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Beyond family-level adversities: Exploring the developmental timing of neighborhood disadvantage effects on the brain

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Abstract

A growing literature suggests that adversity is associated with later altered brain function, particularly within the corticolimbic system that supports emotion processing and salience detection (e.g., amygdala, prefrontal cortex). Although neighborhood socioeconomic disadvantage has been shown to predict maladaptive behavioral outcomes, particularly for boys, most of the research linking adversity to corticolimbic function has focused on family-level adversities. Moreover, though animal models and studies of normative brain development suggest that there may be sensitive periods during which adversity exerts stronger effects on corticolimbic development, little prospective evidence exists in humans. Using two low-income samples of boys

(n = 167; n = 77), Census-derived neighborhood disadvantage during early childhood, but not adolescence, was uniquely associated with greater amygdala, but not prefrontal cortex, reactivity to ambiguous neutral faces in adolescence and young adulthood. These associations remained after accounting for several family-level adversities (e.g., low family income, harsh parenting), highlighting the independent and developmentally-specific neural effects of the neighborhood context. Furthermore, in both samples, indicators measuring income and poverty status of neighbors were predictive of amygdala function, suggesting that neighborhood economic resources may be critical to brain development.

Keywords

amygdala; fMRI; emotion processing; neighborhood disadvantage

Nearly 10 million children in the U.S. live in high poverty neighborhoods, where at least 30% of residents live below the poverty line (*The 2019 KIDS COUNT Data Book*, 2019). Children who grow up in disadvantaged contexts show greater mental and physical health problems than those from more advantaged neighborhoods (Leventhal & Brooks-Gunn, 2000). Recent quasi-experimental evidence suggests that the impact of neighborhood disadvantage on youth outcomes may be stronger for boys (Chetty & Hendren, 2018). Moreover, compared to girls, boys spend more time outside of the home in their neighborhoods (Larson et al., 2011) and are at higher risk for externalizing disorders, in part due to greater exposure to neighborhood-level risk factors (Loeber & Hay, 1997). Given the high social, emotional, and economic costs of growing up in disadvantaged neighborhoods for young men, more research is needed to understand how the neighborhood context "gets under the skin" to undermine positive development (McEwen & Gianaros, 2011). One important way disadvantaged contexts may undermine child development is by sculpting brain development. A growing literature indicates that multiple forms of adversity, from distal (e.g., relative standing on a social ladder, family socioeconomic status [SES]; (Farah, 2017; Gianaros & Manuck, 2010) to more proximal and extreme experiences (e.g. harsh parenting, Gard et al., 2017; maltreatment, Hein & Monk, 2017) are associated with variation in brain function. Much of this work has shown that adversity is associated with reactivity to emotional facial stimuli in nodes of the corticolimbic system, including the amygdala, a neural region linked to salience detection and emotion (Adolphs, 2002; LeDoux, 2000), and the prefrontal cortex (PFC), which supports executive functioning and the regulation of emotional responses (Fuster, 2001). There is considerable functional heterogeneity in the PFC (Etkin et al., 2011), and previous research has identified associations between childhood adversity and activation in both lateral (Colich et al., 2017; Marusak et al., 2017; Tomlinson et al., 2020) and medial (van Harmelen et al., 2014) prefrontal regions. The medial PFC (mPFC) supports emotion regulation by integrating affective evaluations with inputs from other neural regions (e.g., brainstem, thalamus), with dorsal regions more often activated during implicit emotion processing tasks (e.g., van Harmelen et al., 2014). By contrast, the lateral PFC (e.g., inferior frontal gyrus) plays a broader role in response inhibition and is activated during many cognitive control tasks (Hampshire et al., 2010; Tomlinson et al., 2020), including emotion processing tasks that include an explicit cognitive interference component (e.g., Marusak et al., 2015). Thus,

childhood adversity sculpts several regions of the prefrontal cortex, and task design is an important consideration when comparing results across studies.

Environmental adversities are postulated to calibrate corticolimbic function through activation of physiological stress responses (Dedovic et al., 2009; McEwen & Gianaros, 2011) and by guiding attention towards potentially threatening stimuli. For example, greater cortisol reactivity during laboratory stress paradigms has been linked to greater amygdala reactivity to emotional facial stimuli (Henckens et al., 2016; Taylor et al., 2006). Such enhanced sensitivity to salient stimuli under conditions of stress constitutes an adaptive short-term response to physical or psychological challenges, such as living in a disadvantaged neighborhood. Although most of the research in this area has focused on corticolimbic reactivity to signals of interpersonal threat and distress (i.e., angry, fearful facial expressions), amygdala and prefrontal activation to "neutral" faces may be critical to understanding the neurobehavioral effects of neighborhood-level adversities. Neutral faces are ambiguous signals that can be interpreted as threatening, particularly for youth exposed to adversity (Marusak et al., 2017; Pollak et al., 2000). As the corticolimbic system detects, interprets, and drives behavioral and physiological responses to perceived threats (McEwen & Gianaros, 2011), the unpredictability of ambiguous facial expressions makes these stimuli especially salient for youth living in disadvantaged neighborhoods, where many threats may be ambiguous in nature.

One major challenge to understanding the effects of adversity on corticolimbic function is that many forms of adversity co-occur (Green et al., 2010), and much of the existing literature has only focused on one form of adversity at a time, with a major focus on those that occur within the home (e.g., maltreatment). Although decades of research highlight the unique effects of the neighborhood context on youth socioemotional development (Leventhal & Brooks-Gunn, 2000), few studies have evaluated whether there are similarly distinct effects of neighborhood disadvantage (i.e., independent of family-level adversities) on corticolimbic function during emotion processing, a key intermediate phenotype for youth psychopathology (Hyde et al., 2013; Monk, 2008).

Second, though several recent reviews suggest that there may be sensitive periods during which adversity may be most impactful for corticolimbic function (Gee, 2016; Tottenham & Sheridan, 2009), few studies have tested this hypothesis in humans (e.g., Andersen et al., 2008) and no studies have examined neighborhood disadvantage specifically. As the amygdala undergoes the largest rate of volumetric growth during the first few postnatal year (Gilmore et al., 2012; Sabatini et al., 2007), it may be that neighborhood disadvantage in early childhood exerts the largest effects on later amygdala function (Tottenham & Sheridan, 2009). By contrast, a second sensitive period may be observed in prefrontal cortical regions, which continue to develop through adolescence and early adulthood (Casey et al., 2008). Within the behavioral literature, Andersen and colleagues (2014) have proposed similar "early exposure" and "adolescent exposure" models for the effects of neighborhood disadvantage on youth cognitive and behavioral outcomes (also see Anderson, Johnston, & Leventhal, 2019; Anderson et al., 2019). However, there have been no neurodevelopmental studies to test these models longitudinally, nor in sociodemographically-diverse samples.

