Development and Psychopathology (2020), **32**, 865–878
doi:10.1017/S0954579419001123

CAMBRIDGE UNIVERSITY PRESS

Regular Article

Interpersonal childhood adversity and stress generation in adolescence: Moderation by HPA axis multilocus genetic variation

Meghan Huang and Lisa R. Starr
Department of Clinical and Social Sciences in Psychology, University of Rochester, Rochester, NY, USA

Abstract

Research suggests that childhood adversity (CA) is associated with a wide range of repercussions, including an increased likelihood of interpersonal stress generation. This may be particularly true following interpersonal childhood adversity (ICA) and for youth with high hypothalamic-pituitary-adrenal (HPA) axis-related genetic risk. In the current study, we applied a multilocus genetic profile score (MGPS) approach to measuring HPA axis-related genetic variation and examined its interaction with ICA to predict interpersonal stress generation in a sample of adolescents aged 14–17 ($N = 241$, Caucasian subsample $n = 192$). MGPSs were computed using 10 single nucleotide polymorphisms from HPA axis-related genes (*CRHR1*, *NRC31*, *NRC32*, and *FKBP5)*. ICA significantly predicted greater adolescent interpersonal dependent stress. Additionally, MGPS predicted a stronger association between ICA and interpersonal dependent (but not independent or noninterpersonal dependent) stress. No gene–environment interaction (G×E) effects were found for noninterpersonal CA and MGPS in predicting adolescent interpersonal dependent stress. Effects remained after controlling for current depressive symptoms and following stratification by race. Findings extend existing G×E research on stress generation to HPA axis-related genetic variation and demonstrate effects specific to the interpersonal domain.

Keywords: childhood adversity, gene–environment interaction, HPA axis, stress generation

(Received 8 January 2018; accepted 26 May 2019)

Childhood adversity (CA) encompasses significant stressors that occur in childhood (e.g., physical illnesses, financial insecurity, death of loved ones, maltreatment). Exposure to CA results in developmental cascades that give rise to multifinal outcomes. One such consequence is disruption in interpersonal functioning (e.g., Huh, Kim, Yu, & Chae, 2014; Johnson et al., 2002; Salwen, Hymowitz, Vivian, & O'Leary, 2014), which is in turn linked with sustained difficulties within relationships and increased risk for psychiatric disorders and related conditions (e.g., depressive disorders, suicide attempts; Hames, Hagan, & Joiner, 2013; Johnson et al., 2002). However, given that not all individuals experience interpersonal difficulties following CA (e.g., Masten, Best, & Garmezy, 1990; Masten et al., 1999), it is important to consider factors that may contribute to these differing trajectories, such as the interplay between genetic and environmental influences in shaping development. We propose that youth with high hypothalamic-pituitary-adrenal (HPA) axis-related genetic risk may be more likely to contribute to the occurrence of self-generated interpersonal stressors within their relationships (i.e., interpersonal stress generation) following exposure to interpersonal CA (ICA). In testing this notion, the current study sought to elucidate multilevel factors that may amplify the cascading effects of CA within the interpersonal realm.

Author for Correspondence: Meghan Huang, 494 Meliora Hall, Box 270266, Rochester, NY 14627; E-mail: meghan.huang@rochester.edu.

Cite this article: Huang M, Starr LR (2020). Interpersonal childhood adversity and stress generation in adolescence: Moderation by HPA axis multilocus genetic variation. *Development and Psychopathology* **32**, 865–878. https://doi.org/10.1017/S0954579419001123

Stress Generation

An abundance of literature supports the stress generation model (Hammen, 1991), which posits that individuals with vulnerabilities to depression, through personal characteristics and negative cognitive styles, are prone to precipitate or select into stressful experiences in their lives that have the potential to further increase their vulnerability to depression. These stressors are termed *dependent* events because their occurrence is, at least in part, due to the individual, and they stand in contrast with *independent* (i.e., fateful) events, which are not predicted by depression (Hammen, 1991). Importantly, these stress generation effects often occur within the interpersonal domain, and they are closely tied to disruptions in social relationships and interpersonal functioning (Hammen, 2006).

Environmental contributors

Several risk factors have been implicated in the generation of stress, including cognitive and interpersonal factors (e.g., rumination, insecure attachment) and personality traits (e.g., neuroticism; for reviews, see Hammen, 2006; Liu & Alloy, 2010). CA in particular has received attention as a risk factor for stress generation. Initial studies established that CA prospectively predicts increases in negative life events in adolescents and young adults

(Hankin, 2005; Harkness, Lumley, & Truss, 2008; Uhrlass & Gibb, 2007). This link may partly be due to continuity in contextual factors (e.g., family dysfunction, financial instability) that contribute to the occurrence of CA and continued stress exposure beyond childhood (Hazel, Hammen, Brennan, & Najman, 2008; Uliaszek et al., 2012).

