

# Neighborhood Disadvantage Associated With Blunted Amygdala Reactivity to Predictable and Unpredictable Threat in a Community Sample of Youth

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## ABSTRACT

**BACKGROUND:** Childhood socioeconomic disadvantage is a form of adversity associated with alterations in critical frontolimbic circuits involved in the pathophysiology of psychiatric disorders. Most work has focused on individual-level socioeconomic position, yet individuals living in deprived communities typically encounter additional environmental stressors that have unique effects on the brain and health outcomes. Notably, chronic and unpredictable stressors experienced in the everyday lives of youth living in disadvantaged neighborhoods may impact neural responsiveness to uncertain threat.

**METHODS:** A community sample of children ( $N = 254$ ) ages 8 to 15 years (mean = 12.15) completed a picture anticipation task during a functional magnetic resonance imaging scan, during which neutral and negatively valenced photos were presented in a temporally predictable or unpredictable manner. Area Deprivation Index (ADI) scores were derived from participants' home addresses as an index of relative neighborhood disadvantage. Voxelwise analyses examined interactions of ADI, valence, and predictability on neural response to picture presentation.

**RESULTS:** There was a significant ADI  $\times$  valence interaction in the middle temporal gyrus, anterior cingulate cortex, hippocampus, and amygdala. Higher ADI was associated with less amygdala activation to negatively valenced images. ADI also interacted with predictability. Higher ADI was associated with greater activation of lingual and calcarine gyri for unpredictably presented stimuli. There was no three-way interaction of ADI, valence, and predictability.

**CONCLUSIONS:** Neighborhood disadvantage may impact how the brain perceives and responds to potential threats. Future longitudinal work is critical for delineating how such effects may persist across the life span and how health outcomes may be modifiable with community-based interventions and policies.

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In the United States, 16.1% of children live in poverty (1). Financial insecurity causes undue chronic stress, because individuals of lower socioeconomic status are faced with uncertainty and instability in meeting their basic needs, including access to food, health care, and electricity. Socioeconomic disadvantage extends beyond individual households, creating environmental stressors at the community level, e.g., limited education and employment opportunities (2,3), exposure to neurotoxins (lead, pollution) (4,5), and higher trauma prevalence (6,7). Therefore, the neighborhood where an individual lives may have adverse effects—beyond those specific to their own socioeconomic circumstances—on physical and emotional well-being. Critically, childhood adversity, broadly, is a known risk factor for psychopathology across the life span (8). Given the dynamic nature of brain development during childhood, this link may be mediated by adaptations in brain structure and function that occur to cope with chronic stressful

circumstances. Understanding the neural consequences of neighborhood disadvantage is imperative for improving insight into risk and resilience for psychopathology.

Function of the neuroendocrine stress response may underlie links between neighborhood disadvantage and the brain. Stress triggers a robust response via the hypothalamic-pituitary-adrenal axis to release stress hormones, including glucocorticoids and cortisol (9–11). While instrumental for adapting to acute, short-term stressors, prolonged or repeated exposure to chronic stress increases allostatic load and has detrimental effects on the brain (9,11–13). Regions such as the amygdala and prefrontal cortex (PFC) help modulate the hypothalamic-pituitary-adrenal axis and may be particularly sensitive to chronic stress (11,12). Children in disadvantaged neighborhoods are more likely to experience nutritional deficiencies, less social enrichment, and exposure to neurotoxic substances, increasing physiological stress burden that may

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lead to enduring neurodevelopmental effects (14). Theories such as the Adaptive Calibration Model have posited that chronic environmental stress contributes to long-term unresponsiveness in stress reactivity as a form of biological adaptation (15).

The frontolimbic circuits implicated in facilitating a physiological stress response are central to affective and cognitive processing that, when disrupted, may lead to clinical symptoms (16–19). A rich history of translational research has suggested that differences in threat responsiveness play a role in the pathophysiology of anxiety-related disorders (20–22). Threat responding is regulated by a distributed network of subcortical and cortical regions. Sensory information is relayed via the thalamus to the amygdala for threat detection and elicitation of a fear response (23,24), further enhanced by a cortical affective processing network that includes the anterior cingulate cortex and insula (25). Prefrontal regions, including the ventromedial PFC (vmPFC), help dampen arousal when defensive responding is unnecessary (26,27). Extensive research has provided compelling evidence demonstrating that patients with anxiety exhibit hyperreactivity of fear excitatory regions and hyporeactivity of inhibitory regions (28–30). These neurobiological indices directly map onto clinical phenotypes defined by exaggerated fear responding, attentional biases to threat, and disrupted safety learning (20).

Childhood socioeconomic disadvantage is associated with alterations in the structure and function of these same affective circuits, including robust changes in cortical and subcortical brain morphology in the hippocampus, amygdala, and thalamus (31–33). Moreover, these differences may mediate associations between childhood socioeconomic disadvantage and anxiety-related psychopathology (34,35). Socioeconomically disadvantaged children may also struggle to effectively regulate and cope with stress in adolescence and adulthood, in light of differences in amygdala and PFC activation (36), increased sensitivity of the insula to acute stress (18), and weaker functional coupling of the amygdala and vmPFC (36,37).

