



HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2017 October ; 2(7): 582–590. doi:10.1016/j.bpsc.2017.06.005.

The long reach of early adversity: Parenting, stress, and neural pathways to antisocial behavior in adulthood

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Abstract

Background—Early life adversities including harsh parenting, maternal depression, neighborhood deprivation, and low family economic resources are more prevalent in low-income urban environments and are potent predictors of psychopathology, including, for boys, antisocial behavior (AB). However, little research has examined how these stressful experiences alter later neural function. Moreover, identifying genetic markers of greater susceptibility to adversity is critical to understanding biopsychosocial pathways from early adversity to later psychopathology.

Methods—Within a sample of 310 low-income boys followed from age 1.5 to 20, multimethod assessments of adversities were examined at age 2 and age 12. At age 20, amygdala reactivity to emotional facial expressions was assessed using fMRI, and symptoms of Antisocial Personality Disorder were assessed via structured clinical interview. Genetic variability in cortisol signaling (*CRHRI*) was examined as a moderator of pathways to amygdala reactivity.

Results—Observed parenting and neighborhood deprivation at age 2 each uniquely predicted amygdala reactivity to emotional faces at age 20 over and above other adversities measured at multiple developmental periods. Harsher parenting and greater neighborhood deprivation in

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Financial Disclosures: The authors report no biomedical financial interests or potential conflicts of interest.

Supplemental Information: supplemental methods, results; 4 tables, 3 figures

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toddlerhood predicted clinically-significant symptoms of AB via less amygdala reactivity to fearful facial expressions and this pathway was moderated by genetic variation in *CRHR1*.

Conclusions—These results elucidate a pathway linking early adversity to less amygdala reactivity to social signals of interpersonal distress 18 years later, which in turn increased risk for serious AB. Moreover, these findings suggest a genetic marker of youth more susceptible to adversity.

Keywords

early life adversity; stress; fMRI; antisocial behavior; Neurogenetics; harsh parenting

Introduction

Early life adversity casts a long shadow on the developing child by predicting multiple negative outcomes, including psychopathology, physical health disparities, and income inequalities across the lifespan and across generations (1). Specific adversities, such as exposure to community violence, poverty, and a parent who is harsh or depressed, each increase risk for psychiatric disorders (2–3). Less is known about the biological mechanisms linking these experiences to psychopathology and how their timing affects the developing brain. Understanding how early life adversity becomes biologically-embedded to increase risk for psychopathology can ultimately lead to the development of more effective strategies to prevent and treat psychiatric disorders (4).

Neural embedding of early experience—The amygdala, a neural structure important for fear learning, emotional responses, and vigilance (5), is critical in responding to stress. A wealth of animal literature indicates that early life adversity leads to structural changes in the amygdala (6,7). Neuroimaging studies in humans suggest that extreme adversity, including maltreatment and social deprivation (8,9), as well common adversities, such as poverty or parental stress (10,11), alter amygdala development. However, little research has examined the impact of variability in more normative experiences (e.g., parenting), nor the unique contributions of various stressors, on later neural functioning (12). Given the role of the amygdala in threat detection and physiological stress responding (5), one specific dimension of parenting likely to undermine amygdala development is harshness, characterized by physical discipline and verbal hostility. Recent empirical evidence suggests that parental harshness is one pathway through which poverty may affect amygdala development (13). However, poverty is associated with a myriad distal and proximal risk factors (e.g., harsh parenting, neighborhood deprivation, low maternal education, maternal depression) that may undermine child development (14,15), highlighting the need to examine the neurodevelopmental effects of community and family-level adversities simultaneously (16). As studies suggest that early childhood (i.e. 0 – 5 years) may be a sensitive period for brain development (17–19), we examined the effects of adversity during toddlerhood on later neural function. However, as adolescence may also be a sensitive period for neural development (20) and many adversities are stable across childhood, we controlled for parallel measures of adversity in early adolescence to identify the unique effect of adversity in toddlerhood on amygdala reactivity during early adulthood.

Implications for psychiatric and behavioral outcomes—Early adversity predicts a range of psychiatric outcomes, yet little research has examined the impact of adversity on brain function as a mechanistic pathway to psychiatric symptoms. Amygdala reactivity to emotional facial expressions is consistently implicated in the pathophysiology of depression and anxiety (21), as well as antisocial behavior (AB) outcomes, including Conduct Disorder, Antisocial Personality Disorder, and psychopathy, which have been linked to deficits in fear processing (22). For boys living in low-income urban environments, harsh parenting, poverty, maternal depression, and neighborhood deprivation, are robust risk factors for AB (3). Thus, a second aim of this study was to test mechanistic pathways linking early adversity to AB via altered amygdala reactivity to emotional faces, particularly to fearful facial expressions. We tested these aims prospectively in a cohort of boys who, based on living in a low-income urban environment and exposed to substantial adversity, were at elevated risk for AB (3).

