Objective: Children exposed to severe, chronic stress are vulnerable to mental and physical health problems across the lifespan. To explain how these problems develop, the neuroimmune network hypothesis suggests that early-life stress initiates a positive feedback loop between peripheral inflammatory cells and networked brain regions involved in threat and reward processing. The authors sought to test this hypothesis by studying a sample of urban children from diverse socioeconomic backgrounds.

Methods: The authors examined the basic predictions of the neuroimmune network hypothesis in 207 children (mean age = 13.9 years, 63% female; 33% Black; 30% Hispanic), focusing on poverty as a stressor. The children had fasting blood drawn to quantify five inflammatory biomarkers—C-reactive protein, tumor necrosis factor-α, and interleukins-6, -8, and -10—which were averaged to form a composite score. Children also completed two functional MRI tasks, which measured amygdala responsivity to angry facial expressions and ventral striatum responsivity to monetary rewards.

Results: Poverty status and neural responsivity interacted statistically to predict inflammation. Among children living in poverty, amygdala threat responsivity was positively associated with inflammation, and the same was true for ventral striatum responsivity to reward. As children’s socioeconomic conditions improved, these brain-immune associations became weaker. In sensitivity analyses, these patterns were robust to alternative measures of socioeconomic status and were independent of age, sex, racial and ethnic identity, and pubertal status. The associations were also condition specific; no interactions were apparent for amygdala responsivity to neutral faces, or striatal responsivity to monetary losses.

Conclusions: These findings suggest that childhood poverty is associated with accentuated neural-immune signaling, consistent with the neuroimmune network hypothesis.


Children exposed to severe, chronic stressors are vulnerable to a plethora of health problems across the lifespan (1–3). These problems span the continuum of what are traditionally understood to be mental (e.g., depression, posttraumatic stress, substance misuse) and physical (e.g., coronary heart disease, some cancers, autoimmune conditions) illnesses. Little is known about the behavioral and biological pathways underlying risk for this heterogeneous set of health problems.

To stimulate mechanistic research in this area, Nusslock and Miller proposed a neuroimmune network hypothesis (4), which integrates an evolving body of preclinical and translational research (5–8). The framework begins with the observation that even under normal physiologic conditions, brain circuits involved in emotion regulation engage in bidirectional communication with peripheral immune cells that mediate inflammation (5, 6). The framework goes on to hypothesize that severe chronic stress in childhood amplifies this crosstalk, initiating positive feedback loops between peripheral inflammatory activity and the brain’s developing cortico-amygdala and cortico-striatal circuits, which respectively mediate threat and reward processing. As a consequence of the enhanced crosstalk, stress-exposed children are hypothesized to display a phenotype consisting of chronic low-grade inflammatory activity, along with heightened threat responsivity and dampened reward processing. Over time, components of this phenotype are hypothesized to accelerate the pathogenesis of inflammation-mediated health problems.

There is evidence to support the constituent tenets of the neuroimmune network hypothesis. For example, studies have identified stress-related variations in brain development in children exposed to chronic stressors such as socioeconomic disadvantage and parental maltreatment (9, 10). The networks that support threat and reward processing are especially sensitive to these stressors and display what appear to be durable
changes in structure and function (11). A separate literature has
detailed the immunologic correlates of these stressors, dem-
strating that exposed children display larger cytokine re-
 sponses to microbial challenge and signs of chronic low-grade
inflammation (1, 2, 12). Based on initial findings in animals (5, 7),
studies have administered immune-activating stimuli to humans
and found that the resulting inflammation affects functioning of
neural circuits involved in threat and reward processing (13–15).
Observational studies of humans have also consistently reported
associations between activity of these brain circuits and steady-
state levels of inflammatory biomarkers (16).

Nevertheless, no published studies have examined the
validity of the framework’s core hypothesis, namely, that
children exposed to severe chronic stress will display the
phenotype described above. Here, we sought to fill this gap by
studying a sample of urban children from diverse socioeco-
 nomic backgrounds. Although children can experience a
variety of chronic stressors, we focused on socioeconomic
disadvantage here because it is highly prevalent in the United
States. In 2017, 19% of American children resided in
households with incomes below the federal poverty line. An
additional 22% lived in households with incomes considered
near-poor or low-income (17). Although the experiences of
these children vary considerably, on the whole, they are at
increased risk for chronic stressors that include material
hardship, neighborhood violence, family instability, harsh
parenting, and repeated bereavement, among others (18).
Relative to their more advantaged peers, disadvantaged
children also show indications of the dysregulation of the
framework specifies, including low-grade inflammation (19,
20), higher neural threat reactivity (21–24), and blunted
reward processing (21, 25). Given this backdrop, we predicted
that to the extent that children were facing socioeconomic
disadvantage, they would display the phenotype, hypothe-
sized in the framework, consisting of low-grade inflammatory
activity coupled with higher amygdala responsivity to threat
and lower striatal responsivity to reward.