Most literature has focused on individual socioeconomic position; however, accumulating evidence suggests that area-level factors, including living in a socioeconomically deprived community, have unique effects on the brain (38,39). Neighborhood disadvantage has repeatedly been associated with differences in amygdala structure and function (40–43). More broadly, amygdala and hormonal response to threat may be blunted in individuals who experienced various forms of childhood adversity (42,44–47). For youth in disadvantaged neighborhoods, this pattern of blunted stress reactivity may be key for resilience yet may have functional consequences long term. For instance, neighborhood disadvantage has been linked to reduced gray matter myelination (48) and neurocognitive performance, such as poorer inhibitory control and hypoactivation of relevant neurocircuitry (49,50), and widespread alterations in intrinsic functional brain networks supporting cognitive and affective processes (51).

Examining neural response to unpredictable threat may be key to understanding links between neighborhood disadvantage, brain function, and psychopathology. Children living in more disadvantaged communities are faced with ongoing environmental unpredictability (e.g., lack of safety, housing instability). Uncertainty is known to elicit subjective distress

(even in healthy individuals). This anxious apprehension is exaggerated in clinical populations (52–55) and may have maladaptive downstream consequences, including behavioral avoidance (53). Work in youth samples has suggested that the potentiating effects of uncertainty on threat responding are present across development (55–57). Neuroimaging work on threat predictability—conducted primarily in adults—demonstrates involvement of threat circuitry, including the amygdala and thalamus, during various aspects of unpredictable threat anticipation and response (58–61). Robust insula response to unpredictable threat has been consistently replicated in the literature (59,62,63) and is thought to facilitate anticipatory anxiety, while the vmPFC may be involved in evaluating and inhibiting emotional response to uncertainty (53,58,60). Compared with healthy control subjects, preadolescent children with anxiety disorders exhibit greater amygdala and insula response to uncertainty (61). For youth living in disadvantaged neighborhoods, experimental paradigms may provide insight into how individuals respond to unpredictable threats and stressors they encounter within their real-world neighborhoods. Similar to anxiety, hypervigilance related to chronic environmental stress could potentiate uncertainty processing; however, no studies have examined how neighborhood disadvantage relates to neural response to uncertainty.

We conducted whole-brain, voxelwise analyses to examine associations between neighborhood disadvantage and neural response to predictable and unpredictable threat in a community cross-sectional sample of third, sixth, and ninth grade children (aged 8–15 years). Based on previous work (42,44) and theories of biological adaptation to environmental context (15), we hypothesized that greater neighborhood disadvantage would be associated with blunted responding of regions critical for response to threat, including the amygdala and thalamus, when presented with photographs of negatively valenced objects and scenes. Because the insula is sensitive to uncertainty (60,62,63), we also hypothesized that neighborhood disadvantage would be positively associated with insula response to temporally unpredictable pictures. We hypothesized that vmPFC response to unpredictability would be inversely associated with neighborhood disadvantage, given that this region helps modulate anticipatory effects of uncertainty (60) and neighborhood poverty has been linked to less activation in inhibitory circuits (50). Follow-up models included effects of household income to examine whether the effects of neighborhood disadvantage extend beyond individual socioeconomic position. Three-way interactions between neighborhood disadvantage, valence, and predictability were examined, with no specific a priori hypotheses that neighborhood disadvantage would change the magnitude or direction of uncertainty-potentiated threat response.

## METHODS AND MATERIALS

### Participants and Procedure

Children ( $N = 364$ ) were recruited through the ongoing Charleston Resilience Monitoring (CHARM) study, a multiwave, 2-year study investigating prospective risk and resilience for anxious pathology in a community-based sample of typically developing youth. Using an accelerated, longitudinal cohort design, children and their caregivers were assessed three

times annually in paradigms assaying threat responding in multiple objective measures, including functional magnetic resonance imaging (fMRI), event-related potentials, startle reflex responding, and cortisol. Participants were recruited through advertisements in schools, pediatric clinics, and the general community. Participants were eligible if they were enrolled in third, sixth, or ninth grade, 7 to 16 years old, and had a caregiver willing to participate. Exclusion criteria included non-English speaking, history of psychosis, or evidence of developmental delay or functional impairment that would interfere with completing study procedures.

For the neuroimaging substudy, participants were excluded for contraindications for MRI (e.g., irremovable metal in body [including braces]). Eligible participants ( $n = 287$ ) completed an experimental paradigm of predictable and unpredictable threat during an fMRI scan. Caregivers provided demographic information related to race and ethnicity, household income, educational background, and residential address.

Of these participants, 259 had usable fMRI data. Five participants were excluded because the neighborhood disadvantage metric could not be derived. The final sample of 254 includes 210 different families, with 41 families contributing more than one child (siblings) to the sample.

All study procedures were approved by the local institutional review board at the Medical University of South Carolina where data were collected. Participants and their caregivers provided written informed consent and received monetary compensation for their participation.