Genetic susceptibility to early adversity—Finally, although adversity predicts maladaptive outcomes, many children show normative development, highlighting the need to identify markers of who is more susceptible to early adversity. Genetic variation may increase risk by making children more susceptible to poor neurobehavioral outcomes in adverse environments (i.e., diathesis-stress), or may make them more sensitive to both positive and negative outcomes in promotive versus adverse environments, respectively (i.e., differential susceptibility) (23). Animal models suggest that early adversity affects the amygdala via stress-related glucocorticoid signaling (24). Thus, individual variability in cortisol signaling may modulate the effects of stressful experiences on amygdala development. Cortisol signaling is regulated by several receptors, including corticotropin-releasing hormone receptor type 1 (CRHR1), which supports initial activation and negative feedback of the hypothalamic-pituitary-adrenal (HPA) response (25). Extant research linking genetic variation within *CRHR1* to stress-related psychopathology (26) and neuroendocrine function (27,28) has focused on single nucleotide polymorphisms (SNPs) rs110402 and rs7209436, where minor allele carriers are at lower risk for stress-related outcomes in the context of adversity (26–28), although these findings are mixed (29,30). Due to the high density of CRHR1 receptors in the amygdala (31) and studies linking these specific SNPs to stress-related outcomes (26–28), our third goal was to examine whether variability in *CRHR1* moderated the relationship between early adversity and amygdala reactivity to emotional faces.

The current study—In the present study, we examined pathways from early adversity to amygdala function in a longitudinal study of 310 boys living in low-income, urban families, followed from age 1.5 to 20. We examined the unique impact of sociodemographic-, family-, and community-level adversities in toddlerhood on amygdala reactivity to emotional faces in early adulthood (see Figure 1). Importantly, we tested stringent models that controlled for the overlap and co-occurrence of adversities to test unique effects, and included parallel measures of adversities during early adolescence to isolate the neural effects on adversities during early childhood. We also tested whether early adversity predicted AB via effects on amygdala reactivity to fearful facial expressions. Finally, we explored the moderating role of genetic variation in cortisol signaling, by testing if the relationships between early adversity

and amygdala reactivity were stronger among individuals with genetic backgrounds associated with dysregulated HPA-axis function (i.e., *CRHR1* SNPs rs7209436, rs110402). We hypothesized that harsh parenting, specifically during early childhood and above and beyond other risk factors, would predict greater amygdala reactivity to fearful, angry, and neutral facial expressions, which would in turn predict greater AB. Moreover, in an exploratory model, we expected that youth with major alleles within *CRHR1* (compared to youth with minor alleles) would be more sensitive to the neurobehavioral effects of adversity.

Methods and Materials

Participants

Participants are part of the Pitt Mother & Child Project (PMCP), an ongoing longitudinal study of 310 low-income boys and their families recruited in 1991 and 1992 from Allegheny County Women, Infant and Children (WIC) Nutritional Supplement Clinics when boys were 6–17 months old (3). The sample is low income and ethnically diverse (e.g., 52% European-American, 39% African-American of those included at age 20). Children and mothers were seen almost yearly from age 1.5–20 in the laboratory and/or home with assessments that included questionnaires, psychiatric interviews, and at age 20, an fMRI scanning session. fMRI data were available for 167 men (see Supplement and Table S1).

Measures

Harsh Parenting—Harsh parenting was measured at age 2 via observation and parent interview using items from the Acceptance scale of the Home Observation for the Measurement of the Environment (32). The eight-item scale assessed both verbal (e.g., “parent shouts at child”) and physical (e.g., “parent slaps/spanks child”) harshness.

Contextual Sources of Stress—Additional measures of contextual adversities were collected at age 2: (i) parent-reported monthly family income (dollars), (ii) maternal education (less than a high school diploma versus a high school diploma or higher), (iii) maternal depressive symptoms using the Beck Depression Inventory (33), and (iv) neighborhood deprivation, a composite score of impoverishment using U.S. Census data (e.g., median family income, % households on public assistance) (34).

Antisocial Behavior—To create a dimensional measure of AB, symptoms of Antisocial Personality Disorder and responses to screener questions (i.e., Conduct Disorder symptoms) were collected at age 20 through interviews with the participants by a trained examiner using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (35). To confirm that associations were specific to AB rather than other related psychopathologies, we controlled for concurrent symptoms of substance use disorder (SUD), alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD), all collected using the SCID-I (36). To control for earlier AB, parent-reported child externalizing behavior at age 2 was measured using the Externalizing factor of the Child Behavior Checklist (37).