METHODS
Sample
The study involved 277 children from the Chicago area. To be
eligible, they had to be in eighth grade (typically 13–14 years
old), English-speaking, and in good health, defined as being
nonpregnant, without a history of chronic medical or psy-
chiatric illness, free of prescription medications for the past
month, without acute infectious disease for 2 weeks, and
without functional MRI (fMRI) contraindications. Each child
gave written assent and a parent or guardian gave written
consent. Northwestern University’s Institutional Review
Board approved the protocol.

Because of venipuncture problems, inflammation data
were missing for two children. Neuroimaging data were
missing for a number of children (N=32 for the threat task;
N=44 for the reward task), because they arrived too late to
complete the tasks, were too obese or too anxious to enter the
scanner, or had previously unrecognized structural anom-
ali es. No usable data were available for another group of
children (N=36 for threat task; N=59 for the reward task)
because of technical problems with acquisition (brain outside
field of view), excessive motion (>10% of volumes censored
within a paradigm), or limited variability in behavioral re-
 sponse (for details, see the online supplement). Thus, the Ns
were 207 for threat analyses and 172 for reward analyses.
Children for whom fMRI data were missing were more likely
to identify as Black (p=0.003; and 0.001 for threat and reward
tasks). However, they were similar to the broader sample on
age, sex, Hispanic ethnicity, pubertal status, and household
income (p values, 0.11–0.80).

Socioeconomic Conditions
Each child’s parent or guardian completed an interview about
family socioeconomic conditions. From these data, we
computed household income-to-poverty ratio. For most
federal programs in the United States, households with an
income-to-poverty ratio <1.00 are considered to be living in
poverty. In 2014, when the study began, the federal poverty
threshold was $24,008 for a family of two adults and two
children. To facilitate interpretation of the statistical models,
we grouped children into four categories, following con-
vention in the literature: those in poverty (≤0.99) and those
whom we refer to as low-income (1.00–1.99), middle-income
(2.00–3.99), and higher-income (≥4.00).

Low-Grade Inflammation
At the same visit, antecubital blood draw was performed. To
minimize circadian variation, venipuncture was performed
between 8:00 a.m. and 10:00 a.m. Children fasted for 8 hours
beforehand to minimize dietary influences. We measured
serum levels of five inflammatory biomarkers, chosen for
their consistent relationships with early-life stress (1, 2, 12):
C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8
(IL-8), interleukin-10 (IL-10), and tumor necrosis factor-α
(TNF-α). CRP was measured in duplicate by high-sensitivity
immunoturbidimetric assay on a Roche/Hitachi cobas c502
 analyzer. The cytokines were measured in triplicate with a
 four-plex immunoassay on an automated microfluidic plat-
form (Simple Plex, ProteinSimple, San Jose, Calif.). Intra-
assay coefficients of variation were 2.5%–5.1% (for additional
details, see the online supplement).

Most biomarkers were skewed and/or kurtotic, but we
normalized their distributions with log10 transformations.
We then standardized the logged values of each biomarker
(mean=0; SD=1) and averaged the resulting z-scores to form a
composite score (Cronbach’s alpha=0.63), where higher
scores reflect more low-grade inflammation. (Readers may
wonder about including IL-10 in the composite, since its
functions are anti-inflammatory. However, IL-10 is only
expressed under proinflammatory conditions, so it correlates
positively with the other biomarkers assessed here.) The
composite score has two advantages. Statistically, it reduces
the number of tests performed—here, by 80%—and thus the
rate of false positive results. Biologically, a composite better reflects in vivo conditions, where proinflammatory cytokines are released in a cascading fashion and have redundant and synergistic effects on target cells.

**Threat and Reward Paradigms**
At a separate visit, neural responsivity to threat and reward was measured using fMRI. Briefly, to capture amygdala threat responsivity, we administered a morphed faces task (26), where children viewed images of actors displaying emotional facial expressions at varying intensities and were asked to indicate the gender associated with each face. Threat was operationalized as the amygdala’s reactivity to angry faces (relative to fixation). The amygdala response to neutral faces (relative to fixation) was used in specificity analyses. To assess reward, children performed a passive avoidance task (27), comprising 96 trials. In each trial, a shape was presented. Children could respond with a button press, triggering one of four outcomes: win $50, win $10, lose $10, or lose $50. Or they could ignore the shape, in which case no monetary outcome transpired. Outcomes were probabilistic and pseudorandom; responding to two particular shapes triggered wins on 87.5% of trials, and responding to other shapes triggered losses on 87.5% of trials. Afterward, children were paid $5, regardless of performance. Reward response was operationalized as ventral striatal reactivity to winning money (relative to fixation). Ventral striatal reactivity (relative to fixation) to losing money was used in specificity analyses.

