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Impact of childhood adversity on corticolimbic volumes in youth at clinical high-risk for psychosis

Allison M. LoPilato [a, *], Katrina Goines [j], Jean Addington [b], Carrie E. Bearden [c], Kristin S. Cadenhead [d], Tyrone D. Cannon [e, f], Barbara A. Cornblatt [g], Daniel H. Mathalon [h], Thomas H. McGlashan [e], Larry Seidman [k], Diana O. Perkins [i], Ming T. Tsuang [d], Scott W. Woods [e], Elaine F. Walker [a, j]

[a] Department of Psychiatry and Behavioral Sciences, Emory School of Medicine, 12 Executive Park, Atlanta, GA 30329, United States
[b] Department of Psychiatry, Hotchkiss Brain Institute, University of Calgary, 3280 Hospital Drive NW, Calgary, AB T2N4Z6, Canada
[c] Semel Institute for Neuroscience and Human Behavior and Department of Psychology, UCLA, 760 Westwood Plaza, Los Angeles, CA 90095, United States
[d] Department of Psychiatry, UCSD, 9500 Gilman Drive, La Jolla, CA 92093-0761, United States
[e] Department of Psychiatry, Yale University, 300 George St., New Haven, CT 06511, United States
[f] Department of Psychology, Yale University, 2 Hillhouse Ave., New Haven, CT 06520-8205, United States
[g] Department of Psychiatry, Zucker Hillside Hospital, 75-59 263rd St., Queens, NY 11004, United States
[h] Department of Psychiatry, UCSF, 401 Parnassus Avenue, San Francisco, CA 94143, United States
[i] Department of Psychiatry, University of North Carolina, Chapel Hill, 101 Manning Dr, Chapel Hill, NC 27514, United States
[j] Department of Psychology, Emory University, 36 Eagle Row, Atlanta, GA 30322, United States
[k] Harvard Medical School, Department of Psychiatry, 401 Park Drive, 2 East, Boston, MA 02215, United States

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ABSTRACT

Childhood adversity is among the strongest risk factors for psychosis-spectrum disorders, though the nature and specificity of the biological mechanisms underlying this association remains unclear. Previous research reveals overlaps in the volumetric alterations observed in both adversity-exposed individuals and in psychosis-spectrum populations, highlighting the possibility that deviations in corticolimbic gray matter development may be one mechanism linking adversity and psychosis. Given that childhood adversity encompasses a wide range of adverse experiences, there is also a critical need to examine whether these different types of experiences have unique effects on corticolimbic regions. This study examined the association between childhood adversity and cortical, hippocampal, and amygdalar volume in a large sample of youth at clinical-high risk (CHR) for psychosis. We utilized a novel differentiated adversity approach that distinguishes exposures along dimensions of threat (e.g., abuse) and deprivation (e.g., poverty, neglect) to test for differential associations. Participants were drawn from the North American Prodromal Longitudinal Study (NAPLS) and completed an MRI scan and a retrospective assessment of childhood adversity at baseline. We found that deprivation exposure, but not threat, was uniquely associated with smaller cortical volume and smaller right hippocampal volume in CHR youth. These associations were masked in a generalized risk model that utilized a total adversity score. The findings suggest that deprivation exposures during childhood contribute to the subtle volumetric reductions observed in clinical high-risk samples and highlight the importance of disentangling different dimensions of adversity.

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1. Introduction

Childhood adversity has been consistently linked with the psychosis spectrum, including both diagnostic and dimensional outcomes of psychosis. Several meta-analytic studies have found that childhood adversity significantly increases the risk for developing psychosis (Matheson et al., 2013; McGrath et al., 2017; Morgan and GayerAnderson, 2016; Varese et al., 2012), as well as the persistence of psychotic symptoms overtime (Trotta et al., 2015). Rates of childhood adversity and trauma are high among clinical-high risk (CHR) populations (Kraan et al., 2015), and have been found to predict transition from risk states to overt psychosis (Bechdolf et al., 2010; Thompson et al., 2013; Yung et al., 2015). However, despite the consistency of evidence linking childhood adversity to the emergence and maintenance of psychosis, the nature and specificity of the biological mechanisms that underlie

* Corresponding author at: Department of Psychiatry & Behavioral Sciences, Emory University School of Medicine, 12 Executive Park, Atlanta, GA 30329, United States.
E-mail address: allison.lopilato@emory.edu (A.M. LoPilato).

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these associations remain poorly understood.