Neuroimaging

Amygdala Reactivity Paradigm—Amygdala reactivity was assessed using an emotional faces matching paradigm (38). Trials were presented in counterbalanced blocks of angry, fearful, neutral, or surprised facial expressions interleaved with five blocks of a sensorimotor control (see Supplement).

fMRI Data Acquisition and Preprocessing—Each participant was scanned with a Siemens 3-T Tim Trio. As previously described in this sample (38), preprocessing was conducted using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) with post-processing control for artifacts and exclusion of participants with low amygdala coverage (see Supplement for details).

fMRI Analysis—The general linear model of SPM8 was used to estimate condition-specific (e.g., fearful faces > shapes) BOLD activation for each individual scan. Individual contrast images were then used in second-level random effects models to determine mean expression-specific reactivity using one-sample t-tests. As our goal was to examine amygdala reactivity to specific contrasts, the following were estimated and mean cluster values were extracted from SPM8 to be used in path models: fearful facial expressions > shapes and angry facial expressions > shapes to measure neural reactivity to interpersonal distress and threat, respectively (39), which have been implicated in AB (22). We also examined neutral faces > shapes because recent studies show similar amygdala responses to unmasked neutral faces and other expressions of threat (40,41), suggesting that ambiguity may also be interpreted as threatening (42). Across all three contrasts, we hypothesized that early adversity would be related to greater amygdala reactivity to emotional facial expressions. Contrast-specific BOLD parameter estimates were extracted from activated clusters within anatomically-defined amygdala regions (using the AAL Atlas) that survived the Family-Wise Error (FWE) correction in SPM8 of $p < .05$ (see Table S2).

DNA Collection and Genotyping

Genomic DNA was collected when youth were age 17 and isolated from saliva samples using the Oragene™ DNA self-collection kit (DNA Genotek Inc., Canada). DNA was extracted using standard methods. SNPs within *CRHR1* were identified using TaqMan allelic discrimination assays. All genotypes were in Hardy-Weinberg Equilibrium in the full sample, as well as in the African-American and European-American subsamples. Allelic frequencies did not differ from HapMap expected distributions by race (Table S3). Of the 310 participants in the study, valid genetic data were available for 228 (rs110402) and 225 (rs7209436) participants. To maximize information from both SNPs and to avoid multiple comparisons by looking at each SNP individually, we grouped individuals who were homozygous major at both SNPs into one genotype group and individuals who were heterozygous or homozygous minor into another genotype group, consistent with previous studies (26–28) (see Supplement).

Statistical Analysis

All statistical analyses were performed in Mplus 7.2 (43) using full information maximum likelihood (FIML) estimation. FIML estimation uses the covariance matrix of all available

data to produce unbiased estimates and standard errors in the context of missing data (44). Simulation studies indicate that FIML estimation provides unbiased estimates with greater power than listwise deletion even when up to 50% of data are missing (45,46). Thus our analyses used all participants ($N=310$), except when they were missing data on a grouping variable in multi-group models (i.e., when testing *CRHR1* as a moderator; $n=214$). Using listwise deletion ($N=167$) produced a similar pattern of results (see Figure S1).

All models controlled for child race and externalizing symptoms at age 2. First, measures of early adversity were entered into six linear regressions predicting amygdala reactivity (i.e., right and left amygdala reactivity to fear>shapes, anger>shapes, and neutral>shapes). We focus on estimates that survived Bonferroni correction for multiple comparisons ($p=.05/$ six regressions =adjusted p -value of .008). To test developmental specificity, we added measures of adversity from the age 12 assessment to the models (see Supplement). Second, as both AB and multiple measures of adversity were correlated with right amygdala reactivity to fearful facial expressions, for each measure of adversity that predicted right amygdala reactivity to fearful faces, we estimated an indirect effects model linking early adversity to AB via amygdala reactivity using bootstrapping methods to produce unbiased confidence intervals. We could not test any other neural contrasts as mediators in this model because AB was only related to amygdala reactivity to fearful faces, consistent with past work in this sample (38). Finally, we tested whether variation in *CRHR1* moderated pathways from adversities to amygdala reactivity and AB by comparing the model fit of a baseline model to a model where the adversity to brain pathway was specified to vary across *CRHR1* genotype groups (see Supplement). Given the greater statistical power presented by the entire sample ($N=310$), we focus on results of the path analyses in the total sample while controlling for child race. However, given potential effects of ancestry (47), we also present results separated by self-reported race in Figures S2 and S3. For models which tested pathways to AB, we also included symptoms of SUD, AUD, and PTSD at age 20 as covariates. Moreover, in a separate model (Figure S4), we included multiple dimensions of psychopathology as outcome variables to ensure the pattern of findings was specific to AB.

Results

Do early childhood adversities predict amygdala reactivity in adulthood?

Zero-order correlations (Table 1) showed that multiple adversities in toddlerhood were associated with amygdala reactivity to angry, fearful, and neutral facial expressions. In particular, harsh parenting was related to lower right amygdala reactivity to both fearful and angry faces and neighborhood deprivation was related to greater bilateral amygdala reactivity to neutral faces. Though only trend-level, harsh parenting and neighborhood deprivation both predicted neural reactivity in the same direction: less amygdala reactivity to fearful, and greater amygdala reactivity to neutral, facial expressions.

