Functional connectivity in central executive network protects youth against cardiometabolic risks linked with neighborhood violence

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Although violent crime has declined in recent decades, it remains a recurring feature of daily life in some neighborhoods. Mounting evidence indicates that such violence has a long reach, which goes beyond family and friends of the victim and undermines the health of people in the surrounding community. However, like all forms of adversity, community violence elicits a heterogeneous response: Some remain healthy, but others deteriorate. Despite much scientific attention, the neural circuitries that contribute to differential adaptation remain poorly understood. Drawing on knowledge of the brain's intrinsic functional architecture, we predicted that individual differences in resting-state connectivity would explain variability in the strength of the association between neighborhood violence and cardiometabolic health. We enrolled 218 urban youth (age 12–14 years, 66% female; 65% black or Latino) and used geocoding to characterize their exposure to neighborhood murder over the past five years. Multiple aspects of cardiometabolic health were assessed, including obesity, insulin resistance, and metabolic syndrome. Functional MRI was used to quantify the connectivity of major intrinsic networks. Consistent with predictions, resting-state connectivity within the central executive network (CEN) emerged as a moderator of adaptation. Across six distinct outcomes, a higher neighborhood murder rate was associated with greater cardiometabolic risk, but this relationship was apparent only among youth who displayed lower CEN resting-state connectivity. By contrast, there was little evidence of moderation by the anterior salience and default mode networks. These findings advance basic and applied knowledge about adaptation by highlighting intrinsic CEN connectivity as a potential neurobiological contributor to resilience.

resilience | stress | children | neuroscience | cardiovascular

Over the past 25 y, rates of violent crime have declined sharply in the United States, particularly in large cities (1). However, in some urban neighborhoods violence remains a feature of daily life. Recent murder statistics in Chicago illustrate these trends vividly. The city is divided into 77 community areas with average populations of roughly 35,000 people. According to the city's data portal, 10 of these areas recorded more than 26 murders in 2016, more than 2/mo on average. By contrast, nearly all the other community areas had fewer than five murders that year. Much is known about how murder and other violent crimes affect the friends and families of victims. Less well understood is what impact, if any, these events have on members of the surrounding community who are not touched personally by the violence (1).

Studies addressing this question have yielded some indications that community violence can adversely influence the health of youth. One study tracked sleep patterns and cortisol release over multiple days. During the monitoring, homicides or sexual assaults occurred in the neighborhoods of some of these youth; however, none was personally affected. Nonetheless, these youth lost more than 1 h of sleep on the night of the crime, relative to their usual amount, and also released more cortisol the next morning (2). Research on chronic health problems has yielded mixed findings (3–6). However, recent studies with richer data suggest that youth living in violent neighborhoods are more likely to develop asthma than peers in safer areas and to display cardiometabolic risk factors that include obesity, high blood pressure, allostatic load, and short telomeres (7–10).

However, even in studies in which such associations are observed, there is marked heterogeneity in the response to neighborhood violence. For example, one prospective study reported that youth from high-violence communities developed asthma at twice the rate of peers from safer areas (7). However, even among youth living in high-violence areas, asthma incidence was only 25%, meaning that 75% of exposed youth showed what psychologists call "resilience." Results like this are ubiquitous in stress research: Even following severe trauma, a sizeable fraction of people remains healthy and competent (11). This observation raises a fundamental question for basic scientists studying adaptation and for clinical researchers seeking application: In the midst of adversity, what enables some people to remain healthy, whereas others deteriorate (12–14)?

Recent insights into the brain's intrinsic activity may help answer this question. "Intrinsic activity" refers to the spontaneous neural

Significance

There is considerable variability in how people respond to major stressors. Some remain healthy, whereas others deteriorate. Little is known about the brain networks that are involved in shaping these different outcomes, a problem we pursue here. Like previous studies, we find that youth living in neighborhoods with high levels of violence have worse cardiometabolic health than peers from safer communities. Extending this knowledge, we show this connection is absent for youth who display higher connectivity within the brain's frontoparietal central executive network (CEN), which facilitates efforts of self-control as well as reinterpretation of threatening events and suppression of unwanted emotional imagery. These observations suggest that CEN connectivity may be a neurobiological contributor to resilience.

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states that occur when a person is not engaged in a task. This resting-state activity is coordinated by a set of large-scale functional networks, each of which is comprised of anatomically distributed nodes that display correlated patterns of activity (15). This phenomenon is referred to as "resting-state functional connectivity" (rsFC). The degree of rsFC is a temporally stable characteristic of individuals that reflects person-to-person variation in both the anatomical structure and functional history of a network, i.e., how often its nodes have been coactivated (16, 17). By late childhood, individual differences in rsFC are apparent (18).