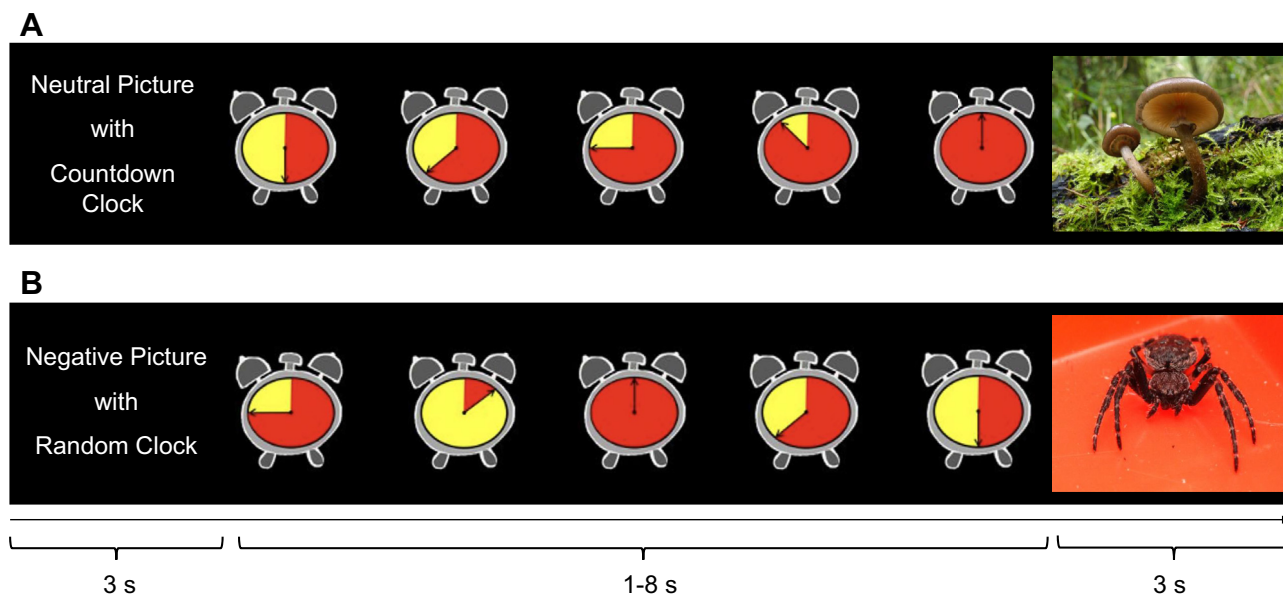
## Measures

**Individual Socioeconomic Position.** Individual demographics (e.g., age, gender, race) were reported by participants' caregivers. As an index of individual socioeconomic

status, caregivers self-reported their annual household income using an ordinal scale (1–14) with steps of \$1000, \$5000, or \$10,000 (1 = \$0–\$1,000/year; 7 = \$30,001–\$40,000/year; 14 = over \$100,000/year).

**Neighborhood Disadvantage.** The Area Deprivation Index (ADI) (64) quantified neighborhood socioeconomic position. ADI rankings are based on census block-group–level data from the National 2014–2018 American Community Survey (64–66). Each block-group represents a geographic area with a maximum of 3000 people or 1200 housing units. National ADI is a factor-based percentile ranking comprising 17 indices related to housing, income, education, and employment (67) within a block-group. ADI ranges from 1 to 100, with higher scores reflecting greater disadvantage.

**Unpredictable Threat Task.** The experimental task was based on previous work by Somerville *et al.* (60) (Figure 1) and models neural response to pictures that vary in valence (negative vs. neutral) and temporal predictability (predictable vs. unpredictable onset). Valence  $\times$  predictability conditions were presented in a mixed block event-related design wherein multiple stimulus presentations of the same type (e.g., negative predictable picture) occur within a larger block. Three blocks of ten trials for each condition were presented over three runs. Block order varied across runs (run order counterbalanced across participants). A 3000-ms written cue alerted participants to trial type at the beginning of each block: predictable negative, predictable neutral, unpredictable negative, and unpredictable neutral. In predictable blocks, a ticking clock appeared on the screen for 1000 to 8000 ms; when the clock hand reached the 12 o'clock position and the clock face was filled with red, the picture appeared on screen for 3000 ms.



**Figure 1.** Depiction of example blocks in experimental paradigm. In predictable blocks, a clock ticks until the clock hand reaches the 12 o'clock position and the clock face is filled with red. Then, a picture that is either neutral or negative in valence is presented. In unpredictable blocks, the clock hand changes position randomly and does not indicate when the picture will be presented. Rows A and B depict predictable neutral and unpredictable negative blocks, respectively.

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During unpredictable blocks, picture presentation could occur at any time, and the clock was effectively meaningless. Between blocks, participants viewed a cross-hair on the screen for 15,000 ms. Visual stimuli were selected from the International Affective Picture System (68). Each trial had a unique picture. Throughout the task, participants indicated by button press whenever a picture appeared to promote task engagement. The task was administered via E-prime 3.0 software (Psychology Software Tools, 2012) running on a Windows computer connected to the MRI scanner.