However, youth with histories of CA may also be more vulnerable to stress generation. Recent research has supported the role of CA in stress generation, demonstrating that CA predicts increased dependent stress (but not independent stress) in samples of youth and emerging adults (Harkness et al., 2015; Kushner, Bagby, & Harkness, 2017; Liu, Choi, Boland, Mastin, & Alloy, 2013). More recent evidence suggests that this effect may be specific to *interpersonal* stress generation, with Hernandez and colleagues (2016) showing that CA predicted higher levels of interpersonal dependent stress (but not noninterpersonal dependent or independent stress) in young adults. Notably, CA has been linked with greater stress reactivity, with CA predicting a stronger association between proximal stressors and depression (Kim et al., 2014; McLaughlin, Conron, Koenen, & Gilman, 2010; Shapero et al., 2014; Starr et al., 2017; Starr, Hammen, Conway, Raposa, & Brennan, 2014). In addition to depression, changes in stress reactivity following CA may result in other negative outcomes, such as increased stress generation. Heightened stress reactivity may permeate interpersonal functioning, in turn leading to negative behaviors and interactions that contribute to the incidence of stressful life events within relationships.

Genetic contributors and gene–environment interactions

Research also indicates that exposure to stressful life events and stress generation tendencies may, in part, be linked to genetic vulnerabilities (Kendler, Karkowski, & Prescott, 1999; Kendler & Karkowski-Shuman, 1997; Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1983). For example, in several twin studies, Kendler and colleagues (1997, 1999) found that individuals with histories of depression experience elevated rates of stressful life events, with genetic factors accounting for about one third of the association between the occurrence of stressors and depressive outcomes. Further, many of the risk factors associated with stress generation processes (e.g., attachment, neuroticism, negative cognitive styles) also appear to be genetically moderated (e.g., Lahey, 2009; Spangler, Johann, Ronai, & Zimmermann, 2009). Nonetheless, few studies have examined the contribution of genetic factors in interpersonal stress generation processes.

One way in which genetic risk may influence stress generation processes is by modifying the influence of environmental risk. Gene–environment interactions (G×E) have often been examined in the context of CA and psychopathological outcomes (for a review, see Manuck & McCaffery, 2014), but fewer studies have examined stress generation as an outcome. Given the potential role of stress reactivity in stress generation, genes related to stress reactivity may be an important starting point. At present, the existing literature on G×Es and stress generation processes has solely focused on a polymorphic region in the serotonin transporter gene (5-HTTLPR), a variant linked in many studies to stress reactivity (Caspi et al., 2003; Karg, Burmeister, Shedden, & Sen, 2011, although also see Culverhouse et al., 2018). Harkness and colleagues (2015) examined the interaction of CA and 5-HTTLPR genotype in interpersonal stress generation processes in a sample of youth and young adults. Their results suggested that 5-HTTLPR risk allele status predicted greater levels of dependent interpersonal stress, but only for those who had experienced CA. Other studies have shown that constructs linked to CA (depression, relational security) also predict later interpersonal stress generation for those with high (but not low) genetic vulnerability (Starr, Hammen, Brennan, & Najman, 2012, 2013). These findings indicate that genetic risk may amplify the effects of CA on stress generation processes. However, the existing literature is limited in several ways. First, previous studies have exclusively considered a serotonergic genetic variant, and genetic variants from other biological systems involved in the stress response, such as the HPA axis, merit consideration. Furthermore, these studies have used a single-variant candidate gene approach, and recently developed polygenic approaches offer vastly improved statistical power.

HPA Axis and HPA Axis-Related Genetic Variation

The HPA axis facilitates the coordination of biological responses to stressors (for a review, see Gunnar & Quevedo, 2007). HPA axis dysregulation has been linked to a wide range of negative outcomes (Anda et al., 2006; Guerry & Hastings, 2011; McEwen, 1998). Stressors that occur over the course of childhood have been shown to produce changes in HPA axis activity and cortisol levels, altering the typical course of HPA axis development (e.g., Kuras et al., 2017; Tarullo & Gunnar, 2006). Indeed, many have pointed to disruptions in the development of the HPA axis and associated neural structures as key biological mechanisms for stress sensitization and increased depression risk following CA exposure (e.g., Cicchetti & Rogosch, 2012; Heim & Nemeroff, 2001; Starr et al., 2017; Tarullo & Gunnar, 2006). Further, HPA axis dysfunction (measured using cortisol responses) in response to a laboratory stressor has been found to predict stress generation among young adults (Morris, Kouros, Hellman, Rao, & Garber, 2014).