Although the functions that intrinsic networks support are still being clarified, mounting evidence indicates they are instrumental in helping us anticipate environmental changes and understand their significance (19). These observations suggest that individual differences in rsFC might facilitate understanding of the heterogeneity in adaptation we highlighted above. Indeed, violent neighborhoods are inherently unpredictable places to live, which people must navigate while balancing two competing demands on cognitive resources: purposefully going about daily activities versus remaining vigilant for threats to safety. In doing so, they are likely to engage the frontoparietal central executive network (CEN), which connects areas of the dorsolateral prefrontal cortex and the 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 threatening stimuli, and suppress intrusive, unpleasant thoughts (20–22). Neighborhood danger is also likely to engage the anterior salience network (aSN), whose nodes functionally connect the dorsal anterior cingulate cortex with regions involved in threat vigilance and salience processing. The aSN is involved in the detection of incoming stimuli, assigning those stimuli meaning, and initiating a biobehavioral response.

Collectively, these observations suggest that variations in the functional connectivity within intrinsic networks might constitute a neurobiological source of resilience or vulnerability. However, to our knowledge, this hypothesis has yet to be evaluated. We do so here in a sample of urban youth exposed to varying amounts of community violence, as reflected in their neighborhood murder rate. The health outcomes included multiple dimensions of cardiometabolic risk, including signs of metabolic syndrome (MetS) and insulin resistance. These signs of risk begin to emerge in early adolescence, and they generally track across the life course (23), so that youth with unfavorable profiles have increased susceptibility to later-life conditions that can include diabetes, heart disease, and stroke.

We hypothesized that individual differences in network functional connectivity would serve as moderators of the relationship between the neighborhood murder rate and cardiometabolic risk. The nature of our predictions varied across networks. As noted, the CEN supports self-control, reappraisal of threats, and suppression of unpleasant thoughts. As such, we reasoned that youth with greater connectivity in this network would be resilient, not manifesting cardiometabolic risk under high-violence conditions. By contrast, the aSN detects incoming stimuli, assigns them meaning, and initiates biobehavioral responses. Therefore, greater connectivity among its nodes should theoretically constitute a source of vulnerability that amplifies a youth's behavioral and biological responses to threats in the environment. Finally, as a check on specificity, we considered the rsFC of the most widely studied intrinsic network, the default mode network (DMN). Anchored in the posterior cingulate cortex and medial prefrontal cortex, the DMN is implicated in self-referential processes, including autobiographical memory and self-monitoring (24). It was not apparent to us how variations in such processes would bear upon youth responses to neighborhood violence. Thus, we made a null prediction for the DMN, reasoning that it would not operate as a moderator.

Results

Overview. Data are from a study of eighth-graders from the Chicago area, all of whom were without a history of serious medical or psychiatric illnesses. Following an overnight fast, youth attended an assessment session during which cardiometabolic risk was assessed. Sessions were held between 8:00 and 10:00 AM to minimize circadian variations. The principal health outcome was MetS, a cluster of interrelated signs whose presence forecasts higher risks of later diabetes, heart disease, and stroke. For youth, a MetS diagnosis requires three or more of these signs: abdominal adiposity, raised blood pressure, elevated glucose, raised triglycerides, and lowered high-density lipoproteins (25). Thus, we measured each youth's waist, recorded his/her blood pressure continuously for 10 min using a CNAP Monitor 500 (CNSystems), and drew antecubital blood from which fasting lipids and glucose were assayed. Because only seven youth met diagnostic criteria, we considered two alternative definitions of metabolic risk (26): the number of signs for which a youth scored above the International Diabetes Federation threshold and a composite formed by averaging z-scored values of each sign. The latter variable addresses concerns that the MetS diagnosis loses useful information by applying binary thresholds to continuously distributed variables (27).

MetS guidelines also have been criticized for omitting signs with prognostic value (28). For example, the MetS definition considers fat in the abdomen but not elsewhere in the body, despite evidence that total adiposity independently forecasts heart disease (29). Also, the MetS definition considers glucose but not insulin, despite evidence that a combined indicator reflecting insulin resistance yields greater sensitivity (30). Thus, we supplemented MetS with indicators of total adiposity [body mass index (BMI) measured in kilograms per square meter], body fatness (measured via bioimpedance using a Tanita BF-350 total body composition analyzer), and insulin resistance [estimated from fasting insulin and glucose using the homeostatic model assessment of insulin resistance (HOMA-IR) equation]. Finally, we considered leptin, a hormone that regulates appetite by mediating cross-talk between adipose tissue and brain regions involved in hunger and feeding. Leptin also regulates a host of cardiometabolic processes, including insulin resistance, blood pressure, and vascular tone (31).

During a separate session, youth underwent functional MRI (fMRI) to quantify rsFC of the aSN, CEN, and DMN. The scan consisted of a 10-min run during which youth were instructed to sit quietly with their eyes open. We selected the regions of interest (ROIs) a priori for each network from meta-analytic research and publicly available atlases (32–34). ROIs for each network are shown in *SI Appendix*, Fig. S1 and Table S1. Functional connectivity within each network was quantified by correlating the average time series in an ROI with the average time series in all other ROIs within the network.