The goal of the current study was to evaluate the specificity and timing of neighborhood disadvantage effects on corticolimbic reactivity to ambiguous neutral faces in boys/men using two independent samples. The first sample included 167 low-income boys followed from infancy through young adulthood. The second sample of 77 boys was recruited from a population-based birth cohort study that followed children through adolescence. By using two independent longitudinal samples with the same geocoded indicators of Census-derived neighborhood disadvantage, but different sampling designs and fMRI tasks to probe corticolimbic function, we sought to validate and conceptually replicate our findings across methods and samples. We hypothesized that neighborhood disadvantage in early childhood would be uniquely associated with subsequent amygdala reactivity, whereas neighborhood disadvantage during adolescence would be uniquely associated with PFC reactivity, particularly in medial regions, to ambiguous neutral faces (Casey et al., 2008; Tottenham & Sheridan, 2009). To confirm the specificity of neighborhood disadvantage effects on the brain, we accounted for multiple family-level adversities previously shown to predict corticolimbic function (e.g., harsh parenting, low family income).

Method

Overview

Data reported in this study were drawn from two longitudinal studies: the Pitt Mother & Child Project (PMCP: $N = 310$; Shaw, Hyde, & Brennan, 2012) and a subsample of children in the Fragile Families and Child Wellbeing study who participated in Study of Adolescent Neurodevelopment (SAND; $N = 237$; Hein et al., 2018). Census-derived neighborhood disadvantage was assessed in early childhood (i.e., ages 1 to 5) and adolescence (i.e., age 15) in both samples, with additional assessments in young adulthood (i.e., ages 20) in the PMCP. Corticolimbic reactivity to ambiguous neutral faces was measured at age 20 in the PMCP and at age 15 in the SAND using similar, albeit distinct, socioemotional processing fMRI tasks (see Figure 1a for a timeline across both studies).

PMCP and SAND Participants

PMCP.—PMCP is an ongoing longitudinal study of child risk and resilience in low-income families (Shaw et al., 2012). In 1991 and 1992, 310 low-income boys and their families were recruited from Allegheny County Women, Infant and Children (WIC) Nutritional Supplement Clinics when the boys were between 6 and 17 months old. At the time of recruitment, 53% of the target children in the sample were identified as European-American, 36% were African American, 5% were biracial, and 6% were of other races (e.g., Hispanic-American or Asian-American). Mothers were predominantly married (43.9%), living with a partner (20.6%) or single (27.7%). Two-thirds of mothers in the sample had 12 years of education or less, and 25% were employed outside of the home. Mean monthly family income was $1044.94 ($1376.73 in 2000 dollars [to compare with SAND birth cohort]), and the average Hollingshead socioeconomic status (SES) score was 24.5, indicative of a low SES sample. Families consented to participating and were reimbursed for their participation. All assessments and measures were approved by the Institutional Review Board of the University of Pittsburgh.

Target children and mothers were seen almost yearly from age 1.5 – 20 in the laboratory and/or home with assessments that included questionnaires, videotaped observations of parent-child interactions and child-only tasks, observations of the neighborhood context, and at age 20, an fMRI scanning session. Of the 186 men who consented and were able to participate in the MRI at age 20, valid neuroimaging data were available for 167 participants (see Supplemental Table 1). Retention rates were generally high at each of the assessment time points, with data available on 92% ($n = 284$) of the initial 310 participants at age 5; 89% ($n = 272$) at ages 10, 11, or 12; 80% ($n = 247$) at age 15, 81% ($n = 250$) at age 17, and 83% ($n = 258$) at age 20. The sample used in the current study was restricted to the 167 young men with neuroimaging data, who did not differ from participants without usable imaging data with respect to monthly income, education, or race and ethnicity (all ps > .10). The young men included in this neuroimaging sample self-identified as African American (41.4%), European American (53.3%), or Native American, Biracial, or other (5.3%).

SAND.—SAND is a cohort of 237 families drawn from the Detroit, Toledo, and Chicago subsamples of the Fragile Families and Child Wellbeing Study (FFCWS). The core FFCWS is a population-based cohort study of 4,898 (52.4% boys) children born in large U.S. cities (200,000 people or more) between 1998 and 2000. The study design called for an oversample of non-marital births (~3:1) (Reichman et al., 2001). At the birth of the target child, 34% of biological mothers had less than a high school diploma or equivalent, 78.3% were unmarried, and average annual household income was $31,755.

Families in the SAND were interviewed via phone and/or home visits at the birth of the target child, and again at ages 1, 3, 5, 9, and 15 years old. Retention of the baseline sample was generally high at each of the assessment periods (77% to 90% for mother or primary caregiver interviews) (for detailed information about cohort retention across waves, see https://fragilefamilies.princeton.edu). At age 15, 237 primary caregivers and adolescents in the SAND study participated in a one-day protocol that included an fMRI scanning session. Usable fMRI data were available for 167 youth (see Supplemental Table 1 for sources of data loss). As our focus was on the neural effects of neighborhood disadvantage in boys, we focused only on the 77 male adolescents with usable neuroimaging data in SAND. Boys with and without valid imaging data did not differ with respect to family income, parental age, education, or employment status, or race and ethnicity (all ps > .10). Of these 77 boys, 59 (76%) self-identified as African American. More than half (51.4%) of the primary caregivers reported annual household incomes of less than $25,000. Parents provided written consent and adolescents provided verbal assent for their participation in the SAND protocol. Families were reimbursed for their participation. All assessments and measures were approved by the Institutional Review Board of the University of Michigan.

Measures

Neighborhood disadvantage.—Consistent with prior work examining the structural components of neighborhood disadvantage (Leventhal & Brooks-Gunn, 2000; Sampson, 2012), neighborhood disadvantage was measured by geocoding addresses according to U.S. Census data (see Supplemental Methods for more details) and generating a composite score comprised of seven indicators aggregated at the block group- or tract-level: (1) median

family income (reversed-scored by multiplying by [−1], to maintain the direction of all of the indicators), (2) percent families below poverty line, (3) percent households on public assistance, (4) percent unemployed, (5) percent single-mother households, (6) percent African American, and (7) percent Bachelor degree and higher (Wikström & Loeber, 2000). This procedure was repeated for every wave of data collection in both samples. To create measures of neighborhood disadvantage during early childhood, adolescence, and young adulthood (Figure 1a), we averaged composite scores of neighborhood disadvantage from waves within each developmental period. To enhance the generalizability of our results, Census data were coded at different spatial units in PMCP (i.e., block group) and SAND (i.e., tract). Previous research indicates that residents' perception of the spatial extent of their neighborhoods is generally consistent with both Census tracts and block groups (Coulton et al., 2001). The number of cases with available neighborhood data varied across ages based on participation, provision of addresses, and geocoding match rate; data were available for 148 (89%) to 152 (91%) youth in PMCP and all 77 (100%) youth in SAND (see Supplemental Table 2 for details). There was significant individual variability in neighborhood disadvantage across developmental periods; Supplemental Figure 1 displays the distribution of change in neighborhood disadvantage across developmental periods, in both samples.

Family-level adversities.—Family-level adversities were measured via questionnaire and/or observation during the same developmental period as neighborhood disadvantage (i.e., early childhood, adolescence). Although some of the measures used to index family-level adversities differed across samples, the constructs were the same; these included maternal education, maternal depression, inter-parental conflict, harsh parenting, and family income. The source measures, descriptive statistics, and inter-correlations between family-level adversities are presented in the Supplemental Methods and Supplemental Tables 3 and 4.

