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Resting-State Functional Connectivity of the Central Executive Network Moderates the Relationship Between Neighborhood Violence and Proinflammatory Phenotype in Children

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ABSTRACT

BACKGROUND: Neighborhood violence increases children's risk for a variety of health problems. Yet, little is known about biological pathways involved or neural mechanisms that might render children more or less vulnerable. Here, we address these questions by considering whether neighborhood violence is associated with the expression of a proinflammatory phenotype and whether this relationship is moderated by resting-state functional connectivity (rsFC) of the central executive network (CEN).

METHODS: The study involved 217 children (13.9 years old; 66.4% female; 36.9% Black; 30.9% Latinx), enrolled in eighth grade and reassessed 2 years later. At time 1, geocoding was used to estimate murder frequency in children's neighborhoods, and functional magnetic resonance imaging was used to characterize CEN rsFC. At both visits, children gave antecubital blood for ex vivo studies, where leukocytes were incubated with stimulators and inhibitors of inflammation, and cytokine production was measured.

RESULTS: Consistent with our hypotheses, the relationship between neighborhood murder and inflammatory activity was moderated by CEN rsFC. Among children with lower rsFC, neighborhood violence covaried with a proinflammatory phenotype, reflected in larger cytokine responses to triggering stimuli and lower sensitivity to inhibitory agents. These associations were generally not apparent for children with higher rsFC, although occasionally they ran in the opposite direction. The same patterns were apparent 2 years later.

CONCLUSIONS: These results advance the understanding of neighborhood violence and its relationship with processes involved in the initiation and resolution of inflammation. They also deepen understanding of variability in children's immunologic responses to stress and suggest that the CEN may be a neurobiological contributor to resilience.

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Neighborhood violence increases children's risk for a variety of adverse outcomes. In the realm of mental health, those outcomes include substance misuse, externalizing behaviors, posttraumatic stress, depressive symptoms, and dysregulated sleep (1–3). In terms of physical health, they include increased risk for developing asthma and signs of early cardiometabolic disease (4–9). Although these risks are largest among children who have been personally victimized, an emerging literature indicates that indirect exposures, which can include witnessing violent acts or hearing about them from others, also portend worse outcomes in some domains of health (1,3,10,11). This pattern raises two broad questions, which are the focus of this paper.

The first concerns mechanisms. Through which biological pathways might neighborhood violence plausibly affect children's health? Many conceptual models in this area emphasize the role of nonresolving inflammation (12–14), a process increasingly recognized as a contributor to chronic health problems, including depression, posttraumatic stress, substance misuse, diabetes, and heart disease (15,16). In multiple studies, neighborhood violence has been linked with circulating biomarkers of inflammatory activity, including classical monocyte counts, C-reactive protein, interleukin 6 (IL-6), and tumor necrosis factor α (17–20). Although these findings are consistent with a role for inflammation, their mechanistic basis remains poorly understood. Cells of the innate immune system are widely thought to be a primary source of inflammatory activity. However, many tissues and organs release IL-6 and tumor necrosis factor α, leaving it unclear where inflammatory biomarkers in circulation originate (16). Here, we address this problem using ex vivo assays, which assess how innate immune cells respond to stimulators and inhibitors of

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inflammation. The stimulators we use mimic the diverse stimuli known to provoke and maintain inflammation. These are not only pathogens but also danger signals released by damaged tissue in response to cellular injuries and environmental toxicants (16). The inhibitors include local and systemic agents that promote resolution of inflammation. We expected that children exposed to neighborhood violence would display a proinflammatory phenotype, as reflected in larger cytokine responses to stimulating agents, and reduced sensitivity to the anti-inflammatory properties of inhibitors.

The second question concerns resilience. Similar to most stressors, neighborhood violence is associated with worse outcomes in the aggregate. However, person-level data reveal that a sizable fraction of children remain in good health despite exposure (21,22). Studies have identified a variety of individual, familial, and contextual factors that protect against the psychosocial consequences of violence (23,24). However, the neural circuitries that underlie resilience to violence are poorly understood. To address this gap, we recently considered whether functional connectivity of the brain's large-scale networks might play a role (11). We reasoned that violent neighborhoods are unpredictable places to live, where children must balance two competing demands on cognitive resources—purposefully going about daily activities and remaining vigilant for threats to safety. To accomplish this, we speculated that they would need to engage the frontoparietal central executive network (CEN), which connects areas of the dorsolateral prefrontal cortex and posterior parietal cortex. At a broad level, this network supports the cognitive regulation of emotion, behavior, and thought. More focally, the CEN is activated during efforts to exert self-control, reappraise threats, and suppress intrusive thoughts (25–27). Consistent with hypotheses, we found that resting-state functional connectivity (rsFC) within the CEN moderated the relationship between neighborhood violence and cardiometabolic risk. Across six distinct outcomes, children living in neighborhoods with high murder rates showed more cardiometabolic risk, but this relationship was only apparent for children with lower rsFC within the CEN.