Preliminary Analyses. Table 1 describes the 218 youth in the analytic sample. They ranged from 12 to 14 y old, and most were at least midway through puberty. The sample was highly diverse, with roughly equal numbers of youth identifying as Hispanic, white, and black. Based on their family's income-to-needs ratio, 18% of youth met the federal poverty threshold, and another 22% were low income.

Using crime data that local police departments supply to the Federal Bureau of Investigation, Applied Geographic Solutions computes a neighborhood murder index (NMI). This index is given at the block-group level of resolution, which corresponds to neighborhoods of 600–3,000 people. The NMI's validity has been illustrated in large-scale studies of violence and health in adults (8). Fig. 1 shows the spatial distribution of NMIs in the Chicago area using values for the 5-y window from 2010 to 2014. As is evident, there is considerable variability across the 192 different block groups in our sample. The NMI is scaled so that a value of 100 represents a block group with murder rates at the national average. The mean value in our sample was 242 (SD = 257, range 3–986), meaning that, on average, murder was 142% more common in study block groups than in the United States as a whole. However, the sample's distribution was skewed to the right, so its median (159) is a better indicator of central tendency.

Table 1. Characteristics of the sample (n = 218)

Characteristic	N (%) or mean (SD)
Age, y	13.9 (0.54)
Sex, female	143 (65.6%)
Self-identified race, white (non-Hispanic)	75 (34.4%)
Self-identified race, black (non-Hispanic)	73 (33.5%)
Self-identified ethnicity, Hispanic (any race)	68 (31.2%)
Pre-, early, or mid-puberty	72 (33.0%)
Late or post-puberty	146 (67.0%)
Annual household income, thousands of dollars	90.3 (83.8)
Household savings, thousands of dollars	106.4 (361.5)
Income below federal poverty line	39 (17.9%)
MetS, no. of signs	0.47 (0.78)
MetS, composite score	0.03 (2.28)
BMI	23.1 (5.0)
Body fat, %	28.8 (15.1)
Insulin resistance, HOMA-IR	3.0 (2.2)
Circulating leptin, ng/mL	16.6 (19.8)

Hypothesis Testing. This dataset has a nested structure in which youth live within block groups. Thus, we tested hypotheses using generalized estimating equations (GEE), specifying block group as a nesting variable and an exchangeable covariance matrix with robust estimation. Each model included terms for the NMI and the rsFC network of interest, a product variable representing their interaction, and a panel of covariates that included age, gender, self-identified racial (white vs. non-white) and ethnic (Hispanic vs. non-Hispanic) category, family income and savings, and pubertal status using a well-validated instrument, the Peterson Pubertal Development Scale (35). *SI Appendix*, Table S2 shows zero-order correlations between these covariates and predictors and outcomes. Reflecting long-term disparities in the Chicago area, lower-income and black youth tended to reside in areas with higher NMI values and show worse cardiometabolic health. *SI Appendix*, Fig. S2 illustrates the strength of the multivariate associations between covariates and outcomes from the GEE models. In both cases, the covariates were occasionally, but not consistently, related to study predictors and outcomes. Because the cardiometabolic outcomes had positive values and were right-skewed, we specified gamma probability distributions with log-links. Relative to more conventional strategies for normalizing skewed data, e.g., trimming and transforming, this approach utilizes all available values, yields more interpretable results, and generally has greater power (36).

CEN. Table 2 summarizes GEEs relating the neighborhood murder rate and CEN rsFC to cardiometabolic health (*SI Appendix*, Table S3). Consistent with hypotheses, significant interactions emerged for all six outcomes considered, including BMI, percent body fat, leptin, insulin resistance, and both MetS indicators (Ps from <0.0001–0.03). Because multiple outcomes were examined, we applied Benjamini and Hochberg's (37) step-up procedure to control the proportion of false discoveries. As *SI Appendix*, Table S4 shows, with the false-discovery rate controlled at 5%, all the observed interactions remained significant.

To decipher the interactions, we used standard procedures (38) to plot cardiometabolic outcomes at lower (−1 SD) and higher (+1 SD) values of the NMI and CEN distributions (Fig. 2). Across outcomes, the neighborhood murder rate and cardiometabolic risk were positively associated but only among youth who displayed lower rsFC within the CEN. To confirm this interpretation, we next estimated the simple slopes relating the neighborhood murder rate to cardiometabolic risk separately for youth at lower (−1 SD) and higher (+1 SD) values of the CEN rsFC distribution (38). As Table 3 shows, these simple slopes were significantly greater than zero for all outcomes at lower values of CEN rsFC. The exception was the MetS composite, for which the slope value was marginal. By contrast, at higher levels of CEN rsFC, the link between the neighborhood murder rate and cardiometabolic health was not apparent, as reflected in the simple slopes being statistically equivalent to zero. Insulin resistance was an exception to this pattern: At higher rsFC the neighborhood murder rate and HOMA were inversely associated. (For some outcomes, main effects were observed for NMI and/or CEN. However, all these main effects were qualified by interactions, so we did not interpret them further.)

aSN. Consistent with aSN predictions, we observed significant interactions for two indicators of adiposity: BMI and percent body fat (Table 2 and *SI Appendix*, Table S5). However, neither of these interactions survived 5% false-discovery controls, so we did not interpret them further. No other significant interactions were apparent (Ps 0.06–0.92) (*SI Appendix*, Table S5), although several main effects of NMI emerged: Youth from neighborhoods with higher murder rates had more adiposity, leptin, and MetS signs.