Which adversities in early childhood have unique effects?—In regression models controlling for all adversities and covariates, harsh parenting in toddlerhood uniquely predicted lower right amygdala reactivity to fearful facial expressions in adulthood (Table 2, Figure 2a). Neighborhood deprivation also uniquely predicted greater bilateral amygdala

reactivity to neutral facial expressions (Table 2). Like harsh parenting, maternal education also predicted less left amygdala reactivity to fearful facial expressions and maternal depression predicted lower right amygdala reactivity to angry facial expressions, but neither of these associations survived correction for multiple comparisons. The direction of effects across adversities was consistent: Harsher parenting and greater neighborhood deprivation both predicted *lower* amygdala response to fearful faces and *greater* amygdala response to ambiguous neutral faces. Moreover, these results remained when controlling for parallel measures of adversities at age 12 (Table S4), indicating that adversity in toddlerhood exerts unique developmental effects on amygdala function in adulthood.

Do early adversities predict AB via amygdala reactivity to fearful facial expressions?

As AB was related to lower amygdala reactivity to fearful faces, we tested an indirect pathway in which harsh parenting and neighborhood impoverishment in toddlerhood predicted AB in adulthood via right amygdala reactivity to fearful faces. To confirm that the indirect pathway was specific to parenting and neighborhood impoverishment, we tested a conservative model that included concurrent measures of all other adversities, early child externalizing behavior, and child race as covariates. The model revealed two significant indirect pathways, in which harsh parenting and greater neighborhood deprivation each uniquely predicted higher AB via lower amygdala reactivity to fearful facial expressions (Figure 2b).

Does variation in *CRHR1* moderate the relationship between early adversity and amygdala reactivity to fearful facial expressions?

We found a statistically significant moderation of the pathway between harsh parenting, (but not neighborhood deprivation) and right amygdala reactivity by variation in *CRHR1*. For individuals who were heterozygous or homozygous minor across both SNPs (i.e., 2 or 4 total minor alleles), but not those homozygous for major alleles, harsh parenting predicted amygdala reactivity to fearful faces (Figure 3a). The results suggest a pattern of differential susceptibility rather than diathesis-stress (Figure 3b). Finally, we found that the indirect pathway from harsh parenting to AB via amygdala reactivity was only significant for individuals who were heterozygous or homozygous minor at both SNPs (i.e., moderated mediation; Figure 3a).

Discussion

The findings offer evidence for neurodevelopmental effects of early adversity across 18 years. In a prospectively-followed sample of young men, we found that multiple adversities, including harsh parenting, neighborhood deprivation, low maternal education, and maternal depressive symptoms in toddlerhood predicted amygdala reactivity to emotional facial expressions in adulthood. Importantly, early harsh parenting and neighborhood deprivation predicted amygdala reactivity over and above the effects of other adverse experiences in both toddlerhood and early adolescence, survived correction for multiple comparisons, and predicted clinically-significant AB at age 20. Specifically, these adversities predicted less amygdala reactivity to interpersonal threat and greater amygdala reactivity to interpersonal ambiguity. We also found evidence suggesting that individuals with minor alleles within

CRHR1 (rs110402 and rs7209436) exhibited greater neurobehavioral sensitivity to harsh parenting. These findings inform a model of neurodevelopment in which early adversity becomes biologically embedded via altered amygdala reactivity, which in turn, increases risk for AB, potentially only for those with “susceptible” genotypes.

One of our most striking findings is that harsh parenting during toddlerhood predicted amygdala reactivity to interpersonal distress and subsequent AB in early adulthood even after accounting for many other adversities and other co-occurring psychopathology. Prior research linking extreme forms of adversity (i.e., childhood maltreatment) or distal measures of adversity (e.g., socioeconomic status) to amygdala function have not consistently accounted for the correlation between multiple types of adversity including sociodemographic- (i.e., income, maternal education), family- (i.e., maternal depression), and community-level stressors (i.e., neighborhood deprivation) (8–11), a strength of the current study. We also found that harsh parenting in toddlerhood predicted amygdala reactivity even when considering parenting behaviors in early adolescence, suggesting that parenting during early childhood has unique effects on later neural function.