Deviations in corticolimbic gray matter development (i.e., hippocampus, amygdala, PFC) are one putative biological mechanism linking childhood adversity and psychosis-spectrum disorders. Corticolimbic regions are a prime substrate for psychiatric dysfunction given their unique vulnerability to stress and experience-dependent plasticity, as well as their role in a range of cognitive and emotional functions disrupted in psychiatric illness (Bogdan et al., 2016; Lupien et al., 2009; Macdonald et al., 2016; Swartz and Monk, 2014; Teicher and Samson, 2016). Childhood adversity has been associated with a number of structural brain changes in corticolimbic regions (Edmiston et al., 2011; Habets et al., 2011; McCrory et al., 2011), including reduced cortical (Dannlowski et al., 2012; van Harmelen et al., 2010; Gold et al., 2016; Teicher et al., 2012; Tomoda et al., 2009) and hippocampal volumes (Dannlowski et al., 2012; Luby et al., 2013; Noble et al., 2012; Teicher et al., 2012), and both enlarged and reduced amygdalar volumes (Edmiston et al., 2011; Luby et al., 2013). Importantly, the structural brain changes associated with adversity exposure overlap with those commonly observed across the psychosis spectrum (Hart and Rubia, 2012; Hirayasu et al., 2001; see review by Jung et al., 2012; Sigmundsson et al., 2001). This overlap, coupled with the high rates of childhood adversity exposure among psychosis-risk and patient populations, suggests that structural changes in corticolimbic regions may represent a neural embedding of adversity that subsequently confers risk for the development of psychosis-spectrum disorders. In addition, there is increasing evidence that individual differences in corticolimbic structure may mediate associations between the early life adversity and the later development of psychopathology (Burghy et al., 2012; Gorka et al., 2014; Rao et al., 2010; Swartz et al., 2015; Tottenham et al., 2011), including psychosis (Sheffield et al., 2013). Disruptions in the development of corticolimbic regions have the potential underlie a number of the cognitive deficits that characterize the psychosis spectrum, including attention, processing speed, concentration, language, and verbal intelligence (Aas et al., 2011).

While most theories linking adversity with brain changes have relied on abnormal stress responses mediated by the HPA-axis and cortisol-induced atrophy (see Lupien et al., 2009), the specific pattern of structural variants and deficits associated with childhood adversity exposure are difficult to fully explain with HPA-driven cellular mechanisms. This raises the possibility that deviations in neurodevelopment following childhood adversity are instilled not only by allostatic wear and tear, but also through the specific functional adaptations and demands that certain experiences place on the developing brain. Developmental neuroscience and animal models have shown that the developing brain is shaped by certain kinds of environmental input, and that deviations from what is needed or anticipated can lead to distinct biological and functional consequences (Fox et al., 2010). Animal models that can manipulate and isolate specific adversity exposures provide evidence for this type of experience dependent neuroplasticity and its impact on synaptic formation and pruning, dendritic density, and cortical thickness (Diamond et al., 1972; Eiland et al., 2012; Markham and Greenough, 2004). In line with this, investigators have recently proposed an alternate approach to conceptualizing childhood adversity that moves away from a purely allostatic stress perspective to one that draws on principles of experience-dependent plasticity and considers the specific effect such deviations from the expectable environment will have on development (Humphreys and Zeanah, 2015; McLaughlin et al., 2014).

McLaughlin et al. (2014) have proposed a conceptual model that categorizes childhood adversity exposures along dimensions of threat (i.e., harmful inputs such as abuse) and deprivation (i.e., inadequate inputs such as neglect, poverty), which are posited to impact at least partially distinct neural, neuroendocrine, cognitive and emotional mechanisms (McLaughlin et al., 2014; Sheridan and McLaughlin, 2014). Specially, threat is proposed to alter development of the substrates that support emotional processing and fear learning, while deprivation is posited to alter neural regions that support cognitive performance and higher-order learning (McLaughlin et al., 2014). Characterizing childhood adversities along dimensions of threat and deprivation aims to address the oversimplification of generalized risk models, which implicitly assume all exposures have a uniform and interchangeable impact. Recent investigations utilizing this model in community adolescent samples have identified differential associations between childhood violence exposure (threat indicator) and poverty (deprivation indicator) in relation to a number of bio-behavioral risk mechanisms including executive functioning (Sheridan et al., 2017), emotion processing (Lambert et al., 2016), reward processing (Dennison et al., 2017), and physiological reactivity (Busso et al., 2017). More specifically, threat has shown specific associations with emotion processing and physiological reactivity (Busso et al., 2017; Lambert et al., 2016), while deprivation has been uniquely associated with cognitive control, associative learning, and reward performance (Lambert et al., 2017; Dennison et al., 2017; Sheridan et al., 2017). These findings provide preliminary evidence for the distinction between threat and deprivation exposures and implicate potential disruptions in corticolimbic regions, which play a critical role in supporting these bio-behavioral processes.