DMN. Consistent with hypotheses, there was minimal evidence of moderation by the DMN (*SI Appendix*, Table S6). For four of the six outcomes, no significant interaction was observed. The exceptions were MetS signs (P = 0.05) and insulin resistance (P = 0.005), but only the latter survived 5% false-discovery rate controls. As *SI Appendix*, Fig. S3 shows, for youth with lower DMN rsFC, the neighborhood murder rate was positively associated with insulin resistance (simple slope = 0.18; SE = 0.08; P = 0.03). By contrast, among youth with higher rsFC in this network, this

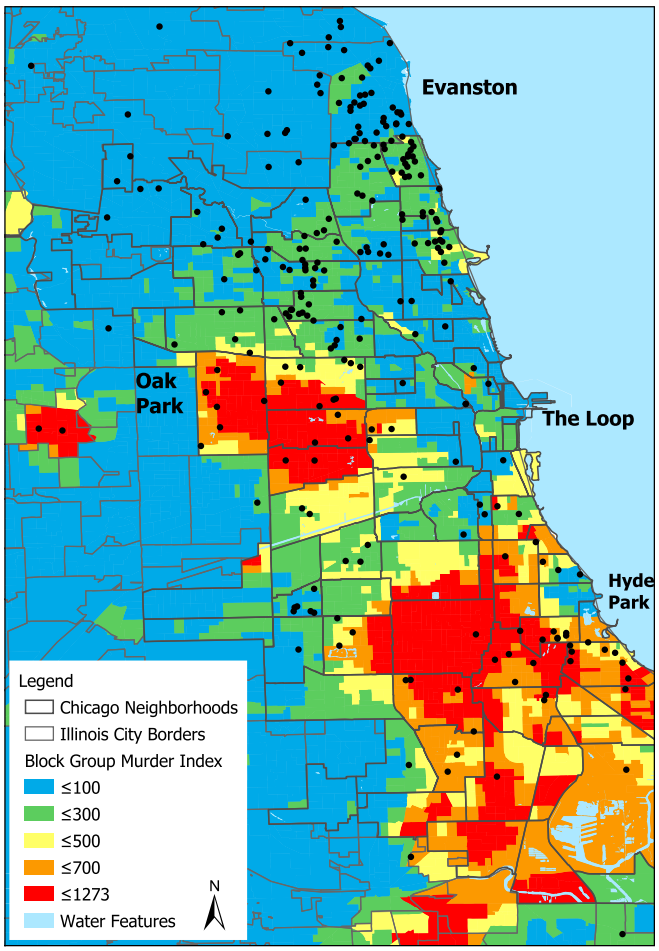

Fig. 1. Spatial distribution of neighborhood murder in the Chicago region. Estimates are based on years 2010–2014 and are derived at the block-group level of resolution. Round dots represent the residential addresses of youth in the sample.

Table 2. Key results from GEEs

	CEN	aSN	DMN
Outcome	B (95% CI)	B (95% CI)	B (95% CI)
MetS count of signs	−0.35 (−0.51, −0.19)	0.01 (−0.17, 0.19)	0.21 (−0.41, −0.00)
MetS composite	−0.17 (−0.30, −0.03)	0.04 (−0.01, 0.09)	−0.05 (−0.12, 0.01)
BMI	−0.04 (−0.08, −0.01)	0.03 (0.00, 0.05)	−0.02 (−0.05, 0.02)
Percent body fat	−0.06 (−0.11, −0.01)	0.04 (0.00, 0.09)	−0.03 (−0.07, 0.01)
Insulin resistance	−0.13 (−0.21, −0.04)	0.03 (−0.04, 0.11)	−0.12 (−0.20, −0.04)
Serum leptin	−0.02 (−0.04, −0.00)	0.02 (−0.00, 0.03)	−0.01 (−0.03, 0.01)

Shown are interactions between neighborhood murder rate and functional connectivity in models predicting cardiometabolic health. B refers to the parameter estimate for the interaction term. Complete results are presented in *SI Appendix*. All models include covariates reflecting the child's age and sex, whether s/he self-identifies as white and/or Hispanic, family income and savings, and pubertal stage.

association was inverse (simple slope = −0.22; SE = 0.09; P = 0.01). For other outcomes, no main effects of DMN rsFC were apparent (Ps 0.07–0.84).