Here, we present a longitudinal follow-up of these children. It builds on the earlier findings by asking whether they generalize to a different biological process, inflammation, and by using a longitudinal design, where inflammatory activity is measured at study entry and 2 years later. With this approach, we can examine whether the CEN's apparent violence-buffering effects are durable over time and whether they precede changes in inflammatory activity, which is a necessary condition for causal inference. In terms of hypotheses, we expected that the buffering patterns observed in the earlier study would generalize to inflammatory activity and be apparent in longitudinal analyses. In other words, we predicted that children from violence-prone neighborhoods would show a durable and worsening proinflammatory phenotype, as described above, but only if they had low CEN rsFC.

METHODS AND MATERIALS

Sample Overview

The study involved children from the Chicago area, recruited through advertisements in media, public transit, and schools. To be eligible, children had to be in eighth grade, English speaking, and in good health, defined as 1) nonpregnant, 2) without a history of chronic medical or psychiatric illness, 3) free of prescription medications for the past month, 4) without acute infectious disease for 2 weeks, and 5) without magnetic resonance imaging (MRI) scanning contraindications. Each child gave written assent to participate, and a parent or guardian gave written consent. Northwestern University's Institutional Review Board approved the protocol.

A total of 277 children enrolled. The time 1 assessment consisted of two sessions, typically spaced 1–4 weeks apart. At the first session, children completed psychosocial measures and gave antecubital blood, while a parent/guardian provided demographic data. At the second session, children underwent structural and functional MRI (fMRI) scans. Roughly 2 years later, children were reassessed using the same format (however, we do not present time 2 MRI data). The mean (SD) duration between time 1 and time 2 was 24.01 (1.48) months. Of the 277 children enrolled at time 1, a total of 257 returned for time 2 (92.78%). Reasons for attrition included death, loss of contact, and relocation.

Neighborhood Violence

At time 1, each child's residential address was geocoded at the block-group level of resolution. Block groups consist of 600–3000 people and are the smallest geographic units for which the U.S. Census Bureau publicly reports information. For each block group, Applied Geographic Solutions estimates a neighborhood murder index (NMI) (CrimeRisk; CoreLogic, Irvine, CA) based on data that local police provide to the Federal Bureau of Investigation. We used NMI values for 2010–2014, the 5-year period before this study began. The NMI's validity has been established in multiple studies (8,11); as further evidence, in our sample, values were positively correlated with children's reports of how frequently their family and friends experienced violence (r = .38).

Inflammatory Response

At both time 1 and time 2, 10 mL of antecubital blood was drawn into a Sodium-Heparin Vacutainer (Becton-Dickinson, Franklin Lakes, NJ). To minimize circadian variations, venipuncture was performed between 8:00 and 10:00 AM. Children fasted for 8 hours beforehand to minimize dietary influences.

Whole blood was diluted to a 9:1 ratio with R10 media. Noting that inflammation is driven not only by microbes but also by a variety of sterile triggers (15,16), we incubated diluted blood with four agents. They mimicked encounters with pathogenic microbes and danger signals released by damaged tissue in response to cellular injuries and environmental toxicants. Specifically, 400 μL of diluted blood was dispensed into wells containing one of the following: 1) 50 ng/mL of lipopolysaccharide, found on gram-negative bacteria (InvivoGen, San Diego, CA); 2) 1 μg/mL of Resiquimod (R848), which activates antiviral signaling (InvivoGen); 3) 0.1 μg/mL of heat shock protein-60 (HSP-60), released by damaged tissue (R&D Systems); or 4) 20 μg/mL of advanced glycation end-product (AGE) derived from bovine serum albumin (BSA) (BioVision, Milpitas, CA). AGEs are found in cigarette smoke, processed foods, and air pollutants. To quantify sensitivity to signals that

regulate inflammation, we also incubated cells with compounds that provide local (IL-10) and systemic (glucocorticoids) anti-inflammatory feedback. Again, 400 μL of diluted whole blood was added to wells containing 50 ng/mL of lipopolysaccharide, plus either 1) hydrocortisone at doses of 2.76×10^{-7} M or 2.76×10^{-6} M or 2) IL-10 at doses of 1.08×10^{-9}, 5.38×10^{-9}, or 2.69×10^{-8} M. Each plate also included a negative control well, where cells were incubated with R10 media, to measure background cytokine release.