**MRI Parameters, Preprocessing, and Analysis**
Imaging data were collected using a Siemens Prisma 3-T scanner with a 64-channel phased-array head coil. Structural imaging consisted of a high-resolution navigated multiecho magnetization-prepared rapid acquisition gradient-echo sequence (TR=2300 ms; TE=1.86 ms, 3.78 ms; flip angle=7°; FOV=256 × 256 mm; matrix=320 × 320; slices=208; voxel size=0.8 mm³). Functional images were acquired using a T2*-weighted gradient echo planar imaging sequence (TR=2000 ms; TE=27 ms; FOV=240 mm; matrix=94 × 94; flip angle=90°). Data were analyzed according to standard procedures consistent with previous work (27), using AFNI (28). Blood-oxygen-level-dependent responses were extracted for each subject from anatomically defined masks, including an amygdala mask for the threat task (Eickhoff-Zilles Architectonic Atlas: 50% probability mask) (29) and a ventral striatum mask for the reward task (accumbens-area map) (30). (Further details of scanning and analysis are provided in the online supplement.)

**Statistical Analysis**
To evaluate hypotheses, we estimated linear regression equations, using model 1 of PROCESS v3.4 (31) in SPSS. The outcome was the inflammation composite score, and covariates included age, sex, self-identified racial (non-White=0; White=1) and ethnic (non-Hispanic=0; Hispanic=1) category, and pubertal status (self-reported on the Pubertal Development Scale [32]). Predictors included covariates, a multicategorical variable reflecting income-to-poverty ratio, a mean-centered variable reflecting amygdala response to angry faces or striatal response to monetary reward, and a product term representing the interaction between income-to-poverty ratio and amygdala or striatal reactivity. The neuroimmune network hypothesis stipulates that in such a model, a statistical interaction should emerge whereby socioeconomic disadvantage increases the likelihood of children displaying a phenotype consisting of low-grade inflammatory activity, heightened threat responsivity, and dampened reward processing. All reported p values are based on two-tailed tests.

**RESULTS**
Table 1 summarizes the characteristics of the analytic sample. The 207 children in the sample ranged in age from 12 to 14 years, and most were at least midway through puberty. They were a diverse group of children, who broadly reflect the Chicago region’s demographic and socioeconomic variation.

**Hypothesis Tests**
Table 2 presents results of primary hypothesis tests. As is evident, none of the covariates was consistently associated with inflammation. In each model, income-to-poverty ratio
TABLE 2. Results of conditional regression models testing the neuroimmune network hypothesis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amygdala Reactivity to Threat</th>
<th>Ventral Striatum Reactivity to Reward</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B 95% CI p</td>
<td>B 95% CI p</td>
</tr>
<tr>
<td>Age</td>
<td>-0.00 (-0.15, 0.15) 0.99</td>
<td>-0.06 (-0.10, 0.22) 0.49</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>-0.11 (-0.31, 0.09) 0.27</td>
<td>-0.14 (-0.34, 0.05) 0.15</td>
</tr>
<tr>
<td>Race (White)</td>
<td>0.06 (-0.14, 0.25) 0.59</td>
<td>0.10 (-0.09, 0.29) 0.29</td>
</tr>
<tr>
<td>Ethnicity (Hispanic)</td>
<td>0.04 (-0.14, 0.23) 0.64</td>
<td>0.03 (-0.15, 0.21) 0.76</td>
</tr>
<tr>
<td>Pubertal stage (continuous 1–5 scale)</td>
<td>-0.03 (-0.16, 0.09) 0.59</td>
<td>-0.01 (-0.13, 0.11) 0.83</td>
</tr>
<tr>
<td>Contrasts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poverty versus low-income</td>
<td>-0.08 (-0.34, 0.17) 0.53</td>
<td>-0.16 (-0.41, 0.10) 0.23</td>
</tr>
<tr>
<td>Poverty versus middle-income</td>
<td>-0.36 (-0.60, -0.11) 0.004</td>
<td>-0.33 (-0.56, -0.09) 0.007</td>
</tr>
<tr>
<td>Poverty versus high-income</td>
<td>-0.24 (-0.49, 0.02) 0.07</td>
<td>-0.21 (-0.46, 0.04) 0.10</td>
</tr>
<tr>
<td>Neural reactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children living in poverty</td>
<td>0.22 (0.05, 0.39) 0.01</td>
<td>0.34 (0.09, 0.60) 0.009</td>
</tr>
<tr>
<td>Low-income children</td>
<td>0.19 (-0.09, 0.46) 0.19</td>
<td>-0.09 (-0.25, 0.07) 0.26</td>
</tr>
<tr>
<td>Middle-income children</td>
<td>0.04 (-0.11, 0.91) 0.58</td>
<td>-0.01 (-0.10, 0.12) 0.87</td>
</tr>
<tr>
<td>High-income children</td>
<td>-0.07 (-0.19, 0.05) 0.26</td>
<td>-0.02 (-0.18, 0.14) 0.80</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.47 (-1.65, 2.58) 0.66</td>
<td>-0.44 (-2.59, 1.71) 0.68</td>
</tr>
</tbody>
</table>