Personal Victimization. Youth from high-violence neighborhoods are more likely to have personal histories of victimization, raising questions about whether the findings above truly reflect vicarious exposure to violence. With that said, few youth in our sample had a history of serious victimization (four had been attacked with a knife and three with a gun), so this is unlikely to account for our findings. When we considered a broader definition of violence, i.e., being "shoved, hit, or kicked" plus gun and knife attacks, a larger proportion (39.0%) endorsed being victimized. However, when the GEEs were recomputed with this broad index as a covariate, the magnitude and significance of the NMI × CEN rsFC interactions were virtually unchanged: BMI (P = 0.03); body fat (P = 0.02); leptin (P = 0.03); insulin resistance (P = 0.003); count of MetS signs ($P \leq 0.0001$); MetS composite (P = 0.04).

Other Neighborhood Risks. Neighborhoods with high violence are likely to have other features that undermine youth's health. Thus, to evaluate the specificity of the findings, we reestimated the GEEs with additional neighborhood-level covariates that could have plausibly contributed to the CEN × NMI interactions. These covariates included the neighborhood's level of environmental hazard, median household income, and racial/ethnic composition. To capture the availability of nutritious food, we also calculated the distance from each youth's home to the nearest full-service grocery store. *SI Appendix*, Table S7 shows that the magnitude and significance of the interactions were virtually unchanged with these covariates in the models.

Psychological Distress. We also considered the possibility that the interactions were simply a reflection of underlying psychological distress, which covaries with the major constructs explored here (39, 40). Accordingly, we recomputed the GEEs after including covariates that reflected symptoms of depression and anxiety, as measured by youth's self-reports on the Revised Child Anxiety and Depression Scale-25 (41). *SI Appendix*, Table S8 shows that including these covariates did not change the magnitude or significance of the NMI × CEN interactions.

CEN Behavioral Correlates. Our CEN hypotheses were based on evidence that it supports the cognitive regulation of thought, behavior, and emotion. However, this evidence mostly comes from task-based fMRI studies rather than rsFC (20–22). Thus, to clarify the meaning of CEN in the resting-state context, we examined its association with the self-regulation of eating behavior, a trait likely to be of importance to cardiometabolic health. As part of their initial session, youth engaged in a standard laboratory

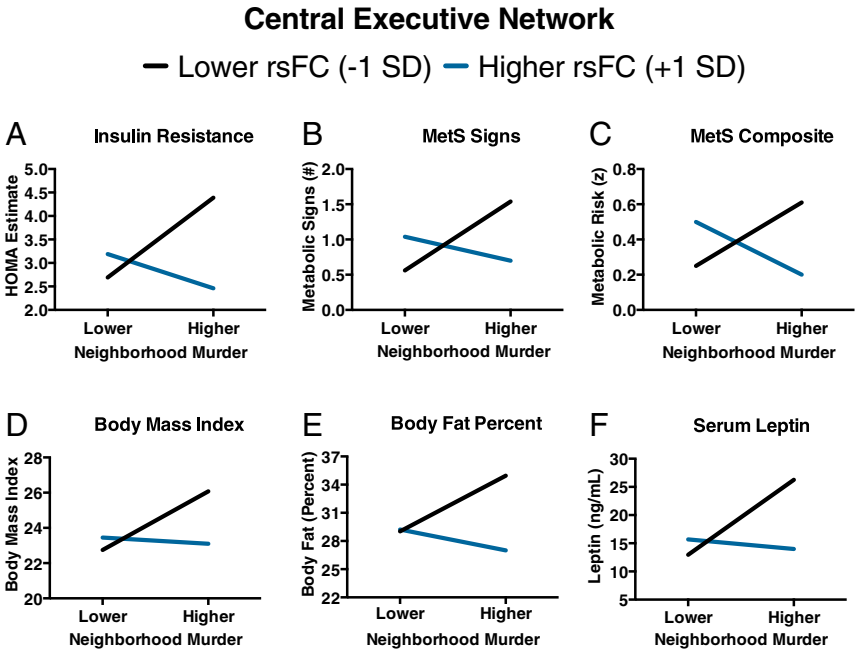

Fig. 2. Cardiometabolic risks associated with the neighborhood murder rate vary according to degree of rsFC within the CEN. (*A–F*) Values of outcome are plotted at lower (−1 SD) and higher (+1 SD) values of the neighborhood murder rate and functional connectivity distributions, as per ref. 38.

Table 3. Results of simple-slope analyses

Outcome	Lower rsFC slope (SEM)	*P*	Higher rsFC slope (SEM)	*P*
MetS count of signs	0.51 (0.12)	<0.0001	−0.20 (0.19)	0.30
MetS composite	0.18 (0.10)	0.08	−0.15 (0.12)	0.19
BMI	0.07 (0.03)	0.01	−0.01 (0.02)	0.70
Percent body fat	0.09 (0.03)	0.007	−0.02 (0.04)	0.55
Insulin resistance	0.24 (0.12)	0.04	−0.13 (0.06)	0.04
Serum leptin	0.04 (0.01)	0.0005	0.00 (0.01)	0.57