HPA axis-linked genetic regions appear to predict both physiological and emotional stress reactivity, which may have implications for stress generation. For instance, research suggests that variation in genotype for the *CRHR1* gene, which influences CRH receptors, affects cortisol responses following laboratory stressors in children (Sheikh, Kryski, Smith, Hayden, & Singh, 2013) and adults (Mahon, Zandi, Potash, Nestadt, & Wand, 2013). In individuals with a history of CA, the *CRHR1* genotype is associated with greater cortisol dysregulation (Cicchetti, Rogosch, & Oshri, 2011; Heim et al., 2009). Genetic variation in the *FKBP5* genotype is linked with glucocorticoid receptor regulation in response to stressors and is also associated with alterations in cortisol reactivity to laboratory stressors (Luijk et al., 2010; Zannas & Binder, 2014). Further, HPA axis dysregulation following stressful events has also been demonstrated in relation to variation in the *NRC31* and *NRC32* genes, which regulate mineralocorticoid receptors (for a review, see Derijk, 2009). HPA axis-related genotypes are also associated with greater cortisol dysregulation following CA (e.g., Buchmann et al., 2014; Cicchetti et al., 2011; Gerritsen et al., 2017; Heim et al., 2009; Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014) and have been shown to moderate the effects of CA on various negative outcomes, such as depression, suicide attempts, and posttraumatic stress disorder (e.g., Gerritsen et al., 2017; Laucht et al., 2013; Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010; Xie et al., 2010).

Most of these studies have applied single-candidate gene approaches to examine G×E effects; however, this method has recently come under fire following prominent nonreplications

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

(de Vries, Roest, Franzen, Munafo, & Bastiaansen, 2016; Dick et al., 2015; Duncan & Keller, 2011), although the issue remains controversial (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Karg et al., 2011; Vrshek-Schallhorn, Sapuram, & Avery, 2017). To address this issue, several research groups have developed *multilocus genetic profile scores* (MGPSs), additive indices of risk alleles from various single nucleotide polymorphisms (SNPs) that are selected due to their association with a given biological pathway (e.g., Nikolova, Ferrell, Manuck, & Hariri, 2011; Pagliaccio et al., 2014; Vrshek-Schallhorn et al., 2015); this theoretically driven approach of capturing cumulative, polygenic effects through the selection of specific SNPs linked to a specific biological system differs from atheoretical, genome-wide association study (GWAS)-derived polygenic risk scores (e.g., Musliner et al., 2015). By capturing polygenic effects within specific biological systems, MGPSs appear to have greater predictive validity than does examining individual SNPs in isolation. Pagliaccio and colleagues (2014) recently created an MGPS using 10 SNPs from HPA axis-related genes (*CRHR1*, *NRC31*, *NRC32*, *FKBP5)* that have been linked to HPA axis dysfunction and depression-related phenotypes. HPA axis-related MGPSs have been shown to predict cortisol reactivity in the context of laboratory stressors and interact with environmental stress (i.e., stressful life events, CA) to predict changes in emotional circuitry within the brain (i.e., amygdala reactivity; Di Iorio et al., 2017; Pagliaccio et al., 2014, 2015), HPA axis dysregulation (i.e., diurnal cortisol regulation, Starr, Dienes, Li, & Shaw, 2019), and affective outcomes (i.e., depression, Feurer et al., 2017; Starr & Huang, 2018). These effects may also extend to other negative outcomes following CA, such as interpersonal stress generation.

Interpersonal CA, HPA Axis-Related Genetic Risk, and Interpersonal Stress Generation

Interpersonal childhood adversities (ICAs) are comprised of significant stressors that occur over the course of childhood that are interpersonal in nature and/or in consequences (e.g., parental conflict or separation, deaths of loved ones). The effects of ICAs on subsequent interpersonal stress generation may be especially likely to be moderated by HPA axis-related genetic risk. ICAs have been identified as potent predictors of interpersonal stress generation (e.g., Chan, Doan, & Tompson, 2014; Hernandez et al., 2016). Moreover, interpersonal stress may serve as a powerful "candidate environment," with some studies suggesting G×E effects are limited to moderation of interpersonal stress, for both serotonergic and HPA axis-related genes (Feurer et al., 2017; Starr & Huang, 2018; Vrshek-Schallhorn et al., 2015). For example, Starr and Huang (2018) found that the effects of ICA (but not noninterpersonal CA) on depression were genetically moderated by HPA axis MGPS, suggesting that genetically vulnerable youth are specifically sensitive to interpersonal adversities. Altogether, these factors may put youth at greater risk for interpersonal stress generation following ICA.