Whether threat and deprivation are uniquely associated with structural corticolimbic brain volumes remains an empirical question. While it is difficult to fully disentangle the specific effects of threat and deprivation on corticolimbic regions in the current human literature, as few studies control for co-occurring exposure types, there is indirect behavioral and neural evidence to suggest that threat and deprivation may have distinct influences on specific corticolimbic regions. For example, emotional functioning and fear-related processing deficits, which are commonly observed in individuals with a history of childhood abuse, have been linked with larger amygdalar volumes in some studies (Mehta et al., 2009; Tottenham et al., 2010). Meanwhile, specific forms of deprivation (i.e., institutionalization, poverty) have been associated with smaller cortical volumes (Hair et al., 2015; McLaughlin et al., 2015; Mehta et al., 2009; Noble et al., 2012; Sheridan et al., 2012) and smaller hippocampal volumes (Hair et al., 2015; Hanson et al., 2011).

Clinical-high risk (CHR) populations are ideally suited to test the effects of childhood adversity, as these samples are enriched for childhood adversity experiences and are characterized by a wider variation of adversity than is typically observed in community samples (Bendall et al., 2008; Larsson et al., 2013). Additionally, childhood adversity and trauma are associated with psychotic-like experiences, such as subclinical delusions, isolated auditory hallucinations, and perceptual aberrations, even in the absence of clinical psychosis (Janssen et al., 2003; Kelleher et al., 2008). Thus there is critical need for a more nuanced approach to examining the effects of childhood adversity on pathophysiological processes associated with psychosis-risk. A differentiated adversity approach that distinguishes exposures along dimensions of threat and deprivation may bolster the identification of potential underlying mechanisms that are obscured using a generalized risk approach.

The current study examined the unique associations of threat and deprivation exposure with corticolimbic structures in a large sample of youth at clinical-high risk for psychosis. We predicted that threat would be associated with larger amygdalar volumes, while deprivation would be associated with smaller cortical and hippocampal volumes, as well as thinner cortices. We compared the results of the differentiated adversity approach, which delineates deprivation and threat, with a traditional generalized risk model (sum score of total adversity), and we predicted that the latter approach would obscure the specificity of associations.

Table 1
Sample characteristics.

	CHR (n = 486)	HC (n = 216)
Age, years (mean ± SD)**	18.85 ± 4.2	20.07 ± 4.6
Sex, n (%)*		
Males	289 (59.5%)	112 (51.9%)
Females	197 (40.5%)	104 (48.1%)
Race, n (%)		
First Nations	7 (1.4%)	4 (1.9%)
East Asian	10 (2.1%)	12 (5.6%)
Southeast Asian	11 (2.3%)	6 (2.8%)
South Asian	14 (2.9%)	6 (2.8%)
Black	80 (16.5%)	40 (18.5%)
Central/South American	21 (4.3%)	8 (3.7%)
Middle Eastern	4 (0.8%)	1 (0.5%)
White	287 (59.1%)	119 (55.1%)
Native Hawaiian/Pacific Islander	2 (0.4%)	0 (0%)
Interracial	50 (10.3%)	20 (9.3%)
Threat exposure, n (%)[a]		
Sexual abuse**	76 (10.6%)	3 (1.4%)
Physical abuse**	120 (16.8%)	9 (4.2%)
Psychological abuse**	177 (24.8%)	10 (4.6%)
Physical bullying**	158 (22.1%)	21 (9.7%)
Psychological bullying**	358 (50.1%)	59 (27.3%)
Deprivation exposure, n (%)[a]		
Emotional neglect**	212 (29.6%)	13 (6%)
Restricted peer relations**	123 (17.2%)	2 (0.9%)
Parental absence**	41 (5.7%)	5 (2.3%)
Poverty	195 (27.3%)	59 (27.3%)
Adversity composites, (mean, SD)		
Threat exposure (0–5)**	1.53 (1.4)	0.47 (0.83)
Deprivation exposure (0–4)**	0.94 (0.90)	0.36 (0.57)
Total exposure (0–9)**	2.47 (2.02)	0.83 (1.12)

[a] Percentages add up to >100% because one participant can score multiple items.
* $p < .05$.
** $p < .01$.

2. Methods and materials

2.1. Sample

See Table 1 for detailed demographic and adversity characteristics. The total sample included 702 individuals between 12 and 30 years of age (mean = 19.2, SD = 4.3). Of the 702 participants, 486 (70%) met clinical-high risk (CHR) criteria for psychosis; 216 (30%) were healthy controls (HC). All participants were recruited as part of the North American Prodome Longitudinal Study (NAPLS-2). Specific details about ascertainment, inclusion, and exclusion criteria have been described in detail elsewhere (Addington et al., 2012). Participants were included in the current study if they completed childhood adversity measures and MRI scans during the baseline visit.