Slope parameters represent the association between the neighborhood violence and cardiometabolic health, estimated at lower (−1.5 SD) and higher (+1.5 SD) values of the sample distribution for CEN rsFC. These associations are net of covariates reflecting the child's age and sex, whether s/he self-identifies as white and/or Hispanic, family income and savings, and pubertal stage.

task (42) in which they were asked to taste three types of candy, and evaluate the taste, texture, and freshness of each. Youth were told they could eat as many pieces of candy as needed to make accurate ratings. After the ratings had been made, we left the bowls of candy out and invited youth to snack as they wished. At the end of the session, we calculated the total amount of candy each youth ate by subtracting the postsession weight of the bowls (in grams) from the presession weight. (As a cover story, we described the task as a measure of sensory perception.) Regression analyses, in which age, sex, racial and ethnic identity, family income and savings, and pubertal status were included, identified an inverse association, such that youth with lower CEN rsFC ate more candy ($B = -0.37$, SE = 0.17, $P = 0.03$). Unfortunately, our protocol did not include behavioral indicators of other conceptually relevant processes supported by the CEN, e.g., threat appraisal or intrusive thoughts.

Discussion

There is increasing recognition that neighborhood violence has a long reach. As Sharkey explains, "violence happens to people, but it also happens to places" (1). Consistent with this observation and with accumulating literature (2–4, 7–9), we found evidence linking neighborhood violence with cardiometabolic risk in urban youth. Extending this knowledge, we identified rsFC of the CEN as a neurobiological moderator of this association, which differentiated the health of youth living in high-violence neighborhoods. Among youth with lower CEN rsFC, the neighborhood murder rate was associated with greater adiposity, more serum leptin and insulin resistance, and higher scores on two MetS indicators. By contrast, no such associations were apparent among youth showing higher CEN connectivity.

This pattern was not attributable to variations in racial or ethnic background, pubertal stage, financial security, psychological distress, or victimization history. It also was not attributable to the degree of environmental pollution, economic disadvantage, or residential segregation in youth's neighborhoods or to the availability of nutritious food. Instead, the findings appear to reflect a scenario in which CEN connectivity moderates how youth respond to the challenges of living in a neighborhood where the threat of violence is ongoing. In such an environment, high CEN rsFC would presumably be salutary because it supports the reappraisal of threatening stimuli and suppression of intrusive thoughts (21, 22). In a variety of stressful conditions, these strategies have been shown to reduce the magnitude of cardiovascular and neurohormonal reactivity and to protect against worsening health (43, 44). For youth in violent neighborhoods, high CEN rsFC would also likely facilitate adaptive self-regulation, reducing the frequency of unhealthy behaviors that people sometimes use to cope with unpredictable stress (e.g., comfort eating, cigarette use). The results from our eating task, in which youth with low CEN rsFC consumed more candy, provide initial support for this self-control scenario. However, further research is needed to substantiate this finding and to delineate what role the other CEN-supported processes we speculate about play.

Relative to the CEN, the other intrinsic networks we considered showed limited evidence of operating as moderators. There were some indications that higher connectivity within the aSN functions as a vulnerability factor, strengthening the association between the neighborhood murder rate and childhood adiposity. However, these patterns did not survive false-discovery controls and were not observed with other cardiometabolic outcomes. These results could indicate the aSN plays a modest role in behavior relevant to energy balance (e.g., dietary intake or physical activity) but that, unlike the CEN, it has limited influence on processes that are clinically downstream of obesity. Another possibility is that, as a consequence of modern digital culture, variations in youths' aSN connectivity are of negligible importance for the phenomena considered here. In today's world, youth are likely to learn about neighborhood violence within minutes of its occurrence and to be saturated with details and imagery of the event via cellphone calls, text messages, and social media. With such large quantities of graphic information so readily available, variations in the kinds of bottom-up threat-detection processes the aSN subserves may have limited functional significance.

Consistent with predictions, we observed minimal evidence that DMN rsFC operated as a moderator of neighborhood violence or had bivariate associations with cardiometabolic risk. As explained in the Introduction, we do not have strong conceptual reasons to hypothesize that such associations exist. However, it is conceivable that our restrictive eligibility criteria precluded such associations from emerging. DMN abnormalities are common in neuropsychiatric disorders such as depression (39). Because youth with any psychiatric history were excluded from the study, we may have insufficient variation in DMN rsFC to definitely evaluate its role.

This study's results should be interpreted in the context of its limitations. Most importantly, the cross-sectional, observational nature of its design precludes inferences about causality. Because of collateral evidence from earlier studies, which used within-person contrasts (2) and threat salience manipulations (45) to facilitate causal inference, we are persuaded that neighborhood violence can, in principle, affect youth health. The causal status of functional connectivity is less certain. A reverse-causation scenario is certainly plausible here, although it would not parsimoniously explain the interactions we observed; in other words, if cardiometabolic health were affecting functional connectivity, why would this be evident only among youth in high-violence areas? This study is also subject to omitted-variable biases: CEN rsFC could be a proxy for other experiences (e.g., early caregiving) or characteristics (e.g., allelic variation, cognitive ability) that are more centrally involved with adaptation. Differential selection could also have played a role if families with hardy, healthy youth preferentially located themselves in more dangerous neighborhoods. Also, although we tested multiple alternative explanations at the individual and neighborhood level, follow-up research with more thorough

covariate assessments would bolster confidence in the specificity and robustness of these findings. Finally, because some youth moved homes during the 5-y window of the murder index, we are likely to have estimated exposure neighborhood violence imprecisely. Although not ideal, the consequence of this misestimation would be to introduce measurement error, biasing models toward null results.