### fMRI Data

Details about scan acquisition parameters are included in the Supplement. FSL (version 6.0, FMRIB, Oxford University) was used for fMRI data analysis. Subjects' structural and gradient field map magnitude images were extracted using BET. Pre-processing steps included head motion correction (MCFLIRT), geometric distortion correction (FUGUE), spatial normalization and 12-parameter affine transformation to standard space (Montreal Neurological Institute), temporal high-pass filtering (cutoff = 50 seconds), and spatial smoothing (full width at half maximum = 6 mm). To produce statistical maps for each subject, individual events associated with picture presentation (duration = 3000 ms) were modeled with four explanatory variables (predictable negative, predictable neutral, unpredictable negative, and unpredictable neutral) and convolved with a double gamma hemodynamic response function and temporal derivatives. Interblock rest intervals and the cues denoting block start and stop were not explicitly modeled (but were identical across conditions and participants). To account for the confounding effects of head motion, regressors for six head motion parameters and volumes with excessive motion (using root mean squared error, as identified with fsl outliers) were included in subject-level statistics. All usable functional runs (mean = 2.60, SD = 0.674) for a subject were averaged for each condition using fixed effects in FSL to produce contrast of parameter estimate (cope) images (see the Supplement).

### Data Analysis

Voxelwise analyses were conducted using AFNI's 3dLMER to examine the effects of neighborhood disadvantage (ADI) on activation across the entire brain. First, predictability (predictable vs. unpredictable), valence (negative vs. neutral), and the interactions of ADI and predictability and valence were modeled as fixed effects, with gender and age included as covariates. Next, to examine whether area-level socioeconomic disadvantage explained neural activation beyond individual socioeconomic position, a fixed effect of household income was added in a follow-up model. 3dClustSim was employed using residuals from FSL to identify significant clusters using a peak threshold  $p < .001$  and cluster threshold  $p < .05$  ( $k > 13$  voxels).

## RESULTS

### Participant Characteristics

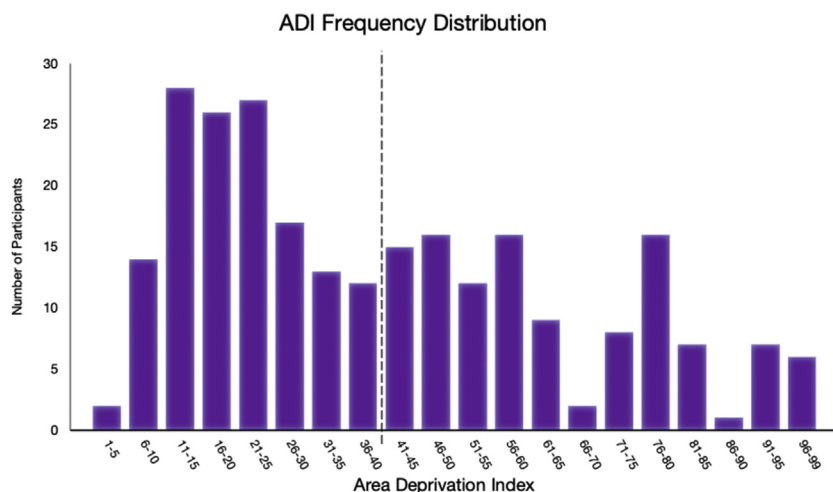
Sample characteristics are reported in Table 1. ADI frequency distribution is presented in Figure 2. ADI was significantly

**Table 1. Sample Characteristics (N = 254)**

Characteristic	n (%) or Mean (SD) [Range]
Gender	
Female	122 (48%)
Male	132 (52%)
Age, Years	12.15 (2.47) [8–15]
Grade	
3rd	78 (30.7%)
6th	91 (35.8%)
9th	85 (33.5%)
ADI	40.57 (25.59) [3–99]
Race	
African American or Black	76 (29.9%)
Multiracial	19 (7.5%)
Other	8 (3.2%)
White	139 (54.7%)
Not reported	12 (4.7%)
Ethnicity: Hispanic	26 (10.2%)
Household Income	
\$0–\$1,000	9 (3.5%)
\$1001–\$5000	3 (1.2%)
\$5001–\$10,000	6 (2.4%)
\$10,001–\$15,000	9 (3.5%)
\$15,001–\$20,000	4 (1.6%)
\$20,001–\$30,000	25 (9.8%)
\$30,001–\$40,000	16 (6.3%)
\$40,001–\$50,000	13 (5.1%)
\$50,001–\$60,000	7 (2.8%)
\$60,001–\$70,000	14 (5.5%)
\$70,001–\$80,000	17 (6.7%)
\$80,001–\$90,000	19 (7.5%)
\$90,001–\$100,000	19 (7.5%)
Over \$100,000	78 (30.7%)
Not reported	15 (5.9%)
Caregiver Education	
Less than high school	10 (4.1%)
High school or GED	19 (7.5%)
Some college	52 (20.5%)
College graduate	76 (29.9%)
Graduate or professional degree	84 (33.1%)
Not reported	13 (5.1%)
Financial Assistance	
Any <sup>a</sup>	59 (23.2%)
SNAP	40 (15.7%)
Section 8	11 (4.3%)
WIC	5 (2%)
SSI	17 (6.7%)
MASC-2	61.10 (22.03) [5–125]
Trauma Exposure (UCLA-RI-5 Screener)	1.64 (1.72) [0–10]

ADI, Area Deprivation Index; GED, General Education Development; MASC-2, Multidimensional Anxiety Scale for Children; SNAP, Supplemental Nutrition Assistance Program; SSI, Supplemental Security Income; UCLA-RI-5, UCLA Posttraumatic Stress Disorder Reaction Index for DSM-5; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

<sup>a</sup>“Any” is not a cumulative percentage as caregivers could report receiving more than one type of financial assistance.



