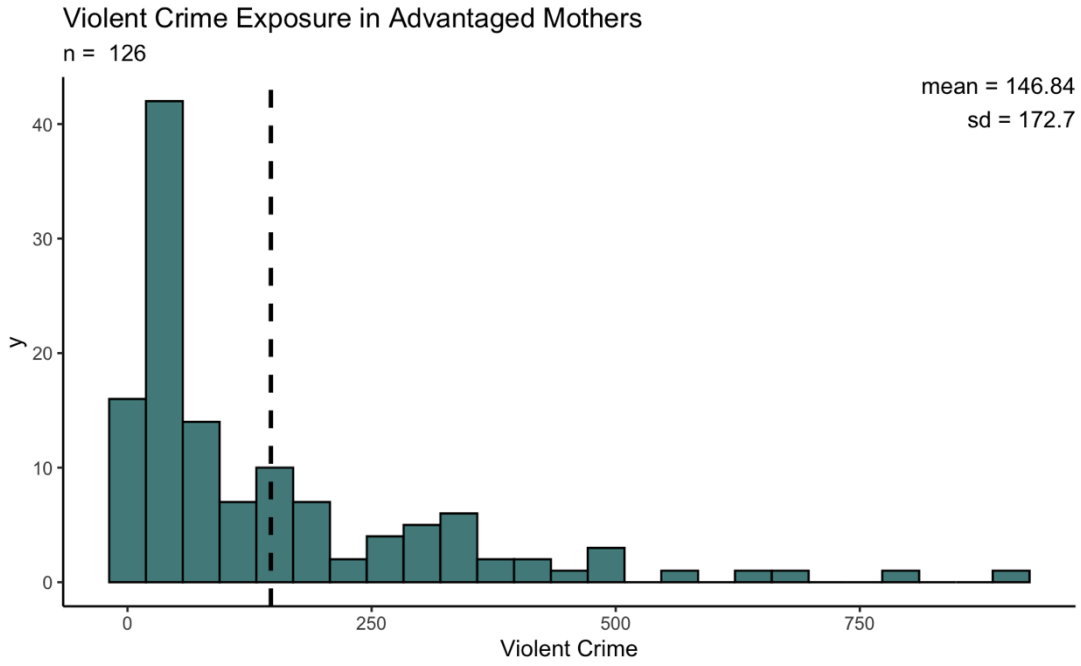
Bi-variate correlations between the frontolimbic fMRI regions of interest and violent crime (columns 2 and 3) and property crime (columns 4 and 5). P values are FDR corrected.

Figure S2. Crime and Adversity by Disadvantage Status

A.



B.



Mothers who are socioeconomically disadvantaged (advantage score <0) are spread between safe and dangerous neighborhoods (Panel A) whereas mothers who are socioeconomically advantaged (advantage score >0) are concentrated in safe neighborhoods (Panel B).

Table S2. Negative Controls for Crime-fc Relationships

	Motor-Motor		**DMN-Motor**		**Motor-Motor**		**DMN-Motor**	
Predictors	*std. Beta*	*p*	*std. Beta*	*p*	*std. Beta*	*p*	*std. Beta*	*p*
Intercept	-0.00	0.095	-0.00	0.733	-0.00	0.077	-0.00	0.884
PMA at Scan	-0.06	0.356	0.01	0.893	-0.06	0.325	0.00	0.969
GA at Birth	0.19	**0.002**	-0.11	0.070	0.19	**0.002**	-0.12	0.054
Property Crime	-0.02	0.727	-0.06	0.312				
Violent Crime					-0.04	0.458	-0.07	0.209
Observations	319		319		319		319	
R^2 / R^2 adjusted	0.032 / 0.023		0.014 / 0.005		0.034 / 0.024		0.016 / 0.007	

Table S3. Violent Crime, Neonatal FC, Advantage, and Lead Levels

	Amgydala-Hippocampus		**Amygdala-aDMN**		**Thalamus-aDMN**		**Thalamus-aFPN**	
Predictors	*std. Beta*	*p*	*std. Beta*	*p*	*std. Beta*	*p*	*std. Beta*	*p*
Intercept	0.00	0.053	0.00	0.587	-0.00	0.239	-0.00	0.103
Violent Crime	-0.16	0.057	-0.12	0.146	-0.22	**0.007**	-0.10	0.204
GA at Scan	-0.12	0.100	0.14	0.056	0.13	0.084	0.19	**0.012**
GA at Birth	0.11	0.139	-0.10	0.144	-0.03	0.722	-0.09	0.228
Advantage	-0.03	0.703	0.16	**0.044**	0.08	0.290	0.10	0.189
Lead Levels	-0.02	0.835	-0.02	0.820	0.05	0.490	-0.00	0.953
Observations	217		217		217		217	
R^2 / R^2 adjusted	0.041 / 0.018		0.089 / 0.067		0.085 / 0.063		0.074 / 0.052	