*a* Shown are results of conditional regression models predicting inflammation composite score from covariates, household income-to-poverty ratio, neural reactivity to threat and reward, and the interaction of the latter two variables. Categorical variables as coded as follows: sex (male=0, female=1), race (non-White=0, White=1), and ethnicity (non-Hispanic=0, Hispanic=1).
will respond. These included the amygdala's reactivity to neutral facial expressions and the ventral striatum's reactivity to monetary losses. In neither of these conditions was there evidence of an interaction between income-to-poverty ratio and neural reactivity (p values 0.11 and .26, for amygdala and striatum, respectively). Moreover, the threat reactivity interaction remained significant when the amygdala's response to neutral expressions was included as a covariate ($\Delta R^2=0.04$, p=0.04). Similarly, the reward reactivity interaction remained significant when ventral striatum responses to monetary losses were included as a covariate ($\Delta R^2=0.05$, p=0.04).

**Specific Inflammatory Biomarkers**

Although the inflammation composite score has advantages, some readers will be curious about the role of specific biomarkers. Thus, Figure S1 in the online supplement presents a heat map summarizing the covariate-adjusted relationship between each inflammatory biomarker and neural responsivity. Several patterns are apparent. First, the inflammation composite score generally had stronger associations with neural responsivity than individual biomarkers. Second, of the biomarkers, CRP and IL-6 had the strongest associations with neural responsivity. Third, some task-related variability was evident, with IL-8 relating more strongly to amygdala compared with striatal responsivity, while the reverse was true for IL-10 and TNF-α.

**DISCUSSION**

To explain the health consequences of childhood adversity, the neuroimmune network hypothesis postulates that early stress amplifies crosstalk between peripheral inflammatory cells and networked brain regions involved in threat and reward processing (4). Although individual components of this hypothesis have been established in the literature, no published studies to date have integrated the data sources...
necessary to evaluate its core prediction. Here we sought to fill that gap in knowledge, using a diverse sample of urban children. In line with the core predictions of the framework, amygdala threat responsivity was positively associated with low-grade inflammation among children living in poverty. Intriguingly, the same pattern was evident for striatal reward responsivity. In households with more favorable socioeconomic conditions, these brain-inflammation associations were smaller in magnitude. The observed relationships were independent of demographic confounders and were robust to alternative measures of socioeconomic status. They also were condition specific: inflammation was associated with amygdala responsivity to threat stimuli, even when adjusting for activity during neutral trials, and with striatal responsivity to monetary rewards, even when adjusting for activity during losses.

The findings related to amygdala threat reactivity converge with previous evidence. Studies indicate that childhood disadvantage is associated with exaggerated behavioral, cardiovascular, and amygdala responses to threatening stimuli, a pattern thought to be adaptive in contexts where stressors can arise suddenly and unpredictably (22, 34). Disadvantaged youths also exhibit indications of a proinflammatory phenotype, as reflected in higher circulating inflammatory biomarkers, and leukocytes that mount larger cytokine responses to microbial challenge and are relatively insensitive to inhibition by glucocorticoids (20, 35). Our study’s findings bridge these distinct literatures and extend them by showing that the relationship between amygdala reactivity and inflammatory biomarkers is strongest among children living in poverty. Assuming this association reflects the crosstalk envisioned in the neuroimmune network hypothesis, it might help explain the excess health risks among disadvantaged children (3). However, because of the study’s observational design, we cannot determine whether these associations reflect causal effects. With that said, experimental studies have illustrated the plausibility of causal effects, revealing bidirectional signaling between the amygdala threat circuitry and peripheral inflammatory cells (14, 36). Such crosstalk is thought to be the substrate of an integrated network that detects threats involving microbial invasion and tissue damage, and subsequently mobilizes behavioral, physiologic, and immunologic resources for coping (37).