After a 6-hour incubation at 37°C, supernatants were harvested by centrifugation and frozen at −80°C. Four inflammatory cytokines were measured—IL-1β, IL-6, tumor necrosis factor α, and IL-8—by multiplex immunoassay (Luminex Performance Human XL Cytokine Discovery Panel; Bio-Techne, Minneapolis, MN) on a Luminex Magpix. Intraassay coefficients of variation for duplicate pairs ranged from 1.59% to 2.28%, and interassay coefficients of variation from 2.67% to 4.03%.

To reduce false discoveries, we conducted primary analyses on two composite end points. The first was a stimulation composite, formed by averaging *z*-scored values across the four cytokines (mean pairwise correlation = .59), then across the four stimulating agents (mean pairwise correlation = .63). The composite was internally consistent (Cronbach's α = .87 and .85 at times 1 and 2, respectively) and scored so that higher values represent larger cytokine responses to stimulating agents. The second was an inhibition composite. It was formed by estimating a child-specific inhibition slope for each cytokine within each condition (28). Thereafter, *z*-scored values of cytokine slopes were averaged (mean pairwise correlation = .52) and collapsed across inhibition conditions (mean correlation = .78). Again, the composite was internally consistent (Cronbach's α = .91 and .88 at times 1 and 2, respectively) and scored so that higher values represent greater sensitivity to anti-inflammatory compounds. Before composites were calculated, all cytokines were corrected for background production by subtracting out values from the negative control well containing R10 alone.

Resting-State Functional Connectivity

Data Acquisition. At time 1, imaging data were collected at Northwestern's Center for Translational Imaging on a Siemens Prisma 3T 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 (repetition time = 2300 ms, echo time = 1.86 ms, 3.78 ms; flip angle = 7°; field of view = 256 × 256; matrix = 320 × 320; 208 slices; voxel size = 0.8 mm^3). Whole-brain functional images were acquired using T2* echoplanar imaging with a fast repetition time sequence (repetition time = 555 ms; echo time = 22 ms; flip angle = 47°; field of view = 208 × 208 mm; voxel size = 2.0 mm^3; multiband factor = 8; partial Fourier Factor = 6/8; 1110 volumes) (29). For the resting scan, children were instructed to remain as still as possible, with their eyes open, for 10 minutes.

Image Processing. fMRI data were preprocessed using in-house pipelines (30). Functional data were despiked, aligned to T1 images, and registered to Montreal Neurological Institute standardized space using a nonlinear transformation (31). The first 10 volumes were removed to allow the signal to reach steady state. Volumes with framewise displacement > 0.5 mm or whole-brain changes in blood oxygen level–dependent signal (DVARS) > 0.9% were regressed out (32), as were white matter and cerebrospinal fluid. Bandpass filtering was applied to remove low- and high-frequency noise (0.01–0.08 Hz). Data were spatially smoothed using a 6-mm full width at half maximum Gaussian filter. After these procedures, children had an average of 8.5 minutes of usable data.

Functional Connectivity Analyses. We defined CEN regions of interest (ROIs) with a publicly available atlas (33). For each of the CEN's 10 ROIs (see Figure 1), we placed a 5-mm sphere around peak activation coordinates for each discrete cluster within the left- and right-hemisphere masks. Time-series data for each voxel were de-meaned and converted to percent signal change scores to reduce variability between children. We then calculated the ROI seed data as the average percent signal change for all voxels in a given region. rsFC was quantified as the Pearson correlation (*r*) relating the average time series in each ROI with the average time series in all other ROIs within the network. After converting these *r* values into *z* scores using Fisher's transformation, we averaged all pairwise *z* scores within the network to form a summary statistic, reflecting the connectivity between all nodes within the CEN. In specificity analyses, we asked whether similar findings would emerge for the anterior salience network. Table S1 and Figure S1 show ROIs for both networks.