2.2. Assessments

2.2.1. Clinical high-risk status

Clinical-high risk designation is based on the Structured Interview for Prodromal Syndromes (SIPS). The SIPS is composed of four symptom domains; 1.) *Positive* (e.g., unusual thought content/ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities, and disorganized communication); 2.) *Negative* (e.g., social isolation, avolition, decreased expression of emotion, decreased experience of emotions and self, decreased ideational richness, and deterioration of role functioning), 3.) *Disorganized* (e.g., odd behavior of appearance, bizarre thinking, trouble with focus and attention, and impairment in personal hygiene or social attentiveness), and 4.) *General* (e.g., difficulty related to sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to normal stress). Clinical-high risk status is based in part on the severity of positive attenuated psychotic symptoms as rated by the SIPS (see Addington et al., 2012 for details).

2.2.2. Childhood adversity exposure

Threat was operationalized to denote adverse experiences involving harm or threat of harm to an individual, such as abuse and bullying. Specific types of threat exposures were assessed using the *Documentation of Trauma Form*, a semi-structured interview that retrospectively assesses negative childhood experiences before the age of 16. Participants where asked whether they had experienced the following: emotional abuse (e.g., "unjustified punishment" "being sworn at"), physical abuse (e.g., "being kicked or punched"), psychological bullying (e.g. "taunted or sworn at by peers"), physical bullying ("physical assaulted at school"), and sexual abuse (e.g., "touched sexually against their will", "sexual contact against their will"). Responses were rated on a categorical 'present' or 'absent' scale. Because these different forms of abuse represent experiences of threat hypothesized to impact corticolimbic regions through similar mechanisms, a total threat score was calculated for each participant. The threat composite score ranged from 0 (no endorsement of threat exposures) to 5 (endorsement of all threat exposures), and was used in all statistical analyses to capture variation in threat exposures.

Deprivation was operationalized to denote experiences involving the absence of expected cognitive and social inputs. In the current study, deprivation items included indices of childhood poverty, emotional neglect, parental absence, and restricted peer relationships during childhood. Poverty was determined by the ratio of income to needs, which was computed by dividing reported family of origins income by US census 2014 poverty line for a family of that size, with a value of <1 indicating that a family was living below the poverty line. Neglect was assessed via the *Documentation of Trauma Form*. neglect item (e.g., "not able to find any attention or support from people at home"). Restricted peer interactions (a proxy of psychosocial deprivation) was determined using the social subscales of *The Premorbid Adjustment Scale* (PAS; Cannon-Spoor et al., 1982), a widely used semi-structured interview designed to retrospectively assess social and academic functioning across development. Interviewers rated participants on a 0–6 scale for peer relationships during childhood (age 5–11 years). Scores falling between 4 and 6, which indicate social isolation and lack of same-aged peer relationships, were used to indicate restricted peer relationships. Finally, absence of a biological parental figure (e.g., no/minimal contact) was determined from a demographic information interview. A deprivation composite score was created by summing items of childhood poverty, childhood peer relations, parental absence, and neglect. This deprivation composite ranged from 0 (no endorsement of deprivation exposures) to 4 (endorsement of all deprivation exposures), and was used in all statistical analyses to capture variation in deprivation exposures. There was a moderate correlation between threat and deprivation exposure ($r = .47$, $p < .01$), which is consistent with the literature on the co-occurrence rates among different types of adversity (Green et al., 2010). However, this modest correlation suggests a degree of independence of the two adversity dimensions.

2.2.3. Neuroanatomical volume and thickness

The brain regions of interest included eight lateralized measurements; cortical volume, cortical thickness, hippocampal volume and amygdalar volume. Cortical volume measurements include a composite of thickness, surface area, and folding (Mechelli et al., 2005). However, cortical thickness and surface area show unique developmental trajectories (Raznahan et al., 2011; Wierenga et al., 2014) and have been shown to be mediated by different neurodevelopmental processes (Rakic, 1988) and genes (Panizzon et al., 2009). Measuring the sensitivity of brain regions to environmental influences may be improved by examining these two cortical parameters separately (Hutton et al., 2009; Wallace et al., 2015). Additionally, twin studies suggest that environmental and genetic factors may differentially influence right and

left brain regions (Yoon et al., 2010), and some studies on maltreatment have shown only significant left-sided or right-sided findings (see Teicher et al., 2016). For each brain region of interest right and left hemispheres were measured and examined separately to test for lateralization effects. We also included lateralized measurements of the insula and thalamus volume to serve as control regions. While childhood adversity has been inconsistently associated with volumetric reductions in these regions (Baker et al., 2013; Frodl et al., 2017; Liao et al., 2013; Lim et al., 2014; Teicher et al., 2016), there is no indirect evidence to suggest that threat and deprivation exposures will have distinct effects on these regions.