To address these limitations, a multiwave longitudinal study is needed that tracks neighborhood conditions, brain development, and cardiometabolic risk across childhood. Such a study could also help answer mechanistic questions we are unable to address here regarding the role of youth's subjective perceptions of violence, how individual differences in rsFC arise, and the pathways by which they shape resilience vs. vulnerability to adversity. Along these lines, preliminary evidence suggests that individual differences in functional connectivity reflect developmental histories of coactivation (17). To the extent this account is accurate, it suggests that youth in our study with high CEN rsFC have a history of using self-control, threat reappraisal, and thought suppression to mitigate biobehavioral responses to neighborhood violence. Formally testing this developmental scenario should be a priority in subsequent research. Another priority should be to consider more fully histories of personal victimization and to determine whether their impact is moderated by functional connectivity in a manner similar to the NMI. We hypothesize the same patterns will be apparent with personal victimization, but we could not definitively test that possibility here because few youth had been victims of severe assaults.

Meanwhile, the observations here advance knowledge about differential adaptation to adversity, highlighting the CEN's intrinsic activity as a potential neurobiological contributor to resilience. For basic scientists, these findings provide clues about the neural circuitries that facilitate or undermine adaptation. Should these observations be substantiated, they could also have implications for intervention strategies. In this regard, preliminary evidence suggests that "network training" programs, which seek to modulate the CEN's functional connectivity, can alter patterns of food choice, drug use, and stress reactivity (46).

Methods

The study consisted of two sessions. At the first, youth completed psychosocial measures and had cardiometabolic health assessed while sociodemographic data were collected from a parent. At the second, youth had structural and functional MRI scans. All youth gave written assent to participate, and a parent gave written consent. Northwestern University's IRB approved the protocol. Additional details are in *SI Appendix*.