Statistical Analysis

Covariates. All models included age (in years), sex (male = 0, female =1), self-reported racial (non-Caucasian = 0, Caucasian =1) and ethnic (non-Hispanic = 0, Hispanic = 1) identity, household income-to-poverty ratio, and pubertal status, assessed with a validated self-report measure (34) that yields scores from 1 (prepubertal) to 5 (postpubertal).

Missing Data. A total of 217 children formed the analytic sample at time 1. Of the 277 children enrolled, 29 were missing rsFC data because they could be not scheduled for fMRI, arrived too late to complete all scans, were too obese or anxious to enter the scanner, or had a structural anomaly. Six children were missing inflammation data because of technical difficulties, and another 6 had addresses that could not be geocoded. After reviewing rsFC data, we excluded another 24 children because of poor data quality (sleeping during the scan, signal drop out owing to inhomogeneities in the magnetic field, and data that did not allow for full node placement). Fifteen children were subsequently lost to follow-up, leaving $n = 202$ for longitudinal analyses. Boys were more likely than girls to have missing data ($p = .02$). Otherwise, subjects with complete and missing data were similar on neighborhood murder, covariates, and inflammation composites at time 1 ($ps > .19$).

Analytic Plan. This dataset has a nested structure, where youth live within block groups. Thus, we tested hypotheses using generalized estimating equations (GEEs), specifying

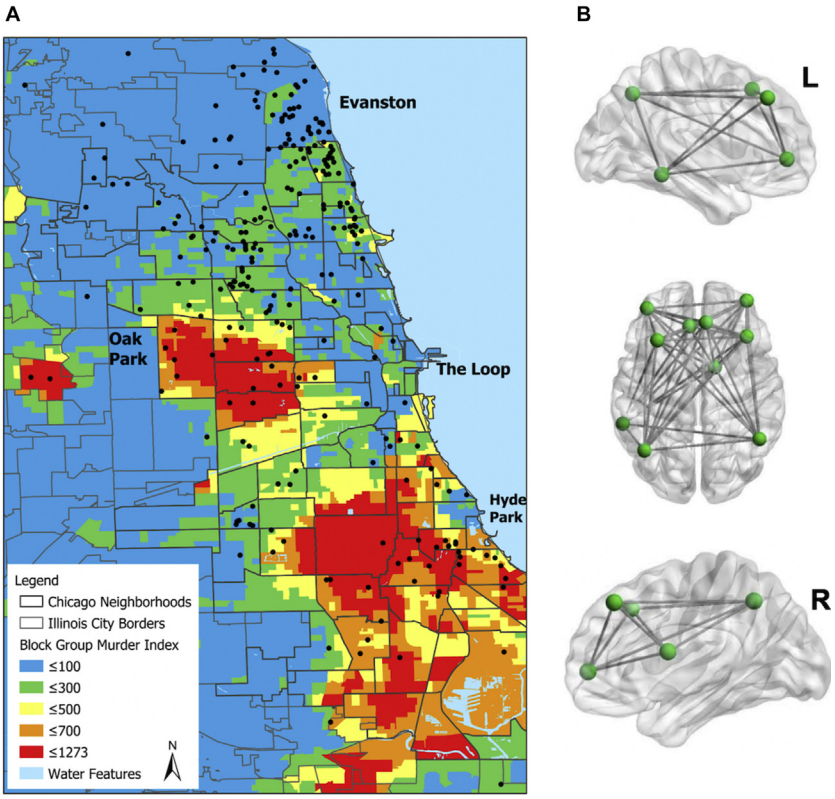

Figure 1. **(A)** Spatial distribution of neighborhood murder in the Chicago region from 2010 to 2014, at the Census block-group level of resolution. Round dots represent the residential addresses of children in the sample. **(B)** Axial and both left (L)- and right (R)-hemisphere sagittal views of regions of interest for the central executive network.

block group as a nesting variable and an exchangeable covariance matrix. Each model included terms for the NMI and CEN rsFC, a product variable representing their interaction, and the covariates above. Continuous variables were group mean centered before the analysis. Significance tests were two-tailed, with $\alpha = .05$.

RESULTS

As a group, the children were racially, ethnically, and economically diverse and generally in the middle to late stages of puberty (Table 1). They lived in 192 different block groups, which had an average NMI score of 242 (SD = 257; range, 3–986) (Figure 1). The NMI is scaled so that 100 reflects the average block group in America. Thus, neighborhood murder was 142% more common for children in our sample relative to the country as a whole.