2.3. MRI data acquisition & image processing

MRI scanning was performed at eight sites. Five sites (UCLA, Emory, Harvard, UNC, and Yale) used Siemens-Trio 3T scanners, two sites (Zucker-Hillside Hospital and UCSD) used GE HDx scanners, and one site (Calgary) used a GE Discovery scanners. All Siemens sites used a 12-channel head coil and all GE sites used an 8-channel head coil. Sequence parameters were optimized for each scanner manufacturer, software version and coil configuration according to the ADNI protocol (http://adni.oni.usc.edu/methods/documents/mri-protocols/). Scans were acquired in the sagittal plane with a 1 mm * 1 mm in-plan resolution and 1.2 mm slice thickness. Siemens scans used a MPRAGE sequence with a 256(axial) × 240(sagittal) × 176 (coronal) mm field of view, TR/TE/TI = 2300/2.91/900 ms and a 9-degree flip angle, while GE scanners used an IR-SPGR sequence with a 26 cm field of view, TR/TE/TI = 7.0/minimum full/400 and an 8-degree flip angle.

Subcortical volumetric segmentation of the hippocampus, amygdala, insula, and thalamus was processed using FreeSurfer version 5.2 at Yale University by investigators who had participated in the FreeSurfer training course at the Martinos Center for Biomedical Imaging. The subcortical segmentation procedure assigns a neuroanatomical label to each voxel of the MRI volume, using a probabilistic atlas and Bayesian classification rule (Fischl et al., 2002). Surface-based cortical reconstruction was performed to extract thickness measures by calculating the shorted distance from each point on the gray/white boundary to the pial surface at each vertex (Fischl and Dale, 2000). See Cannon et al. (2014) for details on the quality assurance procedure.

2.4. Statistical analyses

All statistical analyses were conducted in R (version 3.0.2). Analysis of variance (ANOVA) was conducted to compare adversity exposure between groups; analysis of covariance (ANCOVA) was used to compare corticolimbic measures between groups with age, sex, and total brain volume as covariates. Within the CHR group, we also compared individuals who transitioned to psychosis over a 2-year period (convertors) with those who did not (non-convertors) on adversity exposure and corticolimbic measures. Partial correlations controlling for total brain volume were used to examine correlations between adversity measures (i.e., threat, deprivation, total adversity) and brain measures in the CHR and HC groups separately.

Linear regression was used to examine the associations between childhood adversity and corticolimbic volumes/thickness in the CHR and HC groups separately. A series of multivariate models were estimated to examine threat and deprivation composites as predictors of each corticolimbic and control region measure. Threat and deprivation composite scores were entered into all models simultaneously to isolate the effects of each adversity dimension (e.g. threat), while controlling for the effect of the other (e.g., deprivation). The results from the differentiated adversity approach were compared to those from a generalized-risk approach. To test the generalized-risk approach, a total adversity score (sum of threat and deprivation) was entered as the predictor for each corticolimbic and control region. Prior to analyses, brain measures were corrected for site scanner differences (Siemens vs. GE). Sex, age, and total intracranial volume were included as covariates in all regression models. Standardized betas are presented in results and are used as a measure of effect size. Statistical significance level was set at 0.05.

3. Results

Demographic and adversity characteristics of the sample are shown in Table 1. CHR individuals reported higher levels of childhood adversity exposure [(F (1,701) = 125.12, $p < .01$)], including higher levels of threat [(F(1,701) = 101.71, $p < .01$)] and deprivation [(F (1,701) = 77.41, $p < .01$)] exposures than controls. In the CHR group, 85% endorsed at least one type of adversity exposure, and 60% endorsed two or more co-occurring adversity exposures. There was also variability in exposure to the different dimensions of adversity within the CHR group; 22% (n = 107) endorsed threat only exposures, 16% (n = 75) endorsed deprivation only exposures, 45% endorsed co-occurring threat and deprivation exposures, and 17% reported no adversity exposure. Females endorsed higher levels of both threat [(F (1,485) = 14.21, $p < .01$)] and deprivation [(F (1,485) = 6.83, $p = .01$)] compared to males, and older individuals endorsed higher levels of deprivation compared to younger individuals ($t = 3.63$, $p < .01$). CHR individuals had a smaller left cortical volume [(F(1,701) = 19.25, $p < .01$)], right cortical volume [(F(1,701) = 17.51, $p < .01$)], left hemisphere cortical thickness [(F(1,701) = 10.54, $p < .01$)], and right hemisphere cortical thickness [(F(1,701) = 9.78, $p < .01$)] compared to controls. There were no group differences in hippocampal or amygdalar volumes, or in the two control regions (insula and thalamus). Within the CHR group, there were no differences in adversity exposure or brain measures between convertors (n = 69) and non-convertors (n = 417).