Corticolimbic Reactivity to Ambiguous Neutral Faces

PMCP fMRI task.—The experimental fMRI paradigm implemented in the PMCP consisted of an implicit emotion processing task in which four blocks of a perceptual face processing task were interleaved with five blocks of a sensorimotor control (Hyde et al., 2015; Manuck et al., 2007) (Figure 1b). During the face processing task, subjects viewed a trio of faces and selected one of two faces (bottom) identical to a target face (top). Each face processing block consisted of six images, balanced for sex, all derived from a standard set of pictures of facial affect (Ekman & Friesen, 1976). Each of the four face processing blocks consisted of a different emotional facial expression (i.e., anger, fear, surprise, neutral), and participants were randomly assigned to one of four different orders of block presentation. During the sensorimotor control blocks, participants viewed a trio of simple geometric shapes (circles, vertical and horizontal ellipses) and selected one of two shapes (bottom) identical to a target shape (top). All blocks were preceded by brief instructions ("Match Faces" or "Match Shapes") lasting 2s. In the face processing blocks, each of the six face trios was presented for 4s with a variable interstimulus interval (ISI) of 2—6s ($M = 4$s) for a total block length of 48s. A variable ISI was used to minimize expectancy effects and resulting habituation, as well as to maximize amygdala reactivity throughout the paradigm.

In the sensorimotor control blocks, each of the six shape trios was presented for 4s with a fixed ISI of 2s for a total block length of 36s. Total task time was 390s.

SAND fMRI task.—Participants completed an implicit emotion task using an emotional faces event-related task (Hein et al., 2018). In this task (Figure 1c), participants were presented with a single emotional face and asked to identify the gender of the actor by pressing their thumb for male or index finger for female. Faces from the NimStim set (Tottenham et al., 2009) were counterbalanced for gender and race (European American and African American). There were 100 pseudo-randomized trials, 20 trials each of the following emotions: fearful, happy, sad, neutral, and angry. Each trial consisted of a 500ms fixation cross followed by a face presented for 250ms. A black screen then appeared for 1500ms, during which participants responded to the stimulus presentation, followed by a jittered inter-trial interval (2000, 4000, or 6000ms). Total task time was 8.75 minutes. Accuracy and response times were collected using a non-metallic fiber optic transducer linked to a response box.

fMRI Data Acquisition and Pre-processing

PMCP.—Before collecting fMRI data for each participant, a reference echoplanar imaging scan was acquired and visually inspected for artifacts (e.g., ghosting) and good signal across the entire volume of acquisition. Additionally, an autoshimming procedure was conducted before the acquisition of BOLD data in each participant to minimize field inhomogeneities. Blood oxygenation level–dependent (BOLD) functional images were acquired on a Siemens 3-T Tim Trio with a gradient-echo echoplanar imaging (EPI) sequence (TR/TE = 2000/29ms, FOV = 200×200, 34 interleaved axial 3mm-thick slices). Consistent with previous publications from this ample (Gard et al., 2017; Hyde et al., 2015), pre-processing of whole brain images was conducted in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Images for each participant were slice time corrected, grey matter segmented, realigned to the mean volume in the time series, unwarped to correct for head motion, co-registered to high resolution structural scans (MPRAGE) (TE/TR = 3.29/2200; Flip Angle = 9°; FOV = 256×192 mm2; Slice-Thickness = 1 mm; Matrix: 256×256; 192 continuous slices), spatially normalized into a standard stereotactic space (MNI template) using a 12-parameter affine model, and smoothed to minimize noise and residual difference in gyral anatomy with a Gaussian filter set at 6 mm FWHM. Voxelwise signal intensities were ratio-normalized to the whole-brain global mean. After preprocessing, the Artifact Detection Tools (ART) software package (http://www.nitrc.org/projects/artifact_detect/) was used to detect global mean intensity and translation or rotational motion outliers (> 4.5 SD from the mean global brain activation, >2mm movement or 2° translation in any direction) within each participant's data. Similar thresholds for detecting movement have been used in several recent task-based fMRI studies from independent labs (Aboud et al., 2018; Fehlbaum et al., 2018; Oppenheimer et al., 2020). The number of outlier volumes was not correlated with participant race/ethnicity, or family income or neighborhood disadvantage at any developmental stage (all $ps > .05$). Outlier volumes were individually regressed out of the participant's individual model, and participants were removed if > 20% of the volumes were classified as motion outliers. Following preprocessing, single-subject BOLD fMRI data were included in subsequent analyses if there was a minimum of 90% signal coverage in the

amygdala region of interest (ROI) (defined as the bilateral amygdala using the Automated Anatomical Labeling [AAL] Atlas in the WFU PickAtlas Tool, version 1.04; Wake Forest University School of Medicine, Winston-Salem, NC). As the current paper additionally examined corticolimbic function within the PFC, participants with less than 90% coverage in prefrontal regions were removed from analyses (prefrontal mask described below in the analytic section). Lastly, participants were excluded if accuracy performance on the task was less than 75% (Supplemental Table 1).

SAND.—BOLD functional images were acquired on a GE MR750 3T scanner with an 8-channel head coil and reverse spiral sequence (TR/TE = 2000/30ms, flip angle = 80°, FOV = 22cm; 40 contiguous axial 3mm slices). Slices during the functional scans were prescribed parallel to the AC-PC line (same locations as structural scans). Images were reconstructed into a 64×64 matrix. Slices were acquired contiguously, which optimized the effectiveness of the movement post-processing algorithms. Images were reconstructed off-line using processing steps to remove distortions caused by magnetic field inhomogeneity and other sources of misalignment to the structural data, which yields excellent coverage of subcortical areas of interest. Anatomical images were homogeneity-corrected using SPM12, then skull-stripped using the Brain Extraction Tool in FSL (version 5.0.7) (Jenkinson et al., 2012; Smith, 2002). Consistent with other publications in this sample (Goetschius et al., 2019), pre-processing of whole brain images was conducted in SPM12 (http:// www.fil.ion.ucl.ac.uk/spm/). Functional data were pre-processed in the following steps: removal of large temporal spikes in k-space data (> 2 std dev), field map correction and image reconstruction using custom code in MATLAB, and slice-timing correction. High resolution T1-weighted structural scans were then gray matter segmented (TR/TE = 9.0/1.8; TI = 400ms; Flip Angle = 15°; FOV = 22cm; Slice Thickness = 3mm; Matrix: 256×256; 40 slices). Functional images were realigned to the AC-PC plane in the mean volume of the time series, co-registered to the high-resolution structural scans, normalized into to the MNI Image space, and smoothed using an isotropic 8mm FWHM Gaussian kernel. Following preprocessing, the Artifact Detection Tools (ART) software package (http://www.nitrc.org/ projects/artifact_detect) identified motion outliers (>2mm movement or 3.5° rotation); outlier volumes were individually regressed out of the participant's individual model, and participants were removed if > 20% of the volumes were classified as motion outliers. Similar thresholds for detecting movement have been used in several recent task-based fMRI studies from independent labs (Fehlbaum et al., 2018; Oppenheimer et al., 2020). The number of outlier volumes was not correlated with participant race/ethnicity, or family income or neighborhood disadvantage at any developmental stage (all ps > .05). Following preprocessing, single-subject BOLD fMRI data were only included in subsequent analyses if there was a minimum of 70% signal coverage in the left and right amygdala, defined using the Automated Anatomical Labeling (AAL) atlas in the WFU PickAtlas Tool, version 1.04 (Maldjian, Laurienti, Kraft, & Burdette, 2003). Participants with less than 90% coverage in prefrontal regions were also removed (prefrontal mask described below in the analytic section). Lastly, participants were excluded if accuracy performance on the task was less than 70% (Supplemental Table 1).