Developmental Considerations

Adolescence is a developmental period marked by a confluence of changes relating to higher rates of psychiatric disorders (e.g., depression) associated with CA and stress generation, increases in stressful life events (especially interpersonal stressors), and alterations in HPA axis activity (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Romeo, 2013; Rudolph, 2002). During adolescence, basal HPA axis functioning shifts, resulting in greater release of related hormones and increased stress reactivity (Gunnar et al., 2009). These factors suggest that adolescence may be a sensitive period for stress and HPA axis functioning, so it may serve as an ideal period within which to examine our research questions.

The Current Study

We examined the moderating role of HPA axis-related genetic variation in the association between ICA and interpersonal stress generation in a sample of adolescents. We used an HPA axis-related MGPS based on previously established procedures (Pagliaccio et al., 2014) to examine genetic risk. We hypothesized that ICA would predict interpersonal stress generation (i.e., interpersonal dependent stress) but not independent stress or noninterpersonal dependent stress, in line with prior findings. Additionally, we predicted that this association would be specific to adolescents with high (and not low) HPA axis-related genetic vulnerability.

Method

Participants

The full study sample included 241 adolescents aged 14–17 years (130 female, 111 male[1]) who participated in a larger longitudinal study on adolescent experiences with their primary caregiver. Youth were recruited to participate from the community of a mid-sized metropolitan area. Families were recruited using a range of recruitment methods, including online and community advertisements (50.6% of families), a commercial mailing list of families with potentially age-eligible children (40.2%), and ResearchMatch (4.1%), an online clinical research registry (additional recruitment details are included in Starr et al., 2017). Participants were excluded from study participation if they had a major physical, neurological, or pervasive developmental disorder, a prior diagnosis of any bipolar or psychotic disorders, English language difficulties, or previous participation of siblings or any other household member. Median parent-reported annual family income fell in the $80,000 to $89,999 range. Additionally, 24.1% of adolescents received free or reduced cost school lunches. Mothers comprised the majority of participating parents (87.6%).

As noted below, analyses conducted were largely specific to Caucasian adolescents in order to account for population stratification. The Caucasian sample included 192 youth (M_{age} = 15.89 years, *SD* = 1.08; 53.1% female). Parent-reported median annual family income was in the $90,000 to $99,000 range, with 16.7% of adolescents receiving free or reduced school lunches.

Procedure

Families completed a baseline in-lab session, during which youth and parents provided assent/consent, completed separate interviews, and participated in additional procedures unrelated to the present analyses. Saliva samples were also collected for DNA analysis during this visit. Participating families received $160 for completing baseline session procedures, and they were

[1]Of note, we also assessed nonbinary gender identification; three youth endorsed being genderfluid. We classified these individuals by their biological sex due to the relevance of sex hormones to HPA axis processes.

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

Table 1. Severity ratings and reported incidents of each type of interpersonal childhood adversities

ICA category	Mean ICA Severity Rating (SD)	Total # ICAs Endorsed Across Sample		Percentage of Sample Endorsing	
		Caucasian Sample	Full Sample	Caucasian Sample	Full Sample
Death of a family member or friend	2.22 (.64)	193	244	66.3%	64.3%
Moves between family members' households, family members moving in/out of home, family moves	2.24 (.58)	72	95	33.1%	33.9%
Family conflict	2.46 (.65)	58	69	28.0%	26.7%
Chronic serious physical illness in close family or friends	2.35 (.62)	53	64	24.0%	23.1%
Chronic serious mental illness in close family or friends	2.63 (.74)	53	62	20.6%	20.4%
Parental separation or divorce	3.28 (.42)	37	46	20.6%	20.4%
Chaotic family living circumstances; neglect	3.43 (.80)	35	50	10.9%	12.2%
Family legal troubles (e.g., arrests, trouble with police)	2.44 (.74)	22	31	10.9%	12.2%
Other	2.42 (.67)	90	132	37.7%	39.4%
All Categories	2.47	613	793	91.1%	91.7%

Note: Caucasian subsample $n = 192$, Full sample $n = 241$. ICA = Interpersonal childhood adversity. Data do not incorporate childhood adversities that were coded as noninterpersonal. Mean event severity ratings were calculated in the full sample. Percentage of sample endorsing reflects participants reporting at least one event in each category.

entered into raffles based on compliance. All procedures were approved by the Research Subjects Review Board of the University of Rochester.