**Figure 2.** Frequency of Area Deprivation Index (ADI) scores in sample ( $N = 254$ ). Dotted line represents sample mean of 40.57 ( $SD = 25.59$ ).

correlated with individual household income ( $r = -0.578$ ,  $p < .001$ ). ADI did not significantly vary by age ( $p = .539$ ) or gender ( $p = .170$ ). ADI was significantly correlated with trauma exposure ( $r = 0.197$ ,  $p = .003$ ) but not self-report anxiety symptoms ( $p = .488$ ). Caregivers of children with higher ADI rankings were more likely to report receiving financial assistance ( $t_{235} = 7.709$ ,  $p < .001$ ). ADI was significantly lower ( $t_{209} = -9.772$ ,  $p < .001$ ) in White ( $ADI_{\text{mean}} = 29.612$ ,  $SD = 19.95$ ) than Black ( $ADI_{\text{mean}} = 59.51$ ,  $SD = 23.11$ ) participants (Figure 3). White participants also reported higher household income ( $\chi^2_{13} = 109.319$ ,  $p < .001$ ), had higher caregiver educational attainment ( $\chi^2_4 = 36.922$ ,  $p < .001$ ), and were less likely to be receiving financial assistance ( $\chi^2_1 = 37.285$ ,  $p < .001$ ). Differences between other racial and ethnic groups were not examined due to small cell sizes.

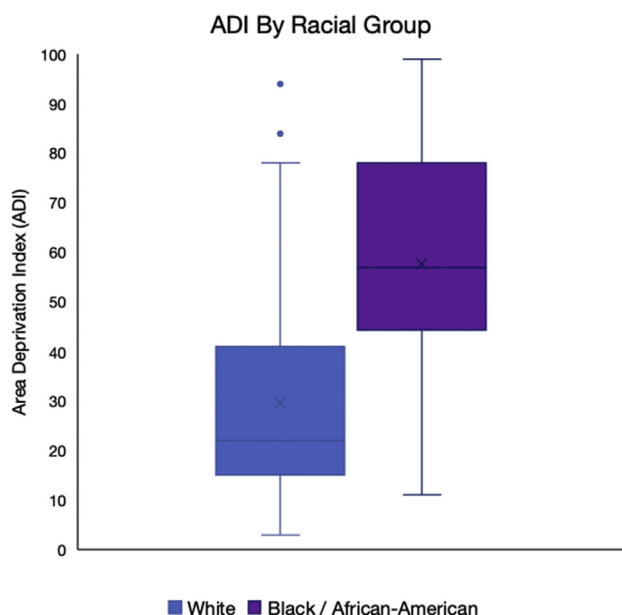
### Effects of ADI on Task Activation

Results of voxelwise interactions are presented in Table 2 and Figure 4. After adjusting for gender and age, there was a significant  $ADI \times \text{valence}$  interaction. Higher levels of neighborhood disadvantage were associated with less activation to negative versus neutral pictures in the right parahippocampal gyrus, hippocampus, and amygdala and greater activation in the left anterior cingulate cortex.

We had strong a priori hypotheses regarding blunted amygdala response to threat, and neutral International Affective Picture System images may be sensitive to individual differences that impact activation of this region (69,70). Therefore, in additional exploratory tests, we examined simple interactions of ADI and negative and neutral images separately, rather than the contrast of negative to neutral (Table 3). Greater ADI was associated with less activation to negatively valenced images in several regions, including the bilateral amygdala/hippocampus, primary motor cortex, calcarine sulcus, and temporal pole (Figure 5).

ADI also interacted with predictability. Greater neighborhood disadvantage was associated with increased activation for unpredictable versus predictable stimuli in lingual and calcarine gyri and the parahippocampal gyrus (Table 2).

When household income was included in the model, the interactive effects of ADI and predictability and valence were identical (see the Supplement). In tests to examine modulatory effects of ADI to negative and neutral stimuli separately, results were much less robust than those observed when household income was not included in the model, with significant interactions of ADI and response to negative images in the temporal pole and temporal and postcentral gyri. Using a more liberal voxelwise threshold ( $p < .005$ ), results were more consistent with initial findings, including several small clusters



**Figure 3.** Box plot depicts Area Deprivation Index (ADI) frequency by racial group. White participants ( $n = 138$ ) lived in significantly less disadvantaged neighborhoods (mean = 29.612,  $SD = 19.95$ ) compared with Black participants ( $n = 71$ , mean = 59.51,  $SD = 23.11$ ). Other racial groups were excluded due to small cell sizes.