3.1. Relationship between childhood adversity and corticolimbic measures

Zero-order correlations and standardized regression coefficients for the associations between adversity exposure and corticolimbic measures in the CHR group are shown in Tables 2 and 3. In the differentiated adversity model threat exposure was not associated with any corticolimbic measure. However, deprivation exposure was associated with smaller left cortical volume ($\beta = -0.06$, $p < .01$), right cortical volume ($\beta = -0.06$, $p < .01$), and right hippocampal volume ($\beta = -0.07$, $p < .05$). Deprivation was not associated with cortical thickness, amygdalar volume or left hippocampal volume. Neither threat nor deprivation was associated with the control regions (insula, thalamus). The generalized-risk model masked the associations between deprivation exposure cortical and hippocampal volume that were observed in the differentiated adversity models. Total adversity score was not associated with any corticolimbic or control brain measure. Zero-order correlations and standardized regression coefficients for the associations between adversity exposure and corticolimbic measures in the HC group are shown in Supplementary Tables 1 and 2. Threat and deprivation exposure, as well as total adversity exposure, were not associated with any corticolimbic or control region measure.

4. Discussion

The current study assessed whether childhood adversity exposure was associated with alterations in corticolimbic volumes/thickness in a sample of CHR youth. We tested a novel conceptual model that distinguishes between threat and deprivation exposures to determine whether these adversity dimensions have unique effects on corticolimbic volume/thickness. We found that

Table 2
Zero-order correlations between adversity dimensions and corticolimbic structure in CHR youth (n = 486).

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Threat	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2. Deprivation	0.47**	–	–	–	–	–	–	–	–	–	–	–	–	–	–
3. Total adversity	0.92**	0.78**	–	–	–	–	–	–	–	–	–	–	–	–	–
4. Left cortical volume	0.01	−0.17**	−0.14**	–	–	–	–	–	–	–	–	–	–	–	–
5. Right cortical volume	0.01	−0.17**	−0.15**	0.96**	–	–	–	–	–	–	–	–	–	–	–
6. Left cortical thickness	−0.04	−0.10*	−0.13**	0.68**	0.67**	–	–	–	–	–	–	–	–	–	–
7. Right cortical thickness	−0.04	−0.11*	−0.13**	0.69**	0.70**	0.95**	–	–	–	–	–	–	–	–	–
8. Left hippocampus	0.03	−0.07*	−0.03	0.21**	0.22**	0.15**	0.16**	–	–	–	–	–	–	–	–
9. Right hippocampus	0.04	−0.07*	−0.01	0.15**	0.16**	0.13**	0.12**	0.72**	–	–	–	–	–	–	–
10. Left amygdala	−0.01	0.04	0.02	0.21**	0.21**	0.12**	0.10*	0.33**	0.38**	–	–	–	–	–	–
11. Right amygdala	−0.00	−0.01	−0.01	0.21**	0.21**	0.10*	0.09*	0.30**	0.35**	0.61**	–	–	–	–	–
12. Left insula	−0.06	−0.07	−0.12*	0.48**	0.47**	0.28**	0.29**	0.13**	0.14**	0.11*	0.13**	–	–	–	–
13. Right insula	−0.07	−0.03	−0.10*	0.42**	0.44**	0.21**	0.23**	0.17**	0.12**	0.05	0.03	0.70**	–	–	–
14. Left thalamus	0.04	−0.05	0.00	0.06	0.06	0.03	0.04	0.24**	0.19**	0.17**	0.23**	0.07	0.06	–	–
15. Right thalamus	−0.08	0.04	−0.05	0.12**	0.11*	0.11*	0.28	0.28**	0.23**	0.23**	0.20**	0.06	0.07	0.72**	–

Note. All correlations control for total brain volume. Correlations for threat and brain measures control for deprivation; correlations for deprivation and brain measures control for threat.
* $p < .05$.
** $p < .01$.

deprivation exposure was uniquely associated with smaller cortical volume and smaller right hippocampal volume in CHR individuals. Notably, these associations were masked in generalized-risk adversity models utilizing a total adversity exposure score. Taken together, these findings suggest that deprivation exposures during childhood contribute to the subtle volumetric reductions observed in psychosis-risk samples and highlight the importance of disentangling different dimensions of adversity.