Measures

Episodic stress

Trained interviewers administered the UCLA Life Stress Interview (LSI; Hammen, 1991), a semi-structured interview based on the contextual threat method of assessing life events (Brown & Harris, 2012) that examines life events across multiple domains, to adolescents to measure youths' episodic stress. During the LSI, interviewers collected information about life events that occurred within the previous 12 months across six domains (romantic relationships, peer relations, close friendships, family relationships, academic experiences, and behavioral functioning). Interviewers also obtained information about the nature, timing, duration, and context for each event and integrated details from both respondents if both discussed the same event. On average, youth reported 2.95 episodic events. An independent team of trained coders consensus-rated each event based on contextual factors and provided an objective rating of negative impact on a scale from 1 (*no negative impact*) to 5 (*extremely severe impact*). Events were also rated on level of independence, which was dichotomized as dependent or independent, and coded on interpersonal status (*interpersonal or not*). Inter-rater reliability based on independent raters recoding negative impact for a subset of episodic events yielded an interclass correlation of .87. Negative impact scores were summed (excluding "nonevents" rated as "1") to obtain indices of total independent stress, interpersonal dependent stress, and noninterpersonal dependent stress.

CA

A modified version of the Youth Life Stress Interview (Rudolph et al., 2000) was completed with parents to assess the adolescents' experience of CA. Information was collected solely from parents due to time constraints and their potential better recall of events from the youth's early childhood. Interview probes related to youths' potential experiences with negative events and circumstances (e.g., parental conflict/divorce, separation from parents, death of close others, financial difficulties) that had occurred from birth through a year before study participation. Interviewers elicited information about the context of each event, including duration and impact. Parents reported an average of 4.56 CA events. A coding team provided an objective rating of the negative impact for each event using the same rating scale as the LSI. Further, each event was also coded as interpersonal or noninterpersonal. A second independent team of coders rated a subset of episodic stress interviews with excellent reliability, achieving an interclass correlation of .87. Impact scores were summed to assess overall noninterpersonal CA and ICA, excluding nonevents (for frequencies of reported ICAs, see Table 1).

Depressive symptoms (covariate)

Youth were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime (KSADS-PL; Kaufman et al., 1997) to assess both past and current symptoms of major depressive disorder (MDD) and dysthymia. For past depression, the worst episode of depressive symptoms was coded. Consistent with prior work (e.g., Rao, Daley, & Hammen, 2000; Steinberg & Davila, 2008), disorder-level and subsyndromal symptoms were rated following a dimensional rating scale: 0 (*no symptoms),* 1 (*mild symptoms*), 2 (*moderate, subthreshold symptoms*), 3 (*meets DSM-IV criteria),* 4 (*meets DSM-IV criteria with high severity/impairment*). Maximum scores between current MDD and dysthymia were used to capture depressive symptoms (consistent with prior GxE studies; e.g., Conway, Hammen, Brennan, Lind, & Najman, 2010). For current depression, 3.6% of adolescents met criteria for a depression diagnosis, whereas 20.8% met criteria for past depression. Independent coders re-rated 20% of completed interviews with 100% reliability.

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

Pubertal Development (covariate)

Participants completed the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988). This measure consists of three questions about physical maturation for both sexes (e.g., skin complexion, growth spurts, and body hair) and two additional sex-specific items (girls: breast development, menarche; boys: facial hair, deepening voice). Items were scored on a 4-point scale from 1 (*has not yet begun*) to 4 (*growth or development is complete*), with a dichotomized menarche item (1 = *no*, 4 = *yes*). Item responses were averaged to create an index of pubertal development.

Genotyping and MGPS Computation

Genotyping

Youth submitted saliva samples using Oragene (DNA Genotek, Ontario, Canada) collection kits. The DNA samples were analyzed by the University of Wisconsin-Madison Biotechnology Center. DNA concentration was detected and quantitated using the Quant-iT PicoGreen dsDNA kit (Life Technologies, Grand Island, NY). Standard salting-out procedure was used for DNA extraction. Genotyping was carried out using KBiosciences' competitive allele specific PCR SNP genotyping assay based on dual FRET (KASPar). KASPar assays were amplified with the Eppendorf Mastercycler pro384 thermal cycler using allele specific primers. End point fluorescence signals were analyzed by the Synergy 2 (BioTek) plate reader and Gen5 software program.