The findings involving reward responsivity in the ventral striatum were more complex. As predicted, children living in poverty displayed the strongest relationship between striatal responsivity and inflammatory activity. However, the direction of this relationship was positive, a pattern the original framework had not anticipated. With that said, the framework was formulated on the basis of studies from a decade ago, which showed that reward sensitivity dampens after administration of inflammatory agents (13, 38). More recent studies indicate that this formulation is overly simplistic, as inflammation’s effects on striatal reward responsivity are context dependent (8, 13, 39, 40). In situations where a reward matches what is motivationally salient to an individual, inflammation heightens striatal responsivity to that reward—for example, receiving social assistance when one is ill. In situations where there is a mismatch between a potential reward and what is motivationally salient, inflammation has the opposite effect, dampening striatal responsivity. This context dependence could explain the patterns seen here.

### FIGURE 3. Associations between the inflammation composite score and amygdala reactivity to angry faces and ventral striatal reactivity to monetary reward, stratified by household income-to-poverty ratio

Scatterplots are in standard deviation units. Each scatterplot depicts a best-fitting regression line with 95% confidence intervals around it.
because monetary rewards would be a highly salient reward for children living in poverty. Indeed, studies indicate that disadvantaged children display higher sensitivity to many appetitive stimuli, as reflected in temporal discounting, decision making, and self-control paradigms (I). Finally, at the trait level, mounting evidence suggests a U-shaped relationship, with individuals at both ends of the reward-sensitivity continuum showing inflammation. This pattern could reflect the tendency of individuals with high reward sensitivity to engage in inflammation-provoking behaviors—for example, consumption of foods rich in trans fats and refined sugars. Together, these observations suggest that the neuroimmune network hypothesis should be elaborated to reflect the context dependence of reward-immune signaling.

The study has several limitations. First, its cross-sectional design precludes inferences about causality, a problem that could be partially addressed in multiwave longitudinal studies. Second, there is currently no technology to directly measure neural-immune crosstalk, so our inferences about its occurrence are necessarily indirect. The brain’s resident immune cells—microglia—appear to be central to this crosstalk (5). As methods to image these cells’ functions develop, they will allow for direct evaluation of the framework’s key tenets. In the meantime, it would be valuable to more thoroughly explicate the neural basis of these results, using functional connectivity analyses to probe the broader cortico-amygdala and cortico-striatal circuits supporting threat and reward processing. It would also be valuable to replicate these findings with different paradigms, to determine whether they generalize to other threat and reward stimuli. Third, while consistent with the framework’s predictions, the interactions we observed were small to medium in terms of effect size, suggesting that to understand the health risks associated with poverty, a more thorough assessment of relevant exposures will be needed in future research. Of likely importance in this regard are the timing and duration of poverty, as well as presumptive mediators of its sequelae (e.g., stressors such as deprivation, violence, and discrimination). Finally, the study did not consider clinical outcomes, so it is unclear whether the hypothesized crosstalk accounts for health problems in the manner the framework suggests.

To summarize, these results provide initial support for the hypothesis that childhood stress amplifies crosstalk between peripheral inflammatory cells and brain regions involved in threat and reward. If substantiated, these patterns will have implications for understanding how early stressors, acting through neural-immune pathways, contribute to the development of a diverse set of health problems. With regard to mental health, this might take the form of a two-hit scenario, where stress-related inflammatory signaling increases risk for fear-related symptoms (e.g., vigilance, worry, rumination) by modulating amygdala circuitry, and motivation-related symptoms by modulating striatal circuitry (e.g., substance misuse, anhedonia, mania). As the neuroimmune network hypothesis suggests, these neural and behavioral changes might, in turn, initiate a positive feedback loop that worsens psychiatric symptoms and extends them into other realms. Of course, longitudinal studies are needed to evaluate this scenario’s validity, but in the meantime it provides a framework for conceptualizing how vulnerability arises. In the long term, this work could facilitate a next generation of interventions that improve psychiatric outcomes by targeting brain-to-immune and/or immune-to-brain signaling.

**AUTHOR AND ARTICLE INFORMATION**

Institute for Policy Research and Department of Psychology, Northwestern University, Evanston, Ill. (Miller, Chen, Nusslock); Boys Town National Research Hospital, Boys Town, Neb. (White).

Send correspondence to Dr. Miller (greg.miller@northwestern.edu).

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