Cross-sectional Associations

The first analysis examined cross-sectional associations between neighborhood murder, CEN rsFC, and inflammatory activity. Table 2 shows primary hypothesis tests, and Table S2 gives full results.

Briefly, cytokine responses to stimulation were higher for boys (relative to girls) and African Americans (relative to White and Latinx children). As predicted, a significant NMI × CEN rsFC emerged. To interpret the interaction, we plotted composite scores and estimated simple slopes at lower (−1.5 SD), mean, and higher (+1.5 SD) values of CEN rsFC (35). Among children with lower CEN rsFC, higher neighborhood murder was associated with larger cytokine responses to stimulating agents. This relationship was not apparent for children with average or higher CEN rsFC (Figure 2A).

Similar patterns were evident for the inhibition composite. Scores were lower—meaning less sensitivity to inhibition—among boys, African Americans, and children in earlier pubertal stages. As hypothesized, a significant NMI × CEN rsFC interaction emerged. Follow-up analyses indicated that among children with lower CEN rsFC, high neighborhood murder covaried with less sensitivity to the anti-inflammatory properties of inhibitory compounds. This relationship was not evident among children with average or higher CEN rsFC (Figure 2B).

To clarify the source of these interactions, we disaggregated the composites and conducted separate analyses of cytokine responses to each stimulating and inhibitory agent (Table S5). Significant NMI × CEN rsFC interactions were apparent in cultures stimulated with HSP-60 and AGE-BSA, which are sterile (nonmicrobial) triggers of inflammation, and in cultures where cytokine production was inhibited with glucocorticoids and IL-10. All these interactions remained significant (Table S5) when Benjamini and Hochberg's step-up procedure was applied to control false discoveries (36). Follow-up probing indicated that the interactions had the same general form as the composites. That is, among children with

Table 1. Characteristics of the Sample at Time 1 (*N* = 217)

Characteristic	*n* (%) or Mean (SD)
Age, Years	13.94 (0.54)
Sex, Female	144 (66.4%)
Race/Ethnicity	
Self-identified race, White, non-Latinx	88 (40.6%)
Self-identified race, Black, non-Latinx	80 (36.9%)
Self-identified ethnicity, Latinx, any race	67 (30.9%)
Puberty Stage	
Pre, early, or mid puberty	72 (33.2%)
Late or post puberty	145 (66.8%)
Income/Poverty Status	
Household IPR	3.59 (3.18)
Households in poverty, IPR < 1.00	41 (18.9%)
Low-income households, IPR 1.00–1.99	45 (20.7%)
Neighborhood Murder Index for 2010–14	243.35 (257.87)
Central Executive Network rsFC	0.05 (0.44)

Children can endorse multiple racial and ethnic identities, so values in these categories exceed 100%.

IPR, income-to-poverty ratio; rsFC, resting-state functional connectivity.

lower CEN rsFC, neighborhood murder covaried with larger cytokine responses to HSP-60 (slope = 0.12, p = .006) and AGE-BSA (slope = 0.10, p = .029) and lower sensitivity to inhibition by glucocorticoids (slope = −0.06, p = .045) and IL-10 (slope = −0.09, p = .015). Among children with higher CEN rsFC, these relationships either were not apparent (HSP-60, IL-10 inhibition) or ran in the opposite direction, i.e., neighborhood murder covaried with smaller cytokine responses to AGE-BSA (slope = −0.13, p = .02) and higher sensitivity to glucocorticoid inhibition (slope = 0.10, p = .02). For children with average CEN rsFC, neighborhood murder was not associated with cytokine response (all ps > .05).

Table 2. Key Results From Generalized Estimating Equations

Outcome	Interaction Term *B* (95% Confidence Interval)	*p* Value
Time 1		
Stimulation composite	−0.14 (−0.22 to −0.05)	.001
Inhibition composite	+0.12 (+0.03 to +0.21)	.011
Time 2		
Stimulation composite	−0.10 (−0.20 to −0.01)	.042
Inhibition composite	+0.14 (+0.04 to +0.25)	.008
Change		
Stimulation composite	−0.05 (−0.16 to +0.05)	.294
Inhibition composite	+0.10 (+0.01 to +0.17)	.016

Primary hypotheses were tested in a series of generalized estimating equations, where inflammatory outcomes were predicted from a panel of five covariates, neighborhood murder, central executive network resting-state functional connectivity, and an interaction between the latter two variables. The covariates were the child's age, sex, pubertal stage, whether she/he self-identifies as White and/or Hispanic, and the household income-to-poverty ratio (all predictors and covariates were measured at time 1). Complete results are provided in the Supplement.