Table S4. Property Crime, Neonatal FC, Advantage, and Physical Danger

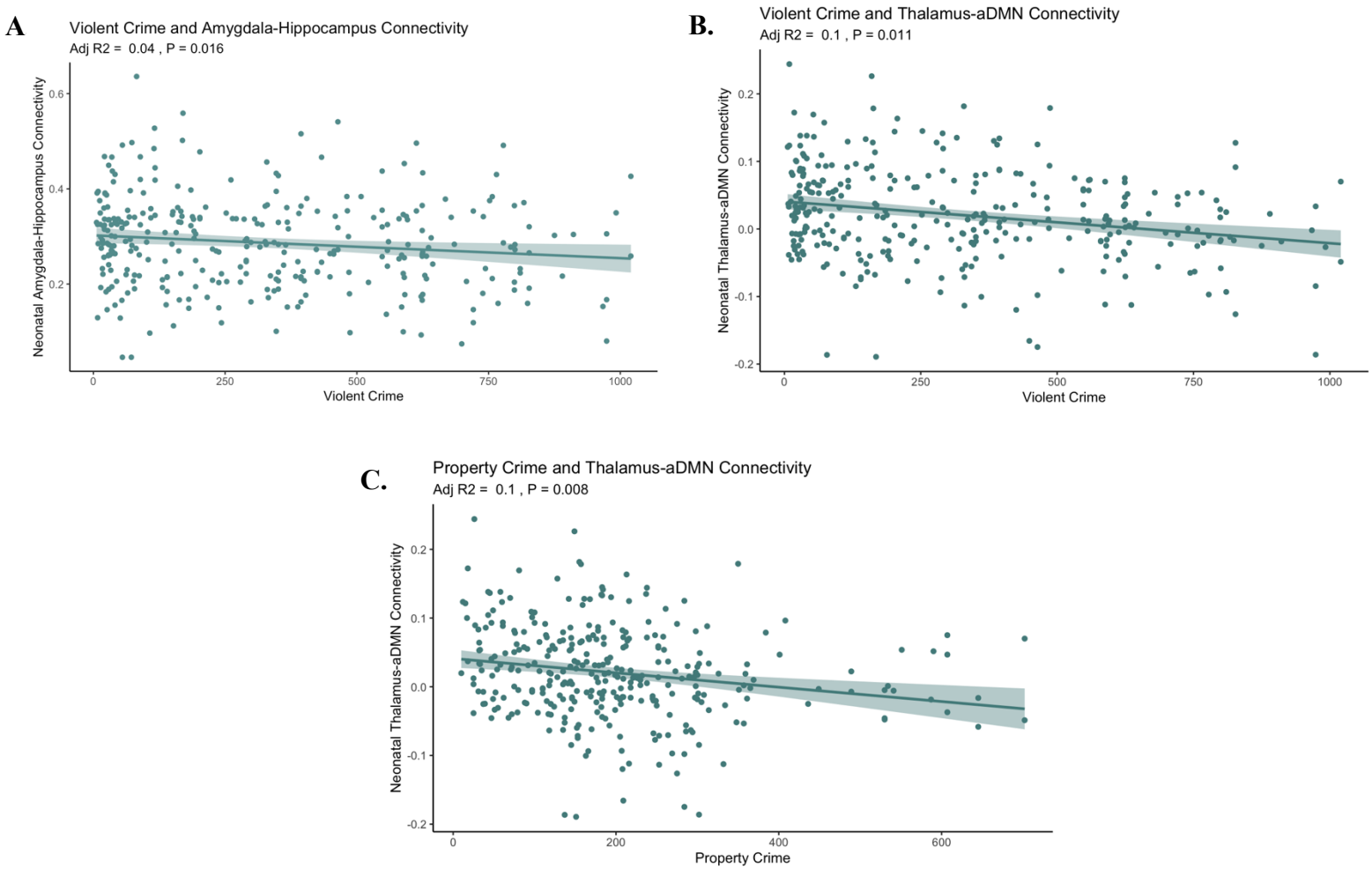
	Thalamus-aDMN	
Predictors	*std. Beta*	*p*
Intercept	0.00	**0.004**
Property Crime	-0.13	**0.019**
GA at Scan	0.23	**<0.001**
GA at Birth	-0.05	0.364
Advantage	0.18	**0.003**
STRAIN Physical Danger	-0.00	0.943
Observations	302	
R^2 / R^2 adjusted	0.128 / 0.113	