Statistical Analysis

PMCP.—All analyses in PMCP were performed in SPM8 to be consistent with previous studies in this sample that also used SPM8 (e.g., Gard et al., 2017; Hyde et al., 2015). First, condition-specific (i.e., neutral faces > shapes) BOLD activations for each individual scan were estimated using canonical hemodynamic response functions. Individual contrast images were then used in second-level multiple regression models to evaluate the associations between neighborhood disadvantage within each developmental period (i.e., early childhood, adolescence) and amygdala and PFC reactivity to neutral faces versus shapes at age 20, controlling for child race and family-level adversities during the same developmental period. All family-level adversities were included simultaneously as covariates. To investigate the timing of neighborhood effects on the brain, we constructed a second set of models that additionally accounted for neighborhood disadvantage at the other developmental period. Note that we did not use multilevel modeling because there was insufficient clustering of participants within neighborhoods to warrant this approach (Raudenbush & Bryk, 2002); 70–83% of participants (depending on the wave of data) were the only child in their neighborhood (see also Anderson, Leventhal, & Dupéré, 2014).

We used an ROI approach to identify amygdala and prefrontal regions that were associated with neighborhood disadvantage. The bilateral amygdala ROI was defined using the AAL Atlas definition in the WFU PickAtlas Tool, version 1.04 (Maldjian et al., 2003). As has been done previously (Kujawa et al., 2016), we also created a large prefrontal mask by combining masks of the frontal lobe and the anterior cingulate cortex in the Talairach Daemon database (Lancaster et al., 1997) within the WFU PickAtlas Tool (Maldjian et al., 2003). As the PFC is heterogeneous in structure, function, and maturational timing (Fuster, 2001; Giedd et al., 1999), using a large prefrontal mask allowed us to (1) simultaneously examine multiple regions of the PFC without increasing the number of distinct ROIs (and, thus, statistical tests), and (2) account for the wide variety of ROIs used in previous studies. We corrected for multiple comparisons using the most recent version of the 3dClustSim program (Cox et al., 2017) in AFNI (Cox, 1996). Consistent with recommendations by Cox and colleagues (2017), we implemented the spatial autocorrelation function (i.e., the –acf option) to model the spatial smoothness of noise volumes. Group-level smoothing values (0.64, 7.09, and 6.86) were estimated from a random 10% of participants' individual-model residuals, using the program 3dFWHMX. 3DClustSim uses a Monte Carlo simulation to provide thresholds that achieve a family-wise error (FWE) correction threshold of $p < .05$ within each ROI (i.e., for our study, either the amygdala or the prefrontal mask). We used a voxel-wise threshold of $p < .01$, resulting in clusters sizes of $k = 21$ contiguous voxels for amygdala ROI analyses and $k = 276$ for prefrontal cortex analyses to achieve $p < .05$ corrected for multiple comparisons. We note that there was no change in the results when using a voxel-wise threshold of $p < .001$, but we retain a voxel-wise threshold of $p < .01$ to be consistent with SAND (see below).

Statistical Analysis: SAND

Analyses in the SAND were conducted in SPM12 to be consistent with previous studies in this sample (Goetschius et al., 2019). Individual-level images for the contrast neutral faces versus baseline were used in second-level multiple regression models to evaluate the effects

of neighborhood disadvantage in early childhood and adolescence, controlling for family-level adversities during the same developmental period, on amygdala and PFC reactivity to neutral faces versus baseline in adolescence. All family-level adversities were included simultaneously as covariates. A second set of models that controlled for all family-level adversities and additionally accounted for neighborhood disadvantage at the other developmental period was used to evaluate the timing of neighborhood effects on corticolimbic function. The amygdala and prefrontal cortex ROIs were identical to those used in the PMCP analyses. Similarly, the 3dClustSim program (Cox et al., 2017) in AFNI, combined with estimation of spatial smoothness (i.e., the –acf option; estimates: 0.55, 6.41, 13.37), was used to correct for multiple comparisons, resulting in target clusters that met a FWE-correction threshold of $p < .05$ within each ROI and a voxel-wise threshold of $p < .01$ ($k = 25$ contiguous voxels for amygdala ROI analyses and $k = 394$ for prefrontal cortex analyses). Models varied in sample size from $N = 62$ to $N = 77$ (see Supplemental Table 3). As in the PMCP, we did not employ multilevel modeling with clustering by neighborhood because 93–97% of participants (depending on the wave of data) were the only child in their neighborhood.

Results

For boys in the PMCP and the SAND, neighborhood disadvantage in early childhood and adolescence were strongly correlated (PMCP: $r = .46$, $p < .001$; SAND: $r = .60$, $p < .001$). During early childhood (i.e., ages 1 to 5 years), neighborhood disadvantage was positively associated with harsh parenting in PMCP ($r = .21$, $p < .05$), but not in SAND ($r = .18$, $p > .10$), and negatively associated with family income in both samples (PMCP: $r = -.35$, $p < .001$; SAND: $r = -.35$, $p < .01$).

When does neighborhood disadvantage in childhood predict corticolimbic reactivity to ambiguous neutral faces?

Neighborhood associations with amygdala function.—In the PMCP within both early childhood and adolescence, greater neighborhood disadvantage was associated with greater amygdala reactivity to ambiguous neutral faces versus shapes at age 20 (Table 1). These associations were significant even when accounting for multiple family-level adversities (i.e., harsh parenting, maternal depression, low family income and maternal education, inter-parental conflict) during the same developmental period, highlighting the robust role of neighborhood-level disadvantage in predicting individual-level amygdala function. In models testing whether there was a sensitive period for neighborhood effects on amygdala function, results showed that only neighborhood disadvantage in early childhood was uniquely associated with greater amygdala reactivity to ambiguous neutral faces at age 20 (Table 1; Figure 2a). Moreover, this association remained statistically reliable after accounting for neighborhood disadvantage at age 20 (i.e., the same age as the neuroimaging data collection).

In the SAND sample of 77 boys, we found evidence of the same effect. Neighborhood disadvantage in early childhood, but not adolescence, was associated with greater amygdala reactivity to ambiguous neutral faces versus baseline at age 15, accounting for concurrent

family-level adversities (Table 1; Figure 2b). The inclusion of neighborhood disadvantage at age 15, reflective of a sensitive period model, attenuated this effect (i.e., the association was significant at a mask-corrected threshold of $p < .10$, but not at $p < .05$).

Neighborhood associations with prefrontal cortex function.—In contrast to findings predicting amygdala function, neighborhood disadvantage in adolescence (or early childhood) was unexpectedly not associated with activation in the PFC in the PMCP. For boys in the SAND, however, neighborhood disadvantage in adolescence was associated with less superior medial frontal gyrus reactivity to ambiguous neutral faces at age 15, accounting for concurrent family-level adversities (i.e., harsh parenting, maternal depression, low family income and maternal education, inter-parental conflict) and neighborhood disadvantage in early childhood (Table 1, Figure 3). As the significant findings in the SAND may reflect the fact that neighborhood disadvantage and PFC function were collected concurrently, we also examined whether neighborhood disadvantage at age 20 in the PMCP sample was associated with prefrontal cortex reactivity to ambiguous neutral faces at the same age. Indeed, neighborhood disadvantage at age 20 was concurrently associated with greater (not less, as in the SAND sample) middle frontal gyrus reactivity to ambiguous neutral faces ([x, y, z] = [50, 10, 46], $t = 4.00$, $k = 704$), although this association did not remain significant after accounting for neighborhood disadvantage in earlier developmental periods.