**Table 2. Clusters Showing Significant ADI Interactions With Valence and Predictability**

Region	Hemi.	k	Peak MNI Coordinates			$\chi^2$
			x	y	z	
<b>Valence × ADI Interaction</b>						
<b>Positive Effect</b>						
Middle temporal gyrus	R	93	62	-24	-16	19.246
Anterior cingulate cortex	L	14	-10	28	20	17.421
<b>Negative Effect</b>						
Parahippocampal gyrus	R	37	36	-28	-18	19.895
Hippocampus	R	22	38	-12	-24	19.024
Amygdala	R	16	28	-6	-30	16.539
<b>Predictability × ADI Interaction</b>						
<b>Positive Effect</b>						
Lingual gyrus	L	114	-22	-88	-16	21.407
Calcarine sulcus	L	100	-10	-98	-6	20.632
Parahippocampal gyrus	R	30	34	-32	-12	16.503
Calcarine sulcus	R	26	14	-92	0	16.884

Voxelwise threshold  $p < .001$ , cluster threshold  $p < .05$ , adjusted for gender and age. ADI, Area Disadvantage Index; Hemi., hemisphere; k, number of voxels; L, left; MNI, Montreal Neurological Institute; R, right.

in the bilateral amygdala, indicating decreased responsivity to negative images as ADI increased (see Table 3 and the Supplement).

There were no significant three-way interactions between ADI, valence, and predictability.

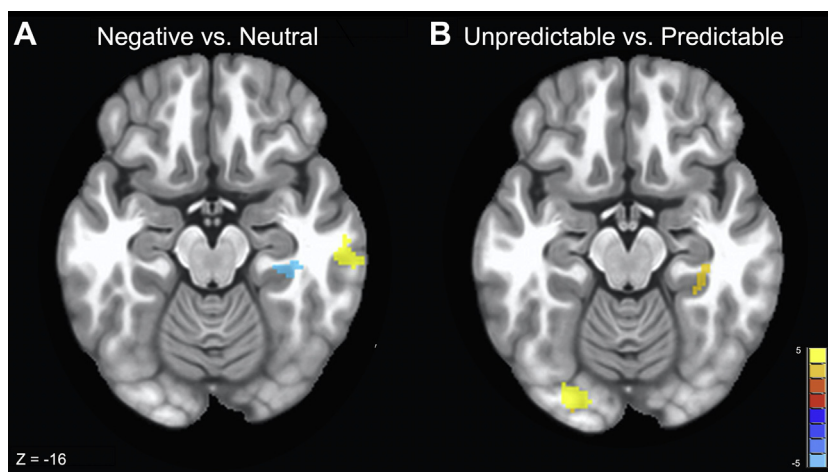
Despite ADI's correlation with trauma exposure, further analyses showed that our findings were unique to ADI. Also, in a subsample where all participants were from unique families ( $n = 209$ ), findings were similar, although the ADI × valence effect in the middle temporal gyrus produced a smaller cluster ( $k = 30$ ). These analyses are presented in the Supplement, along with basic task effects and interactions with age.

**DISCUSSION**

In a community sample of third, sixth, and ninth grade children, neural response to predictable and unpredictable threat was

associated with neighborhood disadvantage. Notably, children living in more socioeconomically deprived communities exhibited blunted bilateral amygdala response to threat, consistent with hypotheses. Greater neighborhood disadvantage was also associated with greater activation in the lingual and calcarine gyri for unpredictable compared with predictable stimuli (regardless of outcome valence).

Individuals living in more disadvantaged neighborhoods are faced with profound adversities stemming from the circumstances of their geographic environments. For children who grow up in deprived communities, the higher burden of chronic stress may alter developmental trajectories of physiological stress responding and confer risk for poor physical and mental health outcomes (9). Consistent with previous work (42), neighborhood disadvantage was associated with blunted amygdala response to threat. The amygdala is instrumental for the detection of threat and facilitation of



**Figure 4.** Clusters depict significant interactions of Area Deprivation Index with task conditions (valence, predictability), adjusted for age and gender with voxelwise  $p < .001$  and cluster threshold  $p < .05$ . (A) Greater neighborhood disadvantage was associated with greater activation in the middle temporal gyrus (62, -24, -16) and less activation in the parahippocampal gyrus (36, -28, -18) for negative versus neutral images. (B) Greater neighborhood disadvantage was associated with greater activation in the lingual gyrus (-22, -88, -16) and parahippocampal gyrus (34, -32, -12) for unpredictable versus predictable images.

**Table 3. Clusters Showing Significant Interactions of ADI With Negative and Neutral Valence Images**

Region	Hemi.	k	Peak MNI Coordinates			z
			x	y	z	
<b>ADI × Negative</b>						
Primary motor cortex <sup>a</sup>	B	199	0	-22	64	-3.661
Calcarine sulcus <sup>a</sup>	R	157	8	-86	6	-3.984
Temporal pole <sup>b</sup>	L	106	-32	22	-28	-4.678
Temporal pole	L	71	-44	22	-20	-3.986
Amygdala/hippocampus <sup>a</sup>	R	70	18	-4	-16	-4.270
Lingual gyrus	R	69	10	-54	6	-3.695
Amygdala/hippocampus <sup>a</sup>	L	58	-18	-4	-18	-3.416
Cerebellum (IV-V) <sup>a</sup>	R	27	16	-38	-16	-3.808
Superior temporal gyrus	R	27	66	-32	14	-3.726
Precentral gyrus	L	26	-46	0	48	-3.718
Lingual gyrus	L	24	-12	-54	2	-3.626
Inferior frontal gyrus	R	15	54	38	2	-3.953
Postcentral gyrus	R	15	18	-32	74	-3.431
<b>ADI × Neutral</b>						
Calcarine sulcus <sup>a</sup>	R	133	8	-86	6	-4.203
Cerebellum (VI) <sup>a</sup>	L	28	-22	-73	-20	-3.730
Cerebellum (VI)	R	23	20	-72	-16	-3.468
Cerebellum (VI)	L	22	-8	-78	-16	-3.589
Calcarine sulcus	R	22	16	-54	6	-3.546
Lingual gyrus	L	17	-2	-70	8	-3.616