Following Pagliaccio's (2014) established MGPS procedures, genotypes for 10 SNPs from four HPA axis-related genes, *CRHR1* (rs4792887 *T* allele, rs110402 *G* allele, rs242941 *T* allele, rs242939 *G* allele, rs1876828 *G* allele), *NR3C1* (rs41423247 *G* allele, rs10482605 *T* allele, rs10052957 *A* allele), *NR3C2* (rs5522 *G* allele), and *FKB5* (rs1360780 *T* allele) were included in the MGPS. Pagliaccio and colleagues (2014) developed this MGPS from a large list of HPA axis-related SNPs, pruning them down to the current 10 SNP profile. These specific SNPs were selected from genes involved in the coding of HPA axis proteins and had been found to be associated with altered stress responsivity (e.g., increased cortisol reactivity), vulnerability to depression, and associated phenotypes (for further detail regarding the development of this MGPS, see Pagliaccio et al., 2014). Individual SNPs were coded based on the presence of at-risk genotypes and summed. Higher MGPS indicated greater HPA axis-related genetic risk. Distributions of genotype frequencies are available upon request. All genotype distributions were in Hardy-Weinberg equilibrium, χ^2 (1) ≤ 2.82, *p*s > .05), except rs1876828, χ^2 (1) = 4.12, $p = .041$. Excluding this SNP in analyses had no influence on the results.

Data Analytic Approach

Analyses were conducted using the SPSS PROCESS macro (Hayes, 2017). Prior to analysis, the data were inspected for univariate outliers (greater than three times the interquartile range away from the 25th or 75th percentiles, consistent with previous work; e.g., Pagliaccio et al., 2015). Skew and kurtosis were in the normal range for all major variables (George & Mallery, 2010). Predictor variables were mean-centered prior to analysis of interaction models. In testing GxE models, ICA, MGPS, and their interaction were entered, with episodic stress as the outcome. In all analyses, gender, pubertal stage, and age were included as covariates as both main and interaction effects (e.g., gender × MGPS, gender × E), following guidelines by Dick et al. (2015). We also conducted Cook's distance tests for the identification of potential multivariate outliers within these models (using a 1.0 threshold for Cook's D; no issues were identified). Significant interactions were examined using simple slope tests ($M \pm 1$ *SD*).

Further, the Johnson-Neyman technique was applied to examine levels of ICA at which MGPS predicted stress outcomes, and alternately, MGPS values at which ICA predicted these outcomes. Finally, we conducted a set of sensitivity tests to assess the effects of individual SNPs in driving potential MGPS interaction effects. First, we examined individual SNP GxE effects in predicting interpersonal stress generation, our hypothesized outcome (given the large number of exploratory tests, we applied False Discovery Rate corrections to reduce the risk of Type I error for these analyses; Benjamini & Hochberg, 1995; results should still be interpreted with caution). Second, we conducted "*n* – *1*" analyses by re-running models after removing single SNPs from the MGPS profile one variant at a time (creating 10 nine-SNP profiles) to test whether MGPS interactions were robust to the removal of individual SNPs (see Vrshek-Schallhorn et al., 2015).

Power analyses

Because no prior studies have examined the prediction of stress generation using an MGPS-based, GxE approach, we derived estimated parameters for power analyses from a variety of sources. On the lower end, we included an estimate of $R^2 = .0015$, based on a recent genome-wide by environment interaction study predicting depression (e.g., Arnau-Soler et al., 2019), which suggested power of 8–9% for the White and full samples, respectively. On the highly optimistic end, we estimated R^2 at .05, based on recent analyses within the current sample of this MGPS interacting with interpersonal childhood adversity to predict depression (i.e., the same model in the same sample, but with a different dependent variable; see Starr & Huang, 2018); this suggested power of 89% to 94%. At this time, it is unclear whether these widely differing estimates are the result of very different methodological approaches (atheoretically versus theoretically selected SNPs, self-report versus interview-based phenotyping) or whether the higher effect size is an outlying effect derived from a much smaller sample. However, readers should be aware that, according to genome-wide-study-based estimates of variance captured by GxEs, our study may be underpowered to detect effects, and the results should be interpreted with a priori caution and an eye towards a need for future replication.

Results

Preliminary Analyses

Population stratification

As a preliminary step, we tested for population stratification effects (i.e., confounding effects that occur when race is correlated with outcomes of interest and specific genotypes). As reported elsewhere (for full details, see Starr et al., 2017), in the current sample, non-Caucasian youth had higher MGPS than did Caucasian youth, t (239) = 2.10, $p = .036$, and race moderated the association between MGPS and depressive symptoms. Race was also marginally associated with ICA, t (239) = 1.68, $p = .094$; scores were higher for non-White adolescents. As a conservative measure to address potential population stratification issues,

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

Table 2. Bivariate main effect and gene-environment correlations and descriptive data