Post-hoc exploratory analyses

Cumulative exposure to neighborhood disadvantage.—We conducted exploratory analyses to further evaluate our most robust finding, that neighborhood disadvantage in early childhood was uniquely associated with amygdala (but not PFC) reactivity to neutral faces in adolescence (SAND) and young adulthood (PMCP). First, although our results suggest that the timing of exposure to neighborhood disadvantage is important, our results could also reflect cumulative risk effects (Anderson et al., 2019; Sameroff et al., 1987) (Evans, Li, & Whipple, 2013). To evaluate this hypothesis, in both samples we calculated the number of developmental periods during which a participant scored in the top quartile of neighborhood disadvantage. In the PMCP, the cumulative risk score ranged from 0 to 3 (i.e., three developmental periods; early childhood, adolescence, young adulthood); most young men (57%) were low risk across all three waves, and roughly 11% of participants scored in the top quartile in all three developmental periods. With two developmental periods in the SAND, the cumulative risk score in this sample ranged from 0 to 2; most youth (64%) were low risk across all three waves, and 13% of participants lived in highly disadvantaged neighborhoods during both developmental periods. In each sample, we evaluated whether the cumulative risk score was associated with amygdala reactivity to neutral faces, controlling for child race (and pubertal development in the SAND). Consistent with the notion that timing of exposure to neighborhood disadvantage is important for later amygdala function, the cumulative neighborhood disadvantage risk score was not associated with amygdala or PFC reactivity to neutral faces in either sample.

Components of neighborhood disadvantage.—Lastly, although the Census-derived indicators that form the neighborhood disadvantage composite are designed to jointly capture the greatest variation between neighborhoods (Leventhal & Brooks-Gunn, 2000;

Sampson et al., 1999), it may be that some Census-derived indicators in early childhood are more predictive of subsequent amygdala function than others. Across both the PMCP and SAND, Census indicators assessing the % of families living below the poverty line and median family income at the neighborhood-level were associated with greater amygdala reactivity to ambiguous neutral faces, even after accounting for one's own family income, exposure to maternal education and depression, inter-parental conflict, and harsh parenting (Supplemental Table 5). Several other Census indicators were also predictive in either the PMCP (e.g., % unemployed) or the SAND (e.g., % single-headed households), but not in both samples.

Neighborhood associations with corticolimbic connectivity.—Although our primary objective was to examine the associations between neighborhood disadvantage and amygdala and PFC *activation* during neutral face processing, environmental adversity is also thought to undermine functional connectivity between these regions. Using generalized psycho-physiological interaction analyses (see Supplemental Methods), we evaluated whether neighborhood disadvantage in early childhood or adolescence was associated with left or right amygdala-prefrontal connectivity during neutral face processing versus baseline. In the PMCP, there were no associations between neighborhood disadvantage during any developmental period and amygdala-prefrontal connectivity. In the SAND sample, greater neighborhood disadvantage in early childhood (but not adolescence) was associated with stronger positive left amygdala – left inferior frontal gyrus (cluster extends into the medial, middle, and superior frontal gyri) and right amygdala – right superior frontal gyrus (cluster extends into the medial frontal gyrus) connectivity during neutral face processing versus baseline. These associations remained significant after accounting for neighborhood disadvantage during adolescence (Supplemental Table 7; Supplemental Figure 2).

Discussion

The current study found unique effects of neighborhood disadvantage, independent of family-level adversities, on amygdala reactivity to neutral faces using two prospectively collected samples of low-income boys. Consistent with existing theories that posit heightened sensitivity of subcortical regions to context in early childhood, we found that neighborhood disadvantage in early childhood was associated with amygdala, but not prefrontal cortex (PFC), reactivity to neutral faces, even after controlling for neighborhood disadvantage during other developmental periods.

Consistent with the developmental trajectories of amygdala structure and function, we found that neighborhood disadvantage in early childhood (i.e., before age 5) was most predictive of amygdala reactivity to ambiguous neutral faces in adolescence (SAND) and young adulthood (PMCP). In humans, the amygdala increases in volume by more than 100% during the first year of life (Gilmore et al., 2012). This rapid period of growth during the early postnatal years parallels functional patterns of greater amygdala reactivity to emotional facial expressions in children than adolescents and adults (Monk, 2008). Animal work suggests that the amygdala is sensitive to environmental inputs during the early postnatal years (Sabatini et al., 2007; Tottenham & Sheridan, 2009). For example, rhesus monkeys separated from their mothers at 1 week of age versus 1 month showed a significant decrease

in gene expression in the amygdala, which was associated with greater self-comforting behaviors and less typical social behaviors (Sabatini et al., 2007). In humans, previously-institutionalized children that were adopted after 15 months of age showed relatively greater amygdala *volume* than children who were adopted before 15 months of age or non-adopted controls (Tottenham et al., 2010), suggesting that developmental timing is important for amygdala development. Results from the current study extend this work to show that early childhood represents a period during which adversity, specifically at the neighborhood level, has a more profound impact on subsequent amygdala *function* during ambiguous face processing and does so using prospectively-collected, repeated measures of geocoded, Census-derived neighborhood disadvantage in two samples. Moreover, the current study builds on previous research that linked harsh parenting and neighborhood disadvantage to amygdala reactivity to fearful faces and youth antisocial behavior (Gard et al., 2017), by providing preliminary evidence for a sensitive period during early childhood when neighborhood disadvantage has the most pronounced effects on amygdala reactivity to neutral faces.

Although understudied compared to expressions of fear or anger, neutral faces also activate the amygdala (Gard et al., 2018; Marusak et al., 2017; Whalen, 1998). Ambiguous stimuli require considerable processing resources to assess the nature of a perceived threat by integrating information about context (Bouton, 1994; Neta & Whalen, 2010). Pollak and colleagues (2000) have shown that children facing adversity perceive less dissimilarity between angry and neutral faces; our results indirectly suggest that this negativity bias may occur via heightened amygdala activation to ambiguous stimuli. Indeed, supplemental analyses showed considerable specificity in the associations between neighborhood disadvantage and amygdala reactivity to emotional facial expressions (Supplemental Table 6). Across both samples, living in a disadvantaged neighborhood was not associated with amygdala reactivity to angry, fearful, happy, sad, or surprised facial expressions after accounting for correlated family-level adversities. Moreover, none of the family-level adversities (e.g., family income, maternal depression, harsh parenting) were associated with amygdala reactivity to neutral faces (Gard et al., 2017; SAND results available upon request), highlighting the salience of neutral faces for youth growing up in disadvantaged neighborhoods. An important future direction is to understand the psychological processes (e.g., attentional control) that facilitate such specificity in neural reactivity for those living in impoverished neighborhoods.