Voxelwise threshold  $p < .001$ , cluster threshold  $p < .05$ , adjusted for gender and age. No clusters emerged where ADI interacted with negative or neutral images to elicit greater activation (i.e., positive effect).

ADI, Area Disadvantage Index; B, bilateral; k, number of voxels; L, left; MNI, Montreal Neurological Institute; R, right.

<sup>a</sup>When income was added to the model, cluster was significant at a more liberal voxelwise  $p < .005$  threshold.

<sup>b</sup>When income was added to the model, cluster was significant at original voxelwise  $p < .001$  threshold (see the Supplement for more details).

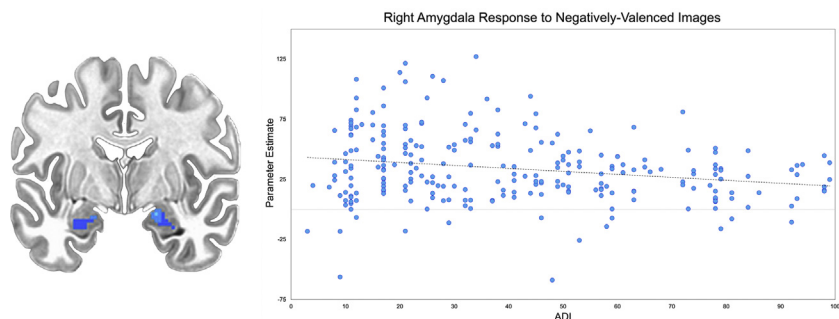
appropriate defensive responding (23), affecting how threats are perceived or processed. Given its role in helping to modulate the neuroendocrine stress response, amygdala function may also impact physiological preparedness to deal with stress (11,12). Future longitudinal work across the life span is needed to elucidate how amygdala responsivity may

play a role in the development of psychopathology, especially at critical periods in development. Given the challenges of making reverse inferences from brain data, it is also imperative for future work to examine behavioral correlates of blunted amygdala responsivity to threat to better understand how this response may reflect different phenomena, such as reduced threat salience.

Greater neighborhood disadvantage was associated with increased activation in several clusters within the visual cortex for unpredictable pictures, regardless of valence. These regions are generally involved in emotional processing circuits (71) and are sensitive to uncertainty (72). Uncertainty-potentiated lingual gyrus response has been shown to characterize clinical (rather than induced) anxiety (73). Perhaps because youth living in more disadvantaged communities face more uncertainty in their day-to-day lives, regions important for visual attention and processing may be especially sensitive to unpredictability and reflect enhanced vigilance and/or more effortful processing in response to a novel stimulus to ascertain whether it is safe.

Contrary to hypotheses, neighborhood disadvantage did not interact with predictability in either the vmPFC or insula. The vmPFC is proposed to exert top-down control over limbic circuits to modulate emotional responding to uncertainty (53) and is sensitive to neighborhood disadvantage (43,50). However, inhibitory function attributed to the vmPFC has largely been demonstrated in threat tasks that involve learning [e.g., fear conditioning and extinction (74,75)] or the opportunity to avoid/control threat (76,77), whereas the task in this study was passive in nature. The PFC is not fully matured until young adulthood (78); therefore, top-down regulation is highly dependent on stage of brain development (79). Indeed, in the current sample, prefrontal activation in response to aversive images was greater in older participants. It has also been proposed that lower-level sensory processes driven by cognitive stimulation shape PFC development (80).

Uncertainty has also consistently been shown to increase insular activation to threat (57,59,62). Although childhood poverty has been linked to exaggerated insula responsivity to acute stress in adulthood (18), other work has demonstrated blunted insula responsivity in youth exposed to other forms of adversity, e.g., maltreatment (81,82), which may reflect an avoidant coping strategy. This neurobehavioral response could be somewhat compensatory but may put them at greater risk of anxiety-related disorders in adolescence and adulthood.



**Figure 5.** Neighborhood disadvantage associated with blunted amygdala response to negatively valenced stimuli ( $k = 70$  voxels [18, -4, -16] and  $k = 58$  voxels [-18, -4, -18]). Scatterplot depicts association between Area Deprivation Index (ADI) and activation in the right amygdala cluster.

## Neighborhood Disadvantage and Neural Response to Threat

There was no three-way interaction among ADI, valence, and predictability. Given the absence of literature on neighborhood disadvantage and unpredictable threat, we did not have specific hypotheses about such an effect. Recent work has suggested that children process unpredictable threat differently than adults (83); additional research is needed to better understand developmental differences in threat processing.