	1	2	3	4	5	6	7	8
1. HPA MGPS	–							
2. ICA	.07	–						
3. Noninterpersonal CA	.07	.10	–					
4. Interpersonal dependent stress	.05	.18*	.09	–				
5. Noninterpersonal dependent stress	−.05	.10	.09	.04	–			
6. Independent stress	−.04	.14	.05	.17*	.05	–		
7. Current depressive symptoms	.16*	.15*	.04	.22**	.10	.13	–	
8. Past depressive symptoms	−.01	.28**	.07	.29**	.08	.17*	.36**	–
M	4.60	7.79	2.72	1.46	.54	3.81	.23	1.02
SD	1.39	6.20	3.39	2.01	1.31	3.21	.68	1.37
Min	2.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Max	9.00	31.50	24.00	9.50	9.50	15.50	3.00	4.00

Note: MGPS = Multilocus genetic profile score, ICA = Interpersonal childhood adversity, CA = Childhood adversity. Data are from the Caucasian sample (n= 192). *p< .05 **p< .01.

primary analyses were restricted to the Caucasian sample (n = 192) and then conducted in the full sample.

Main effects and gene–environment correlations

Descriptive data and bivariate correlations are presented in Table 2. Results show that HPA axis-related MGPS was not significantly correlated with any of the variables, and no gene–environment correlations were found between MGPS and any stress outcomes.

We further examined environmental main effects using linear regression analyses. As hypothesized, there was evidence for an environmental main effect, with ICA and predicting interpersonal dependent stress, ß = .18, p = .012. These effects were largely exclusive to the relationship between ICA and interpersonal dependent stress. ICA marginally significantly predicted independent stress, ß = .14, p = .060, but it did not significantly predict noninterpersonal dependent stress,[2] ß = .10, p = .152. Additionally, noninterpersonal CA did not predict interpersonal dependent stress, ß = .09, p = .223. We also re-ran these analyses controlling for depressive symptoms, given past research indicating that depression predicts stress generation (Hammen, 1991; Rudolph et al., 2000). Following control of both past and current depressive symptoms, ICA marginally significantly predicted interpersonal dependent stress (ß = .11, p = .09). Finally, ICA did not significantly predict independent stress (p = .102) or noninterpersonal dependent stress (p = .155), nor did noninterpersonal CA predict interpersonal dependent stress (p = .267).

Tests of Gene–Environment Interactions

Supporting hypotheses, we found a significant G×E interaction between ICA and MGPS on adolescents' interpersonal dependent stress, interaction term ß = .18, p = .016 (see Table 3); ΔR^2 was .03, suggesting that this G×E interaction explains approximately 3% of the variance in interpersonal dependent stress. Simple slopes analyses (see Figure 1) indicate that ICA did not significantly predict interpersonal dependent stress at low MGPS (M - 1 SD), b = .03, SE = .22, p = .893; however, at high MGPS (M + 1 SD), ICA significantly predicted higher interpersonal dependent stress, b = .72, SE = .19, p = .0002 (see Figure 1). Johnson-Neyman analyses indicated an association between ICA and interpersonal dependent stress at MGPS ≥ 4.34 (49th percentile). Higher genetic risk scores were associated with greater adolescent interpersonal dependent stress at high levels of ICA (Johnson-Neyman significance region beginning at 83rd percentile of ICA). At very low levels of ICA, MGPS predicted marginally *less* interpersonal dependent stress (p = .060; lowest 5th percentile, which encompassed only adolescents who reported zero ICA).

Table 3. Model examining the interaction of HPA axis multilocus genetic profile scores and interpersonal childhood adversity in predicting interpersonal dependent stress

	ß	*b*	*S.E.*	*p*	95% CI
Intercept		1.47	.14	<.001	[1.19, 1.75]
MGPS	.02	.05	.15	.753	[−.24, .34]
ICA	.19	.40	.15	.009	[.10, .70]
MGPS × ICA	**.18**	**.35**	**.15**	**.016**	**[.06, .64]**
Covariates: Gender	.02	.04	.15	.794	[−.26, .34]
PDS	.09	.18	.18	.311	[−.17, .53]
Age	.06	.12	.16	.472	[−.20, .43]
Gender × MGPS	.04	.08	.16	.602	[−.23, .39]
Gender × ICA	.15	.31	.17	.066	[−.02, .64]
PDS × MGPS	−.06	−.12	.20	.546	[−.52, .28]
PDS × ICA	−.01	−.03	.19	.880	[−.40, .34]
Age × MGPS	.05	.10	.19	.589	[−.27, .47]
Age × ICA	.01	.02	.17	.901	[−.31, .35]

Note: MGPS = Multilocus genetic profile score; ICA = Interpersonal childhood adversity; PDS = Pubertal Development Scale. Presented analyses are from Caucasian subsample (n = 192).

[2]It should be noted that fewer noninterpersonal dependent events (M = .32, SD = .68) than interpersonal dependent events (M = .77, SD = 1.03) were reported in our sample; as such, nonsignificant findings may be partially attributable to restricted range.