In contrast to our second hypothesis, we did not find consistent support for unique effects of neighborhood disadvantage on PFC function. In the SAND only, greater neighborhood disadvantage at age 15, but not in early childhood, was uniquely associated with less superior medial frontal gyrus reactivity to neutral faces concurrently, indicative of a developmental timing effect. As the fMRI task was an implicit emotional faces task that captures cognitive rather than regulatory components of emotion processing (Etkin et al., 2011), our identification of dorsal regions of the mPFC is consistent with this literature and previous research using a similar task; van Harmelen et al. (2014) also found that greater childhood adversity was associated with less mPFC activation to emotional facial expressions. Supplemental analyses in SAND further showed that these effects were not specific to neutral faces, as neighborhood disadvantage in adolescence was also associated

with less middle frontal gyrus reactivity to angry and happy facial expressions (Supplemental Table 6). That we did not find any associations between neighborhood disadvantage and prefrontal function in the PMCP could reflect the timing at which the neuroimaging data were collected (i.e., PMCP boys did not undergo MRI scanning until age 20, whereas the SAND youth were imaged during adolescence). Adolescence is hypothesized to be a sensitive period for prefrontal development (Fuhrmann et al., 2015), during which there is greater synaptic plasticity (Selemon, 2013) and, thus greater sensitivity to environmental inputs. Alternatively, null results in the PMCP sample may stem from the fact that, compared to the SAND sample, fewer youth experienced increases in neighborhood disadvantage across childhood (i.e., most PMCP youth were exposed to the highest levels of neighborhood disadvantage in early childhood; Supplemental Figure 1). Lastly, it may be that the fMRI tasks we implemented robustly activate bottom-up regions of the corticolimbic circuit (e.g., the amygdala), more so than top-down cognitive control regions (e.g., inferior frontal gyrus). Thus, as was recently demonstrated (Tomlinson et al., 2020), cognitive-control fMRI tasks (e.g., Go-No-Go) could be leveraged to examine whether there are effects of neighborhood disadvantage on broader prefrontal function.

In post hoc analyses in both samples, we evaluated whether neighborhood disadvantage in early childhood or adolescence was associated with condition-specific amygdala-prefrontal functional connectivity. In the SAND sample only, neighborhood disadvantage in early childhood (but not adolescence) was associated with stronger positive amygdala-prefrontal connectivity (centered in the inferior and superior frontal gyri) during neutral face processing. That greater exposure to adversity was associated with stronger positive amygdala-prefrontal connectivity is consistent with a previous study that measured adversity as family income (Kim et al., 2013). Our results extend this literature to neighborhood-level disadvantage. However, we caution that these analyses were post-hoc and not consistent across samples and, thus, require further replication in other samples.

Although exploratory, we found that two specific Census-derived indicators of neighborhood-level economic resources (i.e., % of families in living below the poverty line, median family income) were associated with amygdala function in both samples, indicating that the income and poverty status of neighbors may be particularly important in understanding the impact of neighborhood effects on the brain. Previous research has shown that indicators of neighborhood-level income often explain the largest percent variance in a latent factor of neighborhood disadvantage (e.g., Sampson, Raudenbush, & Earls, 1999), highlighting the central role of economic resources in neighborhood disadvantage.

Children typically spend more time in the home than outside in their neighborhoods during early childhood (Hofferth & Sandberg, 2001). Thus, it is unclear why neighborhood-level disadvantage during early childhood was associated with subsequent amygdala function. Although we might expect parents to modulate children's exposure to their neighborhoods (Leventhal & Brooks-Gunn, 2000), the inclusion of parenting behaviors in our analyses did not attenuate the neighborhood effect. Several correlated social processes and physical exposures may mediate the effects of neighborhood disadvantage on neural development, particularly during early childhood. First, neighborhood crime and danger are tightly linked to neighborhood income (Pratt & Cullen, 2005) and may impact young children via stress

responses, even when children are in the home. In line with this hypothesis, studies have documented unique effects of neighborhood violence (i.e., after controlling for family violence) on young children's psychosocial outcomes (Briggs-Gowan et al., 2012) and brain development (Saxbe et al., 2018). Exposure to toxicants is another candidate mechanism that may link neighborhood poverty to brain development (Guxens et al., 2018; Trentacosta et al., 2016). The boys in our samples were born into low-income urban settings, where rates of soil-based lead poisoning are higher relative to nonurban settings (Filippelli & Laidlaw, 2010). Soil-based lead exposure may explain the developmental timing effects we observed, as young children are more likely to ingest lead than older children (Trentacosta et al., 2016). Lastly, as school quality is associated with neighborhood income through the local tax base (Leventhal & Brooks-Gunn, 2000) and children enter the schooling environment at the end of early childhood (Hofferth & Sandberg, 2001), the neighborhood effects we observed could be identifying school-level risk factors. More research is needed to determine the *mechanisms* by which neighborhood disadvantage, particularly during early childhood, impacts youth brain development.

It is equally important for researchers to study positive aspects of the neighborhood that may promote adaptive neurobehavioral development. A rich behavioral literature has shown that qualities such as high social cohesion and collective efficacy (i.e., the extent to which neighbors feel connected and are able to engage in community action) may protect youth in disadvantaged neighborhoods from developing psychopathology (Fagan et al., 2014; Xue et al., 2005) and promote adaptive developmental outcomes (e.g., Woolley et al., 2008). Furthermore, although the purpose of the current study was to document neurobehavioral effects of neighborhood disadvantage as distinct from family-level adversities, the ecological system of the family is nested within the broader community context (Bronfenbrenner & Morris, 2007). As has been shown in the behavioral literature (Ceballo & McLoyd, 2002; Klebanov et al., 1994), complex interactions between family- and community-level risk and protective factors are likely to underlie youth brain development.

Limitations

Although we used two independent, prospective longitudinal samples of low-income boys followed through childhood to study neighborhood effects on corticolimbic function, our results are tempered by several limitations. First, although our results suggest that the timing of exposure to neighborhood disadvantage is important for later amygdala function, we did not measure (and thus could not account for) amygdala function in early childhood, which would provide stronger support for the notion of a "sensitive period" in early childhood (Anderson et al., 2014; Leventhal, 2018). Inconsistencies in our results for prefrontal function (i.e., only in the SAND sample was neighborhood disadvantage associated with less mPFC function) may have been magnified by the fact that the studies collected MRI data during different developmental stages (i.e., SAND during adolescence, and PMCP during early adulthood). Second, like many other studies examining task-based corticolimbic function (Carré et al., 2012; Hariri, 2002; Swartz et al., 2015), neither study included a non-shapes face stimulus as a baseline condition (i.e., baseline was indexed by a shapes condition in PMCP, and by a fixation cross in SAND). Thus, our results may capture face processing or visual complexity more broadly than reactivity to neutral faces specifically. At the same

time, we found some degree of specificity in that neighborhood disadvantage was associated with amygdala reactivity to neutral faces only, in both samples. Third, though we focused on boys because they may be particularly sensitive to the neighborhood context (Chetty & Hendren, 2018; Hofferth & Sandberg, 2001; Loeber & Hay, 1997), an important avenue of research is to examine whether there are gender differences in adversity effects on the brain (an issue we could not address in PMCP). Similarly, both samples in the current study explicitly recruited families living in urban environments and, thus, more research is needed to determine whether our results are generalizable to rural communities where poverty may have different sequelae. Fourth, though relatively large for neuroimaging, the SAND sample was relatively small for the hypotheses we tested, and may have been underpowered to detect effects in models with many covariates. Nevertheless, the SAND sample is part of a population-based study, which is a critical addition to the neuroimaging literature that has mostly relied on convenience samples (Falk et al., 2013). Lastly, although we accounted for several family-level adversities that are correlated with more extreme sources of adversity, we did not explicitly measure childhood maltreatment in either study. As much of the work linking early life adversity to corticolimbic function has focused on maltreatment (Hein & Monk, 2017), our neighborhood effects would be bolstered by additional control for this important environmental adversity.