When taking individual socioeconomic position into account (i.e., household income), ADI's effects on neural activation to negatively valenced images were consistent, if less robust. Neighborhood factors, including exposure to crime, pollution, and green space, can have developmental consequences that may diverge from individual socioeconomic circumstances. Although there is limited neuroscientific research on community-level socioeconomic disadvantage, previous findings have also suggested that effects do indeed go beyond the individual (40,43,50,51,84). ADI factors in area-level income, and collinearity makes it challenging to disentangle ADI and individual income. However, as a composite measure factoring in multiple facets of socioeconomic position, ADI provides a much richer characterization of the issues affecting disadvantaged communities. It is becoming increasingly clear that neurobiological function and health of individuals cannot be understood in isolation from their environment; area-level disadvantage may influence critical functions related to threat responding, emotion regulation, and cognition (40–43,50,51). Critically, the scope of economic inequality within the United States severely limits economic mobility and makes it astoundingly difficult for one to better their own financial circumstances (85). In the absence of resources and public support for economic and social policies providing direct aid to low-income families, interventions may be more effective (and more easily implemented) when focused on building stronger communities; such interventions are also likely to reduce the burden of personal financial stress, which perhaps plays a more central role in certain aspects of brain function. Further work is critical to better understand common and dissociable effects of individual and neighborhood socioeconomic position to inform the most effective interventions and reduce disparities in physical and emotional well-being.

It is also imperative to consider the gravity of racial and ethnic disparities in the United States. In this study, we did not examine or control for race or ethnicity; however, we observed substantial disparity within our own research sample. Black participants, on average, lived in considerably more disadvantaged neighborhoods ( $ADI_{\text{mean}} = 59.5$ ) than White participants ( $ADI_{\text{mean}} = 29.6$ ) and held a lower individual socioeconomic position (e.g., income, caregiver education). Previously, Harnett *et al.* (42) demonstrated that differences in neural response to threat between Black and White youth were dramatically reduced once negative life experiences, including neighborhood disadvantage, were taken into account. Socioeconomic status also mediates racial differences in amygdala volume (86). While neuroscientific work typically frames aberrant findings from a deficit perspective, blunted amygdala responsivity may be adaptive for youth residing in disadvantaged neighborhoods, allowing for attenuation or suppression of the neuroendocrine stress response (15,87). However, in the

long term, blunted neural and endocrine stress responsivity is likely to have detrimental effects on well-being (88,89) that may even be perpetuated via intergenerational transmission (90). With socioeconomic adversity disproportionately affecting racial and ethnic minorities, these groups will continue to be burdened with high rates of psychopathology and other health conditions unless systemic changes are implemented to improve the socioeconomic position of marginalized individuals and their communities (91).

This study has several limitations. Individuals of higher socioeconomic position were disproportionately represented. A third of the sample reported household income over \$100,000 and lived within the top quarter of U.S. neighborhoods. In addition, 68% of caregivers had at least a college education. As such, results may not generalize to samples with greater levels of socioeconomic disadvantage. As an index of neighborhood disadvantage, ADI rankings are also limited in that they do not account for other critical area-level variables, such as community violence, that may impact threat-relevant circuitry (92–94). Theories posit that deprivation experiences (e.g., neglect) are more likely to affect cognitive function and prefrontal brain regions, whereas threat experiences (e.g., physical abuse) may have a greater impact on the neural circuits supporting fear regulation and emotional responding (95). Future work would benefit from incorporating individual- and area-level measurements of other adverse experiences to better disentangle whether there are dissociable effects of threat and deprivation on the brain and how this relates to outcomes. Finally, although these findings provide compelling evidence for the impact of neighborhood disadvantage on brain function, these data are cross-sectional and cannot make inferences about causation. Longitudinal work is vital for better understanding these effects and how changes in socioeconomic position relate to changes in brain function across development.

Overall, these findings demonstrate that neighborhood disadvantage is associated with blunted amygdala response to threat; where a child lives may impact how they attend and respond to threats and stressors, potentially having critical implications for their current and future risk for psychopathology. While it has long been known that socioeconomic disadvantage and chronic stress have detrimental effects on diverse health outcomes, there is rapidly accumulating evidence that neighborhood disadvantage has unique and profound consequences on neurobiology (40–43,50,51,96,97). This work should not be simply a scientific exercise but rather should be seen as a call to action. Community-level interventions may help overcome some of the shortcomings of existing interventions and policies targeted at individuals by providing more widespread aid that improves outcomes for large groups of people. Although adverse experiences during childhood may negatively shape the cascade of neural development that occurs throughout young adulthood, increased neural plasticity during childhood may also make it a key time point to intervene and lessen the impact of these effects. Indeed, positive family and school environments have been shown to moderate associations between neighborhood disadvantage and the brain (51,96), suggesting an important role for more structural, community-based interventions and policies. Building better bridges between science and public



policy will aid in evaluating efficacy of interventions, directing local and federal aid, developing community resources, and improving education and employment quality and availability, which can hopefully lessen the persistent burden that neighborhood disadvantage has on brain health and well-being.

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