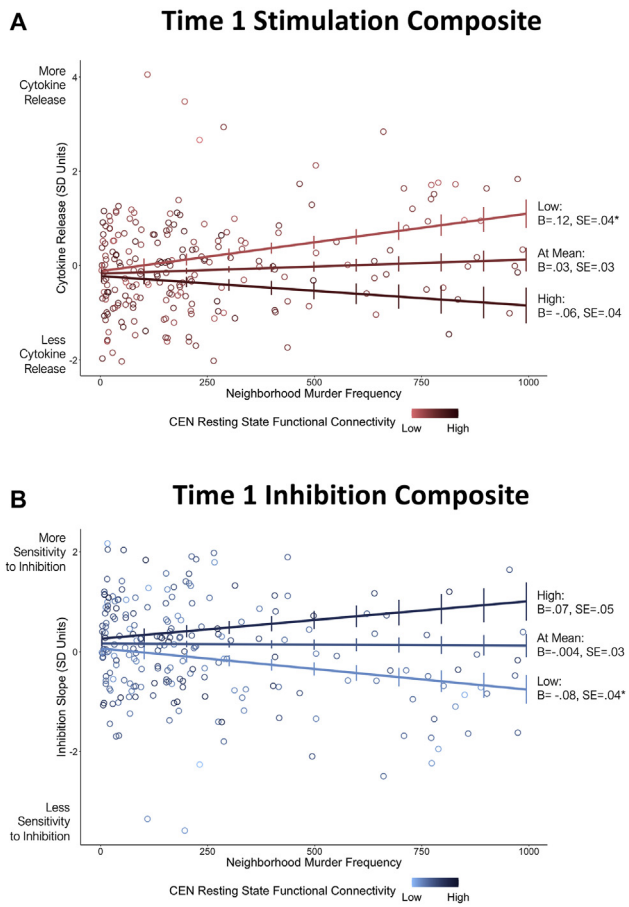

Figure 2. Cross-sectional relationship between neighborhood murder and inflammatory activity differs according to resting-state functional connectivity within the central executive network (CEN). Upper panel **(A)** depicts stimulated cytokine production, and lower panel **(B)** depicts sensitivity to inhibition. Dots represent individual data points and bars represent standard errors. *p < .05.

Durability at Follow-up

We next considered whether these patterns continued to be evident 2 years later. Thus, GEEs were estimated predicting inflammatory activity at time 2 from covariates and predictors measured at time 1. Primary results are presented in Table 2 and full models in Table S3. For both composites, significant NMI × CEN rsFC interactions were observed. Among children with lower CEN rsFC, high neighborhood murder was associated with both larger cytokine responses to the stimulating agents, and reduced sensitivity to anti-inflammatory compounds (Figure 3). For children with average and higher levels of CEN rsFC, neighborhood murder was unrelated to the stimulation composite. However, among the latter it covaried positively with the inhibition composite, meaning that as NMI scores increased, so did sensitivity to anti-inflammatory compounds. In secondary analyses using disaggregated composites (Table S5), interactions were apparent in cultures stimulated