That less amygdala reactivity to interpersonal distress was related to greater AB is consistent with previous work in this sample (38) and a broader literature implicating low amygdala reactivity to interpersonal fear in severe AB (particularly psychopathy; 22,48). However, that harsh parenting was related to *lower* amygdala reactivity to fearful facial expressions contrasts with our hypotheses and previous studies among adolescents, in which child maltreatment (8) and social deprivation (9) predicted *greater* amygdala reactivity to angry and fearful facial expressions relative to calm faces, respectively. However, a recent paper using a sample at risk for AB reported that greater childhood family adversity also predicted *blunted* amygdala reactivity to emotional facial expressions (49), consistent with our results. Thus, it could be that the differences in directionality between our findings and the maltreatment literature (8, 9) are due to sample characteristics including the prevalence of AB and the all-male nature of our sample, with boys being at greater risk for AB (22,48). Second, as research indicates that amygdala reactivity to emotional faces may peak in adolescence and decline into adulthood (50), our findings could also reflect differential developmental trajectories of risk on amygdala reactivity. Finally, we focused on neural contrasts between fearful facial expressions and a non-face shapes stimuli. The neutral facial expressions used in our task were “neutral” as opposed to “calm” (neutral morphed with some happy) faces used in previous studies (8,9). Indeed, we found that multiple adversities predicted greater amygdala reactivity to neutral faces, suggesting that these ambiguous faces may be interpreted as hostile, at least for the males in this study living in dangerous neighborhoods (51), a hypothesis supported by recent studies in similarly high risk contexts (40,41).

Importantly, the direction of findings across different types of adversity was consistent: poorer neighborhood conditions and harsher parenting predicted less amygdala reactivity to fearful facial expressions and greater amygdala reactivity to ambiguous neutral facial expressions. Moreover, neighborhood deprivation during early childhood predicted amygdala reactivity to faces in adulthood even after controlling for neighborhood effects in early adolescence. While this might be surprising because toddlers have more direct contact

with parents than the broader neighborhood context (52), impoverished neighborhoods expose families to multiple stressors, including community violence, crowding, and poor quality (pre)schools (15, 53). Neighborhood impoverishment could undermine amygdala development differently at each developmental stage through exposure to various aspects of neighborhood stress (e.g., low quality preschool education early; witnessing community violence later) (53). A recent theory (54) suggests that the effects of adversity on the brain may depend on the type of stress (i.e., *threat* versus *deprivation*). Thus, according to this theory, our results could be highlighting the impact of threatening aspects of neighborhood deprivation (e.g., community violence) on the family, child, and amygdala. Clearly more research is needed to understand the ways in which specific aspects of impoverished contexts affect neurodevelopment (14,15).

Previous studies linking early adversity to neural function and psychopathology have examined internalizing outcomes (10,11). Our results extend this literature by describing a mechanistic pathway to AB whereby harsh parenting and neighborhood deprivation were related to higher levels of AB via lower amygdala reactivity to interpersonal distress. Moreover, we tested a stringent model by controlling for comorbidity with substance use and PTSD symptoms (55,56), as well as a separate model in which multiple measures of psychopathology were modeled as outcomes in addition to AB (Figure S4), thus demonstrating that these neurodevelopmental effects of early adversity were specific to AB.

Importantly, these pathways showed variability across participants, as there was preliminary evidence that *CRHR1* genotype moderated the neural effects of early adversity. Our findings suggested differential susceptibility, such that individuals with minor alleles at two *CRHR1* SNPs demonstrated the lowest amygdala reactivity (and greatest risk for AB) when exposed to harsh parenting, but the highest amygdala reactivity (and lowest risk for AB) when exposed to more positive parenting. Though this result is difficult to reconcile with regards to most studies linking greater amygdala reactivity to psychopathology (21), given our findings of the specificity of these results to AB and previous findings in this sample and others that low amygdala reactivity predicts poor outcomes (22,38,48), it may be that amygdala reactivity acts in a different way in predicting risk among high-risk urban young men. That minor allele carriers evinced the greatest risk for poor outcomes was contrary to our hypothesis and some prior research (26–28), though not several other studies (29,30). Our results suggest that among boys living in low-income urban neighborhoods, interventions to reduce harsh parenting and to develop and sustain positive parenting, are critical for long-term neurobehavioral outcomes, but may be particularly effective for youth with “susceptible” alleles within *CRHR1* (57).

Although we tested a conservative model by controlling for multiple adversities using observational measures, prospective data at two time points, and correcting for multiple comparisons when examining multiple regressions, our complex imaging gene x environment interaction results need to be replicated in larger samples with greater power to detect smaller and more complex genetic moderation effects (58), and to minimize the risk for false positive associations that can arise in smaller samples (59). As we studied a sample socio-demographically enriched for externalizing psychopathologies, several of the young men could not participate in the MRI (e.g., history of concussion, incarceration),

highlighting a broader sampling problem for studies of antisocial participants (60). Further, without ancestry informative markers, we were unable to control for genetic admixture within our sample (47). However, self-reported race is highly correlated with ancestry (61), potentially addressing this limitation. Additionally, though these results suggest that contextual factors may affect neurodevelopment, we only measured amygdala reactivity at one time point and did not examine trajectories of AB or cumulative effects of adversity across childhood. Finally, we cannot exclude potential gene-environment correlations (62). Future studies using genetically-informed designs (63) may be able to parse heritable and non-heritable effects from pathways linking adversity to neurobehavioral outcomes.