Table S5. Distinctions between Amygdala and Thalamic Functional Connectivity

	Amygdala Connectivity	Hippocampal Connectivity	T-Statistic
Motor	0.01	-0.02	-12.2***
Temporal Lobe	0.01	0.01	-0.04
Posterior Frontoparietal	-0.07	-0.07	-1.84
Posterior Cingulate Cortex	-0.03	0.05	34.3***
Lateral Visual	-0.04	-0.03	8.37***
Medial Visual	-0.02	0.04	24.8***
Dorsal Attention	-0.019	-0.05	-16.1***
Anterior Frontoparietal	-0.013	-0.02	-3.48***
Cingulo-opercular	0.14	0.09	-15.3***
Default Mode	0.016	0.003	-4.72***
Unspecified	0.12	0.18	18.6***
Thalamus	0.20	0.17	-5.54***
Caudate	0.20	0.12	-15.9***
Putamen	0.22	0.11	-22.1***
Globus Pallidus	0.20	0.11	-17.8***
Hippocampus	0.29	0.44	20.1***
Amygdala	0.35	0.29	-8.54***
Cerebellum	0.09	0.09	-0.97

This table shows that the contrast between the amygdala's functional connections (Fisher z-transformed Pearson correlations) to a variety of brain networks and regions (listed in column 1) and the thalamus' functional connections to those same brain regions. Columns two and three display the mean functional connectivity for the 319 eLABE subjects included in primary analyses. Significant differences between the mean functional connectivity in columns two and three are displayed in column four. ***p < .001, **p < .01, *p <.05.

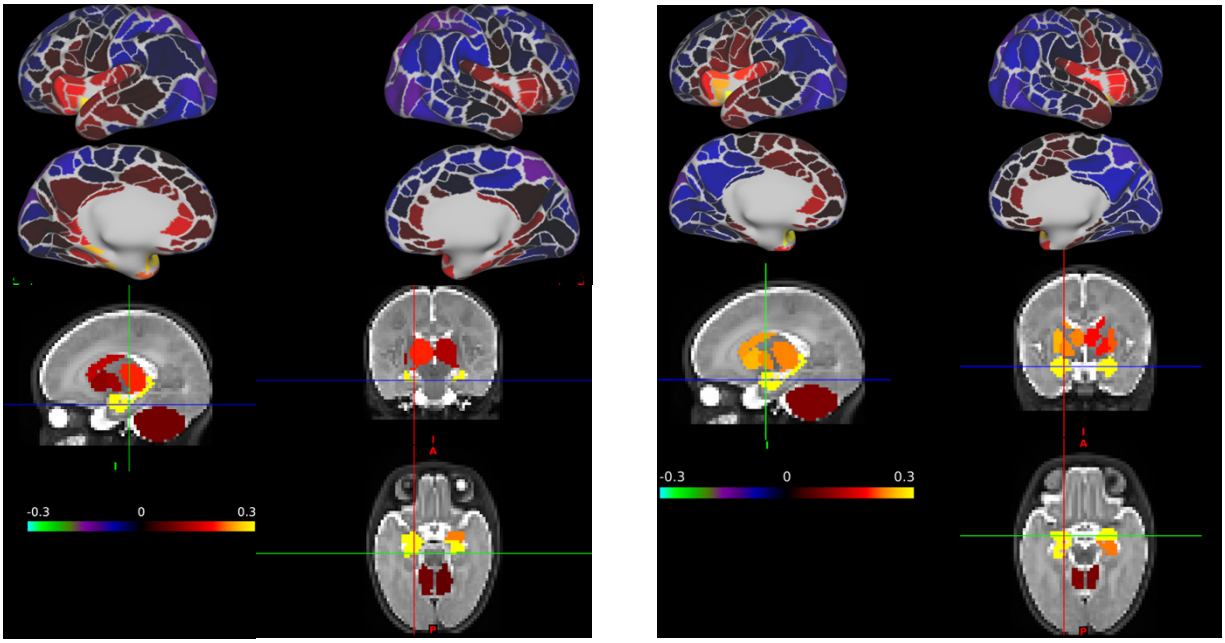
Figure S3. Prenatal neighborhood crime exposure and neonatal brain function



Scatter plots represent the associations between violent crime (top row) or property crime (bottom row) with the neonatal frontolimbic connections that remained significant after controlling for adversity and correcting for multiple comparisons. The Adjusted R2 values on each plot represents the R-squared value for the linear model controlling for gestational age at birth, postmenstrual age at scan, and advantage. The p-value represents the significance level of the coefficients for violent crime and property crime, respectively.

Figure S4. Comparisons of Average Brain-Wide FC for the Thalamus and Amygdala

A. Hippocampal Connectivity B. Amygdala Connectivity



Panel A shows average, z-scored hippocampus connectivity with the rest of the brain, including cortical regions (top) and subcortical regions (bottom). Panel B shows average, z-scored amygdala connectivity with the rest of the brain, including cortical regions (top) and subcortical regions (bottom).