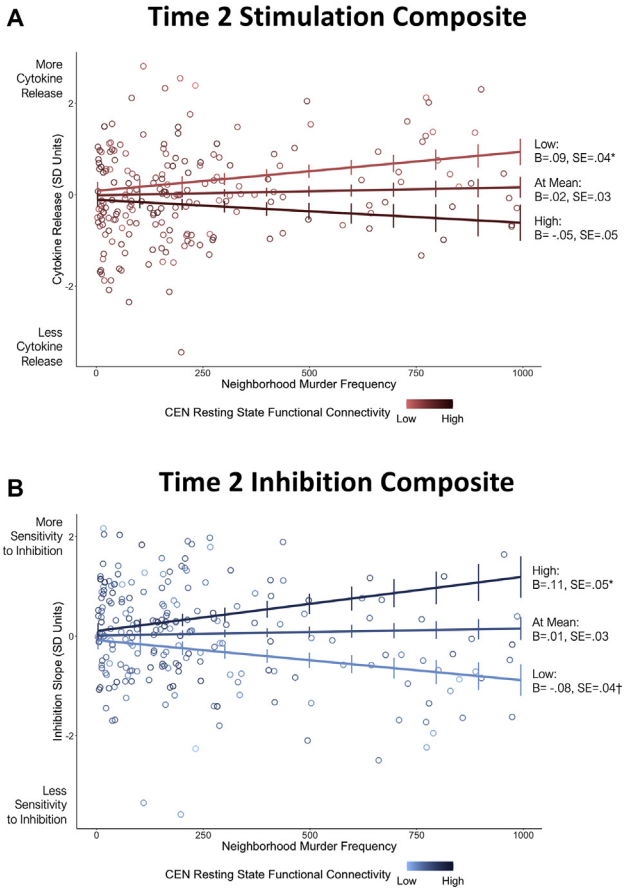

Figure 3. Longitudinal relationship between neighborhood murder and inflammatory activity differs according to resting-state functional connectivity within the central executive network (CEN). Upper panel **(A)** depicts stimulated cytokine production, and lower panel **(B)** depicts sensitivity to inhibition. Dots represent individual data points and bars represent standard errors. *$p < .05$; †$p < .06$.

with lipopolysaccharide and those where glucocorticoids and IL-10 were used as inhibitors. These findings remained significant when false discovery was controlled at 10%, but only the IL-10 effect persisted when a stricter 5% threshold was applied.

Changes Across Time

We next considered whether the NMI × CEN rsFC interaction forecasted changes over the 2-year follow-up. Thus, we estimated GEEs where the outcome was a time 2 inflammation variable, and the predictors were that variable's value at time 1 and the covariates and predictors from time 1 used above.

As Table 2 shows, the NMI × CEN rsFC interaction was not associated with change over time in the stimulation composite. However, it did forecast change in the inhibition composite. Specifically, neighborhood murder presaged a decline in inhibition sensitivity for children with lower CEN rsFC, but an increase for children with higher CEN rsFC (Figure 4). The latter slope was statistically significant, but the former slope was not.

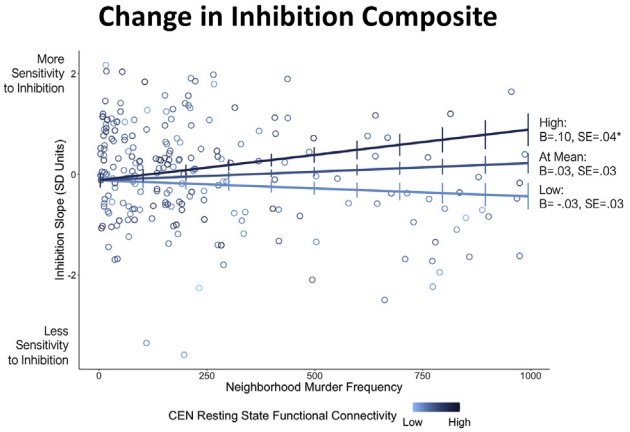

Figure 4. The longitudinal relationship between neighborhood murder and the 2-year change in sensitivity to inhibition from time 1 to time 2. Dots represent individual data points and bars represent standard errors. *$p <$ .05. CEN, central executive network.

In disaggregated analyses, the NMI × CEN rsFC interaction predicted longitudinal changes in IL-10 sensitivity (B = 0.11; 95% confidence interval = 0.03–0.19; p = .009). For children with lower CEN rsFC, neighborhood violence was associated with a decline in IL-10 sensitivity (slope = −0.05, p = .02). This relationship ran in the opposite direction for children with higher CEN rsFC—neighborhood violence was associated with increasing IL-10 sensitivity (slope = 0.11, p = .005). The interaction was not associated with change in glucocorticoid sensitivity (p = .11). For children with average CEN rsFC, neighborhood murder was unrelated to changes over time.

Further Analyses

To evaluate sensitivity to fMRI motion artifacts, we re-estimated the primary GEEs with an additional covariate, mean framewise displacement. All of the observed NMI × CEN rsFC interactions were similar or larger in magnitude. In specificity analyses, we considered whether the same interaction would emerge when more general neighborhood conditions were substituted for NMI. The answer was no—median household income in the block group did not interact with CEN rsFC to predict inflammatory composites ($ps > .69$). We also asked whether the NMI would interact with rsFC of the anterior salience network, which is involved in monitoring the salience of external and internal events (37). However, there was no evidence of such interactions for the inflammatory composites ($ps > .38$).

DISCUSSION

Although violent crime has declined in recent decades, it remains stubbornly persistent in some American neighborhoods (10). There is mounting evidence to suggest that this violence increases children's risk for mental and physical health problems (1–9). In this longitudinal study of children, we observed three broad patterns, which provide clues about how those health problems arise and who is most vulnerable to them.