Although these limitations call for replication, the current study demonstrates the impact of early adversity on neurobehavioral development using longitudinal measurement of observed environmental adversities from toddlerhood to adulthood, a widely-used fMRI task to probe amygdala reactivity, a cohort of predominantly low-income men exposed to multiple environmental stressors, greater racial diversity than most fMRI studies, an innovative developmental imaging gene x environment interaction model (64), and interviewer-assessed clinically-meaningful antisocial behaviors. These results provide a model by which chronic stressors prevalent in low-income, urban environments increase risk for later AB via their effect on the developing brain, and suggest why only some individuals have poor outcomes under these conditions. These findings inform a model for the development of AB across the lifespan and provide further evidence for the neurotoxic effects of early life adversity within the home and community.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The research reported in this paper was supported by grants to D.S.S. (R01 MH50907, R01 MH01666, and K05 DA25630), D.S.S. and E.E.F (R01 DA026222), L.W.H. (L40 DA036468), and A.M.G (T32 HD00710936) by the National Institutes of Health. A.R.H. received support by National Institutes of Health grant R01 DA033369, R01 DA031579, R01 AG049789, and R21 MH106715. Dr. Hyde's work is also supported by the Avielle Foundation. We are grateful to the work of the staff of the Pitt Mother & Child Project for their many years of service, and to our study families for sharing their lives with us and making the research possible.

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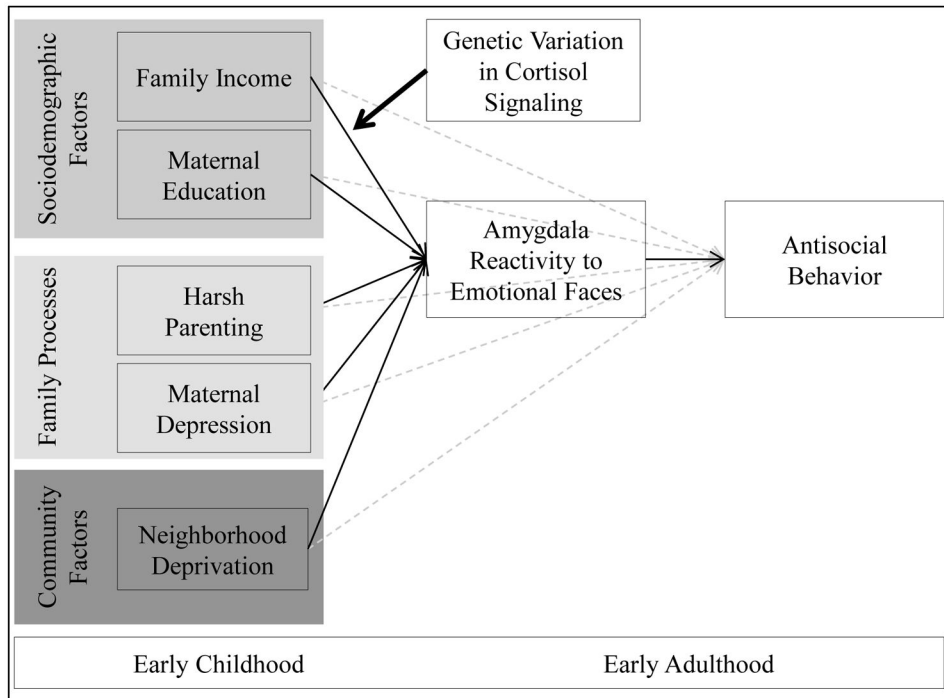


Figure 1. Conceptual model of study aims

We were guided by a bioecological model of psychopathology (16), process models specifying sociodemographic, family, and community adversities associated with poverty (14,15,53), and neurogenetics and Imaging Gene x Environment interaction models (58,64). We hypothesized that specific adversities present in impoverished contexts put children at differential risk for psychopathology, particularly antisocial behavior in boys, via their effects on brain development and subsequent neural reactivity to emotion and threat. We hypothesized that early adversities would predict antisocial behavior in early adulthood via amygdala reactivity to emotional faces and that this pathway would be stronger among those with genes associated with dysregulated cortisol signaling (24). Specifically, we hypothesized that harsh parenting, as the most proximal factor for young children, would predict greater amygdala reactivity to social signals of threat, distress, and ambiguity, which in turn, would predict antisocial behavior. Moreover, we hypothesized that those with genotypes related to greater cortisol dysregulation would be particularly sensitive to these effects (26–28). Given the need to delineate if these effects are consistent with a diathesis-stress model (i.e., these genes put children at risk for poor outcomes in harsh environments) versus a differential susceptibility model (i.e., these genes mark children who are more sensitive to the environment, for better or worse; 20), we examined the pattern of interactions in Figure 3.