Volumetric reductions in both cortical and hippocampal regions have been documented in first-episode and patient populations, but it has been less clear whether these changes are a result of disease processes or environmental precursors. Our findings provide evidence for subtle deprivation-specific effects on these regions among CHR youth and support the idea that environmental experiences in childhood contribute to the structural abnormalities observed in the psychosis-spectrum. These finding are consistent with previous work in a sample at genetic-high risk for psychosis in which individuals with a history of childhood adversity had smaller cortical surface areas (a component of cortical volume) compared to those with no history (Barker et al., 2016b). Interestingly, the lateralized effect on the right hippocampus is consistent with previous studies of childhood adversity in clinical-high risk and genetic-high risk samples (for review see Ganzola et al., 2014; Barker et al., 2016a). However, in these and other studies with psychosis-spectrum populations, childhood adversity is primarily indexed by abuse exposure (e.g., sexual, physical, emotional abuse), and co-occurring exposures that fall along the deprivation dimension are rarely controlled for. This makes any specific impacts of different types of adversity difficult to discern. In contrast, our results provide preliminary evidence that exposures such as poverty, neglect, and social deprivation may actually have a stronger influence on cortical and hippocampal volume than abuse exposures. In fact, threat exposure was not associated with amygdalar volume, or any other corticolimbic region, when controlling for deprivation. Longitudinal studies have found that childhood maltreatment is associated with larger amygdalar volumes at baseline, but smaller volumes during adulthood relative to healthy controls (McEwen et al., 2016; Whittle et al., 2013) and a similar developmental pattern is observed in psychiatric populations (Frodl et al., 2003; Frodl et al., 2008; Lange and Irle, 2004; Weniger et al., 2006). Given the age range of this sample, and variability in the distance from time of documented threat exposure, it is possible that the impact of adversity on amygdala volume differs in magnitude or direction across development and is washed out in the current sample. It is also important to note that threat and deprivation were not associated with our control regions (i.e., insula, thalamus) which underscores the specificity of our findings.

Table 3
Associations between adversity dimensions and corticolimbic structure in CHR youth (n = 486).

	Differentiated model				Generalized model	
	Threat		Deprivation		Total adversity	
Brain measures	β	SE	β	SE	β	SE
Regions of interest						
Left cortical volume	0.01	0.02	−0.06**	0.02	−0.03	0.02
Right cortical volume	0.00	0.02	−0.06**	0.02	−0.03	0.02
Left cortical thickness	−0.03	0.04	−0.03	0.05	−0.06	0.04
Right cortical thickness	−0.03	0.04	−0.02	0.05	−0.05	0.04
Left hippocampus	0.04	0.04	−0.06	0.04	−0.00	0.04
Right hippocampus	0.05	0.04	−0.07*	0.04	−0.01	0.04
Left amygdala	0.01	0.04	0.03	0.04	0.00	0.03
Right amygdala	0.01	0.04	−0.01	0.04	−0.01	0.03
Control regions						
Left insula	−0.04	0.04	−0.03	0.04	−0.06	0.04
Right insula	−0.05	0.04	−0.01	0.04	−0.05	0.04
Left thalamus	0.04	0.03	−0.05	0.03	−0.00	0.03
Right thalamus	−0.05	0.03	0.03	0.03	−0.03	0.03

Note. All models control for total brain volume, sex, and age.
* $p < .05$.
** $p < .01$.

While the findings should be considered preliminary, and are in need of replication, they provide a basis for speculating what may underlie these volumetric differences. From a traditional stress perspective smaller cortical and hippocampal volumes could result from HPA-dysregulation and excess cortisol exposure, which has been shown to produce dendritic atrophy in these regions (Cerqueira et al., 2005; McEwen et al., 2016; Sousa and Almeida, 2012). However, the specificity of the findings to deprivation and the null findings in the generalized risk models suggest that other mechanisms are at play. Drawing on principles of experience-dependent plasticity, it may be that inadequate cognitive and social stimulation constrain the morphological plasticity that accompanies adaptation to increased environmental complexity and stimulation (Humphreys and Zeanah, 2015; McLaughlin et al., 2014; Sheridan et al., 2012). For example, animal models utilizing enriched environment paradigms demonstrate experience-induced morphological plasticity via synaptogenesis, dendritic reorganization, and neurogenesis in response to environmental enrichment (Fiala et al., 1978; Greenough et al., 1973; Greenough, 1986). In contrast, deprivation may disrupt neuromaturational processes such as synaptic pruning, which is a primary mechanism

of experience-dependent plasticity across development (McLaughlin et al., 2017). Lower levels of learning and stimulation may result in exaggerated synaptic pruning, as infrequently used synapses are selectively eliminated, which may subsequently result in reductions in brain volumes (McLaughlin et al., 2017). Additionally, it is worth noting that deprivation exposures (and adversity more broadly) are likely to influence neurodevelopmental processes in concert with genetic risk factors or via changes in epigenetic regulation (Babenko et al., 2015; Cecil et al., 2016).

The masking of the deprivation-specific effects in the generalized-risk model underscores the importance of assessing the nature of childhood adversities. While there is ample evidence for cumulative effects of adversity throughout the literature (see Evans et al., 2013), this approach can provide an inaccurate and incomplete picture of the magnitude or direction of the specific impacts. The pattern of findings in the current study suggests that adversity exposures do not have a uniform, dose-dependent relationship with corticolimbic volume. This may be particularly important in psychosis-risk populations in which different dimensions of adversity exposure may also be associated with distinct subgroups characterized by more severe clinical manifestations and biological alterations.