Conclusions

Using two prospective studies, we found evidence that neighborhood disadvantage was associated with amygdala reactivity during ambiguous face processing and that these effects may be most potent during early childhood, a potential sensitive period for amygdala development. These effects did not extend to PFC activation and were distinct from many family-level adversities, which have been the overwhelming focus of studies examining environmental effects on brain development. These results highlight that where children live, not just their family's resources, may be critical for early brain development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Research Highlights

- Census-derived neighborhood disadvantage was associated with corticolimbic function over-and-above family-level adversities including low family income and maternal education, maternal depression, harsh parenting, and inter-parental conflict

- Across both samples, neighborhood disadvantage in early childhood, but not adolescence, was associated with greater amygdala reactivity to neutral faces

- In one sample, neighborhood disadvantage in adolescence, but not early childhood, was associated with less prefrontal reactivity and stronger positive amygdala-prefrontal connectivity during socioemotional processing

- The effects of neighborhood disadvantage on corticolimbic function were specific to the processing of ambiguous neutral faces, rather than fearful or angry facial expressions
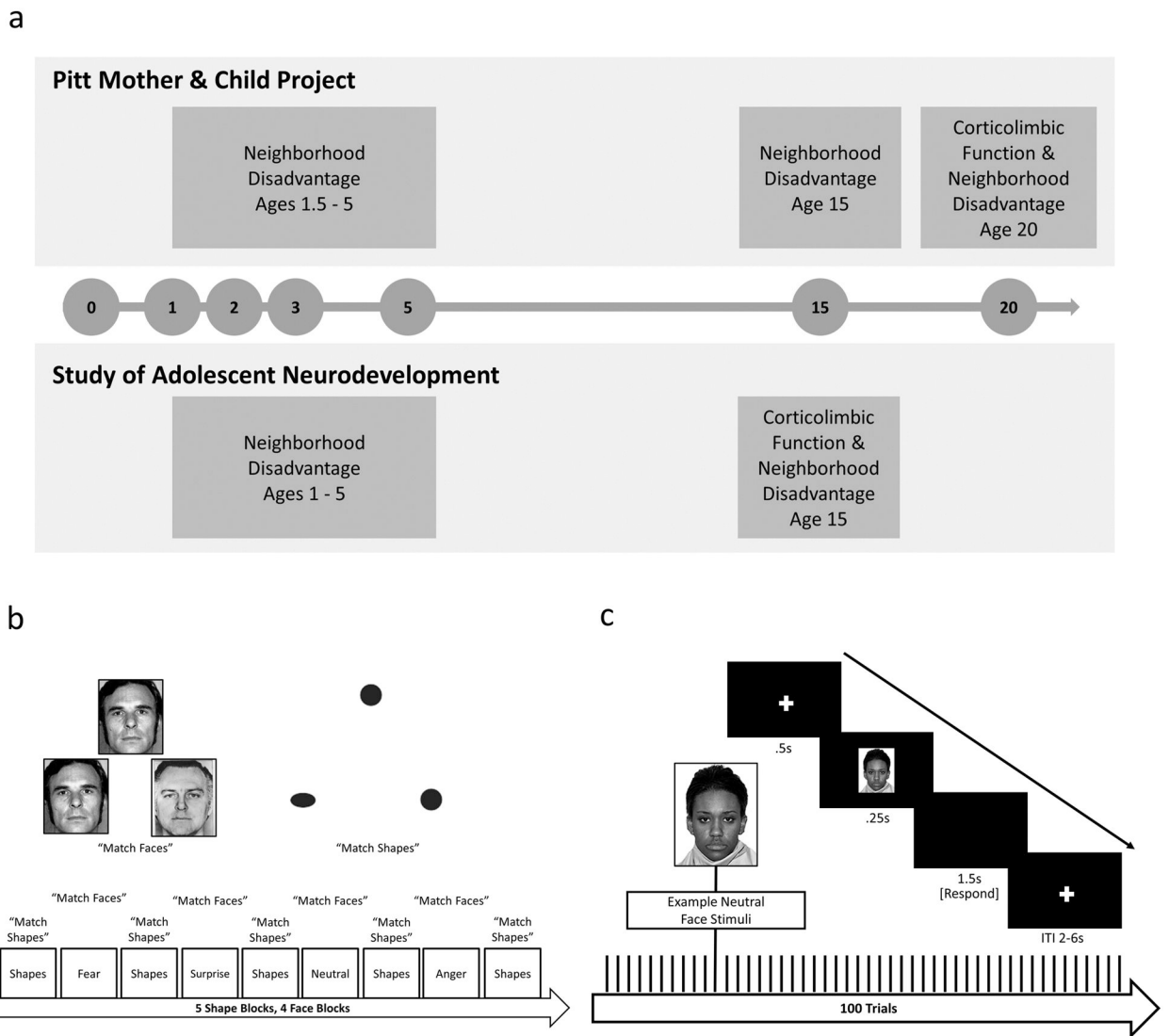
Figure 1.
Overview of data collection and fMRI tasks