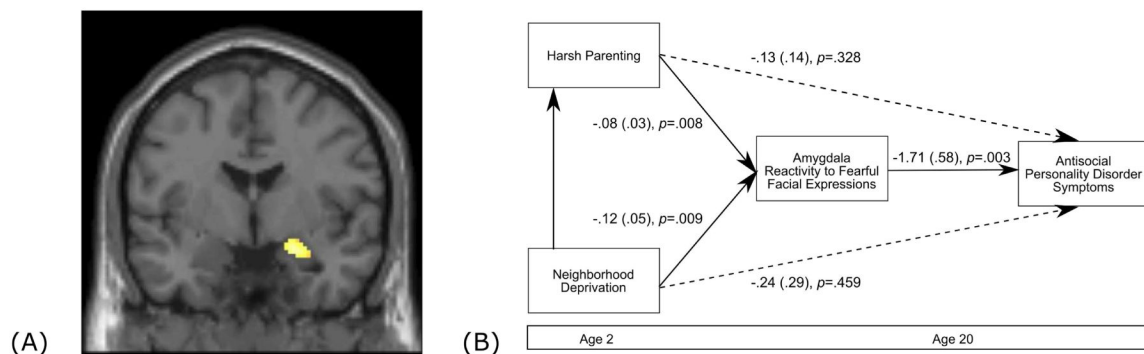


Figure 2. Harsh parenting and neighborhood deprivation predict antisocial behavior via low amygdala reactivity to fearful facial expressions

(A) Main effect of fearful facial expressions versus shapes in the right amygdala (Table S2).

(B) Path model linking harsh parenting and neighborhood deprivation at age 2 to symptoms of Antisocial Personality Disorder at age 20 via right amygdala reactivity to fearful facial expressions. Covariates include child race, toddler externalizing symptoms, maternal education, family income, and maternal depression symptoms at age 2, and at age 20, symptoms of SUD, AUD, and PTSD. Paths are marked with unstandardized coefficients. For indirect effects, we provide the unbiased bootstrapped CI of this effect ($p < .05$) as well as an estimate of the product coefficients ($\alpha\beta$) (i.e. the 'sobel test') as an index of gross effect size. Indirect paths were: Harsh parenting to right amygdala reactivity to fearful facial expressions to Antisocial Personality Disorder symptoms ($\alpha\beta = .06$, $p = .046$; bootstrapped 95% CI = .13 to .001). Neighborhood deprivation to right amygdala reactivity to fearful facial expressions to Antisocial Personality Disorder Symptoms ($\alpha\beta = .06$, $p = .043$; bootstrapped 95% CI = .002 to .124). The path model demonstrated good fit, $X^2 = 2.11$ (6) $p = .90$, CFI = 1.00, RMSEA = .00 CI (.00 to .03), SRMR = .01.

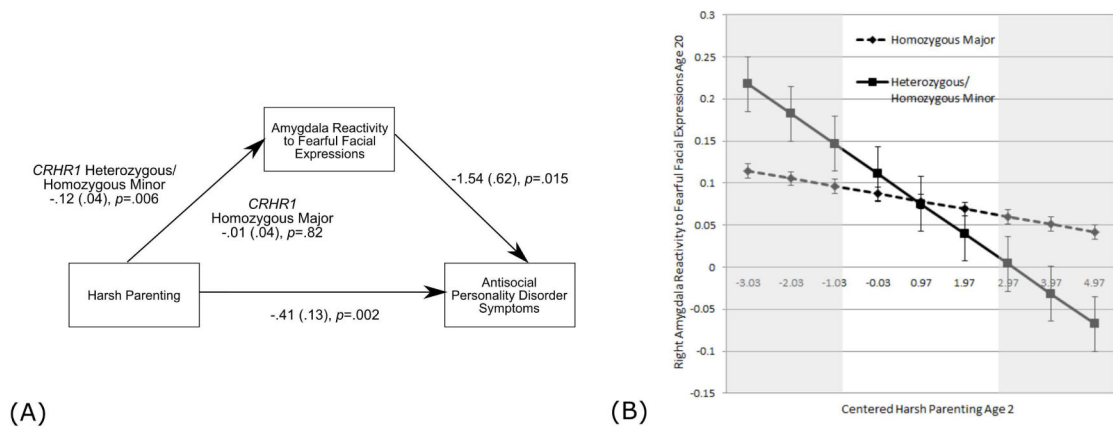


Figure 3. *CRHR1* genotype moderates the relationship between harsh parenting and amygdala reactivity to fearful facial expressions