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1. Sharkey P (2018) The long reach of violence: A broader perspective on data, theory, and evidence on the prevalence and consequences of exposure to violence. *Ann Rev Criminol* 1:85–102.
2. Heissel JA, Sharkey PT, Torrats-Espinosa G, Grant K, Adam EK (2018) Violence and vigilance: The acute effects of community violent crime on sleep and cortisol. *Child Dev* 89:e323–e331.
3. Midei AJ, Matthews KA (2011) Interpersonal violence in childhood as a risk factor for obesity: A systematic review of the literature and proposed pathways. *Obes Rev* 12: e159–e172.
4. Wright AW, Austin M, Booth C, Kliewer W (2017) Systematic review: Exposure to community violence and physical health outcomes in youth. *J Pediatr Psychol* 42: 364–378.
5. Burdette HL, Whitaker RC (2004) Neighborhood playgrounds, fast food restaurants, and crime: Relationships to overweight in low-income preschool children. *Prev Med* 38:57–63.
6. Cohen RT, Canino GJ, Bird HR, Celedón JC (2008) Violence, abuse, and asthma in Puerto Rican children. *Am J Respir Crit Care Med* 178:453–459.
7. Sternthal MJ, Jun HJ, Earls F, Wright RJ (2010) Community violence and urban childhood asthma: A multilevel analysis. *Eur Respir J* 36:1400–1409.
8. Theall KP, Drury SS, Shirtcliff EA (2012) Cumulative neighborhood risk of psychosocial stress and allostatic load in adolescents. *Am J Epidemiol* 176(Suppl 7):S164–S174.
9. Theall KP, Shirtcliff EA, Dismukes AR, Wallace M, Drury SS (2017) Association between neighborhood violence and biological stress in children. *JAMA Pediatr* 171:53–60.
10. Wilson DK, Kliewer W, Teasley N, Plybon L, Sica DA (2002) Violence exposure, catecholamine excretion, and blood pressure nondipping status in African American male versus female adolescents. *Psychosom Med* 64:906–915.
11. Bonanno GA, Mancini AD (2008) The human capacity to thrive in the face of potential trauma. *Pediatrics* 121:369–375.
12. Masten AS (2007) Resilience in developing systems: Progress and promise as the fourth wave rises. *Dev Psychopathol* 19:921–930.
13. Davidson RJ, McEwen BS (2012) Social influences on neuroplasticity: Stress and interventions to promote well-being. *Nat Neurosci* 15:689–695.
14. Chen E, Miller GE (2012) "Shift and persist" strategies: Why being low in socioeconomic status isn't always bad for your health. *Perspect Psychol Sci* 7:135–158.
15. Raichle ME (2015) The restless brain: How intrinsic activity organizes brain function. *Philos Trans R Soc Lond B Biol Sci* 370:20140172.
16. Gratton C, et al. (2018) Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. *Neuron* 98:439–452.e5.
17. Gabard-Durnam LJ, et al. (2016) Stimulus-elicited connectivity influences resting-state connectivity years later in human development: A prospective study. *J Neurosci* 36: 4771–4784.
18. Grayson DS, Fair DA (2017) Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature. *Neuroimage* 160:15–31.
19. Vatansever D, Menon DK, Stamatakis EA (2017) Default mode contributions to automated information processing. *Proc Natl Acad Sci USA* 114:12821–12826.
20. Turner BM, et al. (January 24, 2018) On the neural and mechanistic bases of self-control. *Cereb Cortex*, 10.1093/cercor/bhx355.
21. Gagnepain P, Hulbert J, Anderson MC (2017) Parallel regulation of memory and emotion supports the suppression of intrusive memories. *J Neurosci* 37:6423–6441.
22. Wessing I, Rehbein MA, Postert C, Fürniss T, Junghöfer M (2013) The neural basis of cognitive change: Reappraisal of emotional faces modulates neural source activity in a frontoparietal attention network. *Neuroimage* 81:15–25.
23. Juonala M, et al. (2010) Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: The Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. *Circulation* 122:2514–2520.
24. Raichle ME (2015) The brain's default mode network. *Annu Rev Neurosci* 38:433–447.
25. Zimmet P, et al.; IDF Consensus Group (2007) The metabolic syndrome in children and adolescents–An IDF consensus report. *Pediatr Diabetes* 8:299–306.
26. Miller GE, Chen E, Yu T, Brody GH (2017) Metabolic syndrome risks following the great recession in rural black young adults. *J Am Heart Assoc* 6:e006052.
27. Goodman E (2008) Metabolic syndrome and the mismeasure of risk. *J Adolesc Health* 42:538–540.
28. Cornier MA, et al. (2008) The metabolic syndrome. *Endocr Rev* 29:777–822.
29. Wormser D, et al.; Emerging Risk Factors Collaboration (2011) Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: Collaborative analysis of 58 prospective studies. *Lancet* 377:1085–1095.
30. Turchiano M, Sweat V, Fierman A, Convit A (2012) Obesity, metabolic syndrome, and insulin resistance in urban high school students of minority race/ethnicity. *Arch Pediatr Adolesc Med* 166:1030–1036.
31. Blüher M, Mantzoros CS (2015) From leptin to other adipokines in health and disease: Facts and expectations at the beginning of the 21st century. *Metabolism* 64:131–145.
32. Anderson JS, Ferguson MA, Lopez-Larson M, Yurgelun-Todd D (2011) Connectivity gradients between the default mode and attention control networks. *Brain Connect* 1:147–157.
33. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD (2012) Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex* 22: 158–165.
34. Kohn N, et al. (2014) Neural network of cognitive emotion regulation–An ALE meta-analysis and MACM analysis. *Neuroimage* 87:345–355.
35. Petersen AC, Crockett L, Richards M, Boxer A (1988) A self-report measure of pubertal status: Reliability, validity, and initial norms. *J Youth Adolesc* 17:117–133.
36. Coxe S, Aiken LS, West SG (2013) *Oxford Handbook of Quantitative Methods, Volume 2: Statistical Analysis* (Oxford Univ Press, New York), pp 26–51.
37. Benjamini Y (2010) Discovering the false discovery rate. *J R Statist Soc* 72:405–416.
38. Preacher KJ, Curran PJ, Bauer DJ (2006) Computational tools for probing interaction effects in multiple linear regression, multilevel modeling, and latent curve analysis. *J Educ Behav Stat* 31:437–448.
39. Menon V (2011) Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn Sci* 15:483–506.
40. Nusslock R, Miller GE (2016) Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. *Biol Psychiatry* 80:23–32.
41. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE (2000) Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behav Res Ther* 38:835–855.
42. Tice DM, Bratslavsky E, Baumeister RF (2001) Emotional distress regulation takes precedence over impulse control: If you feel bad, do it! *J Pers Soc Psychol* 80:53–67.
43. Chen E, Miller GE (2013) Socioeconomic status and health: Mediating and moderating factors. *Annu Rev Clin Psychol* 9:723–749.
44. Gianaros PJ, et al. (2014) An inflammatory pathway links atherosclerotic cardiovascular disease risk to neural activity evoked by the cognitive regulation of emotion. *Biol Psychiatry* 75:738–745.
45. Chen E, Langer DA, Raphaelson YE, Matthews KA (2004) Socioeconomic status and health in adolescents: The role of stress interpretations. *Child Dev* 75:1039–1052.
46. Tang YY, Posner MI, Rothbart MK, Volkow ND (2015) Circuitry of self-control and its role in reducing addiction. *Trends Cogn Sci* 19:439–444.