Note. (a) Data collection timeline in both study samples. (b) fMRI emotional faces matching paradigm used in the Pitt Mother & Child Project. The contrast of interest was neutral faces versus shapes. (c) fMRI implicit emotional faces paradigm used in the Study of Adolescent Neurodevelopment. The contrast of interest was neutral faces versus baseline.
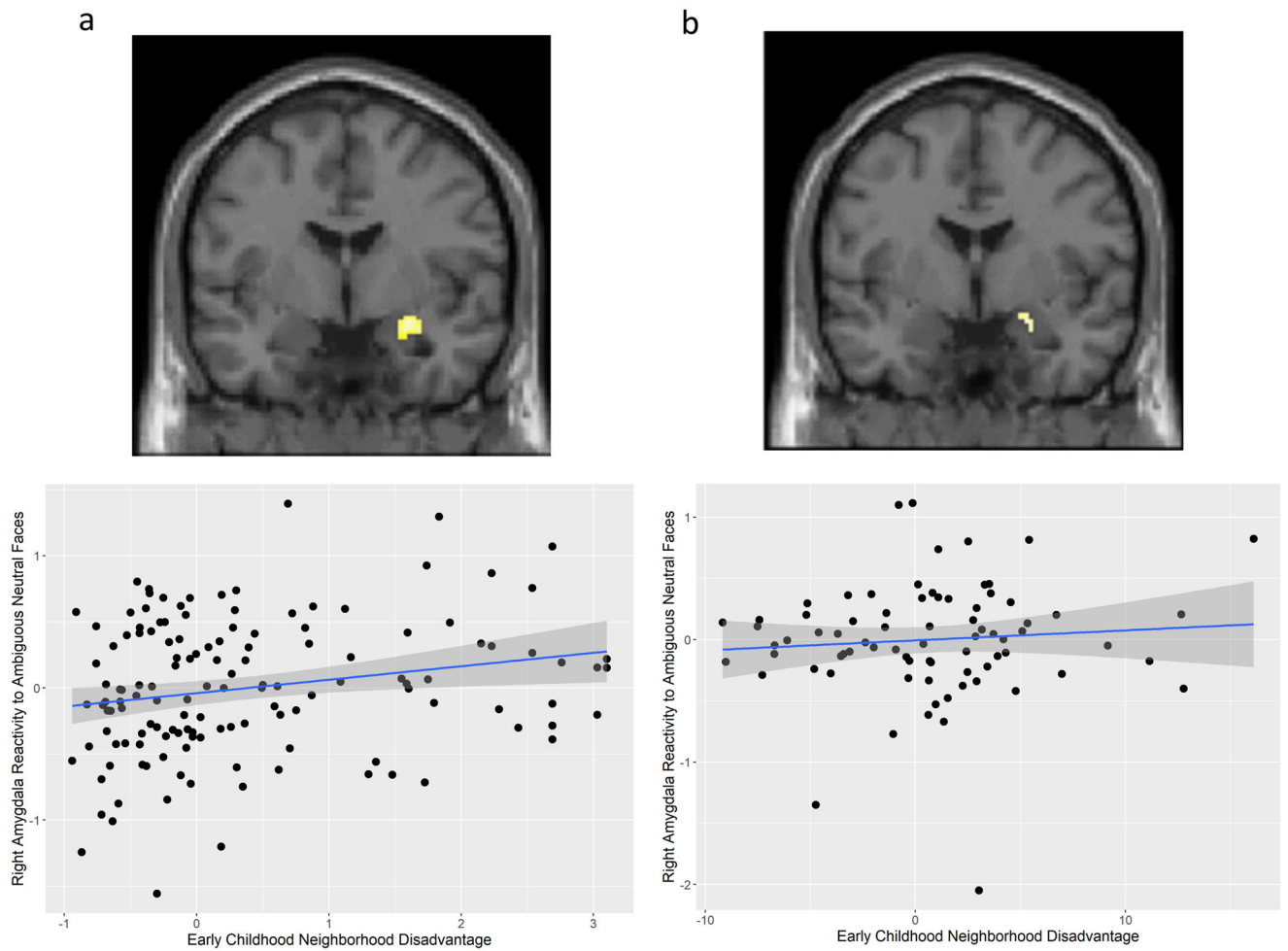
Figure 2.
Neighborhood disadvantage in early childhood is associated with greater amygdala reactivity to neutral faces in two independent samples

Note. (a) Pit Mother & Child Project; right amygdala (x,y,z) = (26,−4,−14), extent threshold $t = 3.56$, cluster size $k = 81$. (b) Study of Adolescent Neurodevelopment; right amygdala (x,y,z) = (22,−4,−18), extent threshold $t = 2.91$, cluster size $k = 36$. In both samples, the depicted associations account for family-level adversities during the same developmental period.
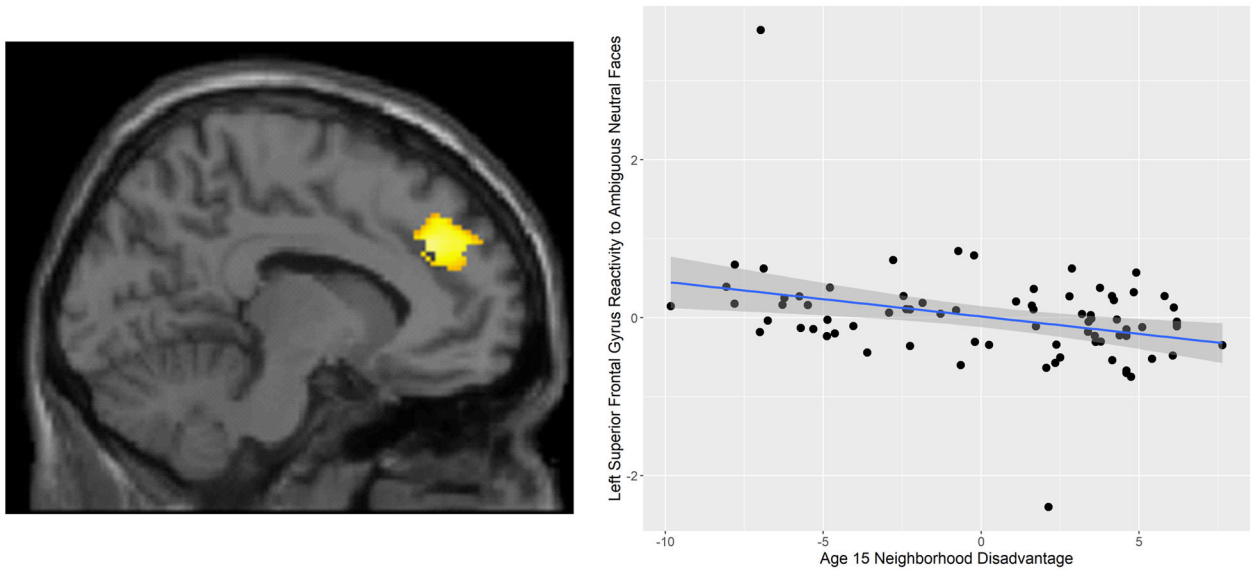
Figure 3.
Neighborhood disadvantage in adolescence is associated with less superior medial frontal gyrus reactivity to neutral faces in the Study of Adolescent Neurodevelopment
Note. Left superior medial frontal gyrus (x,y,z) = (−10, 38, 30), extent threshold $t = 3.81$, cluster size $k = 484$. The depicted association accounts for family-level adversities during the same developmental period and neighborhood disadvantage during early childhood. Results were unchanged when the outliers shown in the top left and bottom right quadrants of the figure were removed.

Table 1.

Neighborhood disadvantage in childhood is associated with corticolimbic reactivity to ambiguous neutral faces in two independent samples

	Pitt Mother & Child Project (PMCP)	Study of Adolescent Neurodevelopment (SAND)
	(x,y,z) *t-threshold* and voxel extent (*k*)	(x,y,z) *t-threshold* and voxel extent (*k*)
Early Childhood		
Neighborhood Disadvantage	(+) Right Amygdala[†δ]: (26, −4, −14), t = 3.56, k = 81 No associations in the PFC	(+) Right Amygdala: (22, −4, −18), t = 2.91, k=36 No associations in the PFC
Adolescence		
Neighborhood Disadvantage	(+) Left Amygdala: (−22,−2,−12), t = 3.52, k = 35 No associations in the PFC	No associations in the amygdala (−) Left Superior Medial Frontal Gyrus[†]: (−10, 38, 30), t = 3.12, k = 484

Note. $127 > N_{PMCP} > 152$; $62 > N_{SAND} > 77$

All models control for child race and family-level adversities during the same developmental period. Models in the SAND data also control for pubertal development at age 15.

[†] significant when controlling for neighborhood disadvantage at the other developmental period

[δ] significant when controlling for neighborhood disadvantage at age 20 (PMCP only)