(A) Path model indicates that only among individuals who are heterozygous or homozygous minor at both *CRHR1* SNPs is parenting at age 2 related to right amygdala reactivity to fearful faces at age 20. Covariates include child race, toddler externalizing symptoms, neighborhood deprivation, maternal education, family income, and maternal depression symptoms at age 2, and at age 20, symptoms of SUD, AUD, and PTSD. Paths are marked with unstandardized coefficients. Moderation was tested by comparing model fit (X^2) of the baseline model (see Supplement) to a model where harsh parenting to amygdala reactivity was allowed to vary across genotype groups, $X^2=3.88, df=1, p=.04$ (indicating significant moderation). In addition, we report an indirect effect for individuals who are heterozygous or homozygous minor, but no indirect effect for those who were homozygous major, from harsh parenting to amygdala reactivity to Antisocial Personality Disorder symptoms ($\alpha\beta = .12, p=.042$; bootstrapped 95% CI = .01 to .70). The path model demonstrated good fit, $X^2 = 61.43 (61) p=.47, CFI = 1.00, RMSEA = .10$ CI (.00 to .06), SRMR=.06. **(B)** Predicted values of amygdala reactivity to right fearful facial expressions at each value of harsh parenting for individuals who are homozygous major ($n=89$) versus heterozygous or homozygous minor ($n=125$) at both *CRHR1* SNPs. The plotted points were calculated using unstandardized beta estimates from a regression model using a continuous interaction term to test moderation by genotype (see Supplement). The shaded gray boxes indicate regions where the standard errors of each plotted point for each genotype group do not overlap (i.e., regions where the expected values of amygdala reactivity are significantly different by genotype group). Thus, this figure depicts a pattern of differential susceptibility to harsh parenting, where heterozygotes and individuals who are homozygous minor at both *CRHR1* SNPs show lower amygdala reactivity in the context of high harshness but greater amygdala reactivity in the context of low harshness, with respect to the other genotype group.

Zero-order correlations between toddlerhood adversities and amygdala reactivity to emotional facial expressions at age 20

Table 1

	Fear			Neutral			Angry			Min	Max
	Right	Left	Right	Left	Right	Left	Right	Left	Right		
Adversities (2 years)											
Harsh parenting	-.21*	-.11	.153	.14	-.163	-.173	4.97(1.93)	0	8	8	8
Monthly family income in dollars	.04	-.01	.03	-.11	.07	.10	1094.60 (695.59)	249	40,000	249	40,000
Neighborhood deprivation	-.133	-.10	.16*	.23**	-.10	-.05	.38(1.19)	-2.04	3.40	-2.04	3.40
Maternal education in years	-.08	-.09	-.09	-.14*	.123	.03	12.62(1.55)	8	18	8	18
Maternal depression	.12	.143	.002	.02	-.17*	-.08	7.59(6.28)	0	36	0	36
Psychopathology (20 years)											
Antisocial Behavior	-.20*	-.22*	-.03	-.02	.01	-.04	2.43(3.89)	0	18	0	18

N=310;

† $p < .10$

* $p < .05$,

** $p < .01$,

*** $p < .001$.

Table 2
Early parenting and neighborhood deprivation uniquely predict amygdala reactivity to emotional faces in adulthood

	Fear				Neutral				Angry			
	Right		Left		Right		Left		Right		Left	
	B(SE)	β	B(SE)	β	B(SE)	β	B(SE)	β	B(SE)	β	B(SE)	β
Harsh parenting	.07(.03)	-.25***	.05(.02)	-.163	-.05(.03)	.163	-.03(.03)	.11	.03(.02)	-.11	.05(.03)	-.163
Income	.001(.01)	.001	-.003(.01)	-.04	.01(.01)	.13	.001(.01)	.01	-.001(.01)	-.02	.01(.01)	.08
Neighborhood deprivation	-.11(.05)	-.23*	-.09(.05)	-.183	.20(.05)	.36***	.13(.05)	.27***	-.05(.05)	-.09	-.02(.05)	-.04
Maternal education	-.24(.12)	-.14*	-.23(.13)	-.143	-.15(.14)	-.08	-.18(.10)	-.11	.21(.13)	.12	-.01(.15)	-.003
Maternal depression	.01(.01)	.15*	.02(.01)	.17*	.001(.01)	.01	.002(.01)	.02	-.02(.01)	-.17*	-.01(.01)	-.06

N=310.

† $p < .10$

* $p < .05$,

** $p < .01$,

*** $p < .001$,

indicates that the estimate survives Bonferroni correction for multiple comparisons ($p < .05/6$ regressions=.008 adjusted p -value).

Each column presents one linear regression model where all predictor variables are listed in the rows. All predictor variables were collected at age 2 years. Child race was also included as a covariate and emerged as a significant predictor in the linear regression models predicting right fear faces > shapes and right neutral faces > shapes. European Americans had less right amygdala reactivity to fear faces > shapes ($\beta = .22, p < .05$) and greater right amygdala reactivity to neutral faces > shapes ($\beta = -.31, p < .001$) compared to African American and biracial participants.