The first pattern bears on generalizability. In an earlier paper, we observed that CEN rsFC moderated the relationship between neighborhood violence and cardiometabolic risk (11). Here we extend this phenomenon to functional indicators of inflammation. Specifically, among children with lower rsFC, neighborhood violence covaried with a proinflammatory phenotype, reflected in larger cytokine responses to triggering stimuli and lower sensitivity to inhibitory agents. These associations were generally not apparent for children with higher CEN rsFC, although in some instances, they ran in the opposite direction, particularly at follow-up. Considered alongside the earlier report (11), these patterns suggest that the CEN has a role in shaping children's cardiometabolic and inflammatory responses to living in violent environments.

The second pattern concerns biological durability and temporal precedence. Extending the earlier cross-sectional results, we observed that 2 years later, the same NMI × CEN rsFC interactions were still apparent. The durability of these patterns may reflect continuity in children's neighborhood conditions and/or intrinsic brain networks. Alternatively, it may reflect more sustained alterations in brain-immune crosstalk elicited by earlier violence (38). Either way, the durability of inflammatory phenotypes suggests that these results have implications for understanding how neighborhood violence could potentially influence the diseases with a protracted evolution. Results of the longitudinal analyses are also consistent with this possibility. Perhaps more importantly, the longitudinal analyses provide evidence of temporal precedence, meaning that neighborhood violence and CEN rsFC predate children's inflammatory responsivity, at least in terms of sensitivity to inhibitory agents.

Although establishing temporal precedence is essential for causal inference, it does not eliminate other threats to interpretation. Unmeasured confounds could be inflating the associations seen here, and predictor variables could be proxies for other causal agents. A definitive way to clarify these issues would be a randomized controlled trial using training to bolster CEN rsFC (39,40) while monitoring neighborhood violence and health outcomes. In the meantime, observational studies could help answer questions about psychological mechanisms underlying the findings here. Pinpointing the cognitive, behavioral, or emotional pathways involved would help build theory and could provide targets for risk stratification or clinical intervention. Task-based studies of the CEN provide clues about mechanisms to consider, including individual differences in the ability to exert self-control, reappraise threatening stimuli, and suppress intrusive thoughts (25–27). Besides questions about mechanisms, future studies should consider whether CEN rsFC is itself sensitive to the psychosocial environment. Preliminary evidence indicates that it is (41), suggesting that adverse conditions might undermine its capacity to provide buffering.

The final pattern involved potential mechanisms. Among children with lower CEN rsFC, neighborhood violence covaried with multiple aspects of inflammatory activity. Their innate immune cells released larger volumes of proinflammatory cytokines when stimulated ex vivo and were less sensitive to both local (IL-10) and systemic (glucocorticoid) inhibitory signals. These patterns were apparent at baseline and maintained 2 years later. For sensitivity to inhibition, they became larger with time. Interestingly, there was variability across time in which triggers accounted for the larger cytokine response, with stimuli that mimic tissue damage predominating at baseline and bacterial products predominating at follow-up. Why responsivity to individual triggers would shift across time is not evident, but given the secondary nature of these analyses, we are reluctant to read too much into them. The inhibition sensitivity findings were more consistent across time, especially with IL-10, which could indicate that neighborhood violence has a more durable relationship with processes that mediate the resolution of inflammation, as opposed to those involved in its initiation.

Similar to any study, this one has limitations that must be considered. We sought to minimize residual confounding by adjusting for multiple demographic and biobehavioral characteristics. However, this approach is fallible, even in a longitudinal study. Hence, subsequent research should take advantage of designs that permit stronger causal inferences, e.g., discordant-twin, within-person, and time-series approaches (42–44). The clinical relevance of our findings must also be evaluated by studying these processes in disease settings where neighborhood violence has known effects, e.g., posttraumatic stress, asthma, heart disease. Finally, research is needed to examine generalizability beyond our sample of Chicago youth.

Despite these limitations, this study advances the understanding of neighborhood violence and its relationship with processes involved in the initiation and resolution of inflammation. It also deepens understanding of variability in children's responses to neighborhood violence, highlighting a role for the CEN in adaptation. If these patterns are substantiated in future studies with stronger designs, CEN connectivity could become a target for psychosocial and/or neuromodulatory interventions attempting to ameliorate stress-related health problems.

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ARTICLE INFORMATION

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