There were no differences in either adversity exposures or brain measures between CHR individuals who transitioned to psychosis compared to those that did not. These findings suggest that although childhood adversity exposure, particularly deprivation, may not be specifically associated with clinical psychosis, it may confer vulnerability for sub-threshold psychotic syndromes. This is consistent with previous evidence that childhood adversity is a pluripotent risk factor for a range of psychiatric disorders (Kraan et al., 2017; Teicher et al., 2016). It is possible that the risk conferred by childhood adversity, when coupled with other inherited or acquired vulnerabilities and risk factors (e.g., genetic, dopaminergic), leads to clinical psychosis. Future research utilizing this differentiated adversity approach in the context of other known psychosis-risk factors will be important.

We did not find any associations between adversity exposure and brain measures in our control group. This is not surprising, given the relatively low rates and restricted range of adversity exposure in this group. It is noteworthy that the rate of sexual (1.4%) and physical (4.2%) abuse in the HC group was significantly lower than national prevalence rates (10% and 9–19% respectively) (Finkelhor et al., 2009; McGrath et al., 2017; Saunders and Adams, 2014). These differences are likely due to study criteria for the HC group, which excluded individuals who were on psychotropic medication, met criteria for an Axis I disorder, or had a family history of psychosis. Thus, our control group would be expected to have lower adversity exposure than randomly-selected community samples. These null findings should be interpreted with caution and do not necessarily indicate that adversity exposure has a different effect on brain structure in CHR youth. Adversity exposure increases the risk of experiencing sub-threshold psychotic symptoms (McGrath et al., 2017), and thus also meeting criteria for CHR status. As a result, any adversity-related neurobiological sequalae will be more apparent in CHR groups compared to controls, even if the same mechanisms are at play for both.

Finally, it is important to note that while our differentiated multivariate approach statistically delineates the specific effects of threat and deprivation, these exposures tend to co-occur in adversity-exposed individuals (Kessler et al., 2010). In the CHR group almost half of the sample (45%) experienced both threat and deprivation. Thus, while these exposure types may have specific effects on underlying neural substrates, it is not clear how these anatomical traces will appear at the individual level in someone with both threat and deprivation exposures. However, the high rates of co-occurring adversity exposures reinforces the importance of research using more nuanced and differentiated approaches to conceptualizing childhood adversity. Understanding more about the specific effects of adversity type increases our ability to identify the mechanisms linking adversity and psychosis risk, and develop more targeted interventions.

There are limitations to the current study that should be noted. First, measures of self-reported childhood adversity and brain morphology were assessed concurrently, and as such, they are correlational and cannot provide evidence of a cause-effect relationship. Additionally, as is common in human studies, we do not have pre-exposure measures of brain characteristics and thus, cannot rule out the possibility that observed differences are congenital. Second, our adversity measurement relied on subjective retrospective reporting, which is vulnerable to errors in recall and/or biases in reporting. Adversity measures did not include information regarding the frequency, intensity, or timing of specific exposure types (e.g., times of sexual abuse, intensity of physical abuse). Third, the poverty variable may index multiple components of environmental risk that can affect brain development such as family stress, maternal drug use, negative parenting, nutrition deficiencies, and environmental toxins that are not related to social-cognitive deprivation. Fourth, the adversity experiences included in this study do not encompass all forms of threat (e.g., community violence, witnessing domestic abuse) or deprivation, nor do they include parental psychopathology or non-interpersonal forms of trauma (e.g., car accidents, injuries, natural disasters). Finally, we did not statistically control for substance abuse and medication status in our models, because these variables can be consequences of symptom severity as well as adversity exposure.

In summary, we have demonstrated an association between childhood deprivation exposures and cortical and right hippocampal volumetric reductions in a large sample of CHR youth. These findings support the idea that adverse experiences in childhood may disrupt gray matter development in the brain regions implicated in psychosis-spectrum disorders. The findings also highlight the importance of attending to the nature of adverse exposures and examining different dimensions of adversity independently in order to understand their specific impacts on brain development.

Conflicts of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study. Dr. Cannon reports that he is a consultant to Boerhinger Ingelheim Pharmaceuticals. NAPLS investigators (all authors excluding Drs. LoPilato and Goines) are co-inventors on a pending patent of a blood-based predictive biomarker for psychosis.

Contributors

Dr. LoPilato conducted the statistical analyses and drafted the manuscript. Drs. Goines and Walker contributed to data interpretation and manuscript writing. All other authors had an equal share in designing the study methodology, recruiting subjects, and overseeing data collection. All authors have contributed to the manuscript and have approved the final manuscript.

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Appendix A. Supplementary data

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