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

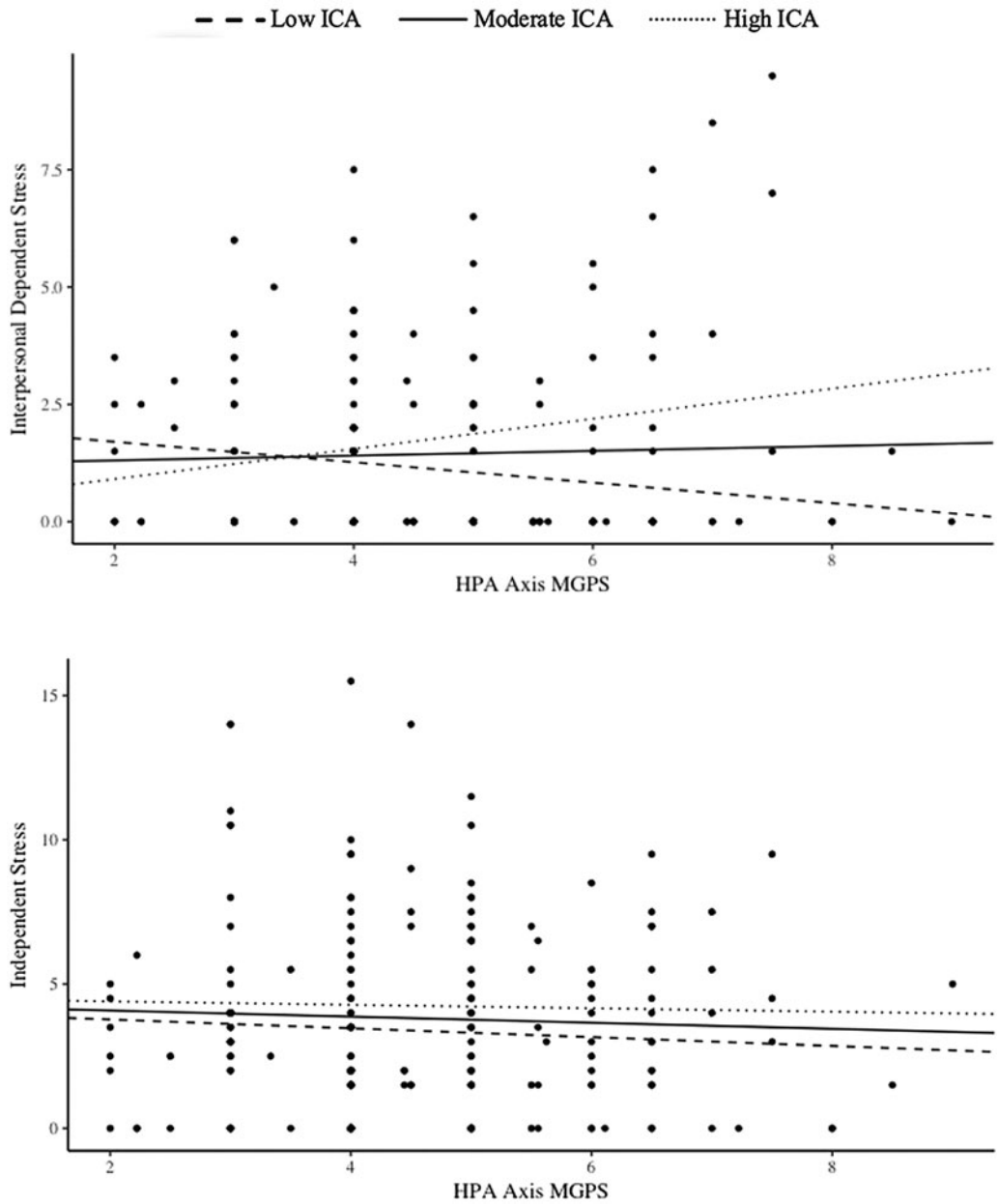

Figure 1. HPA axis MGPS at low moderate, and high level of interpersonal childhood adversity (ICA) predicting (a) interpersonal dependent stress and (b) independent stress. Data presented are from the Caucasian subsample ($n = 192$).

We re-ran the model including both current and past depressive symptoms as covariates; the G×E interaction remained significant (interaction term ß = .17, $p = .027$), and simple slope patterns were unchanged. Further, to test that the findings were specific to stress generation results, analyses were repeated with independent (i.e., fateful) stress as the outcome. In line with hypotheses and the stress generation model, MGPS did not significantly moderate the association between ICA and independent stress (see Figure 1), interaction term ß = .02, $p = .836$; results were similar in a robust model including all interactive covariates, ß = .03, $p = .733$.

We next confirmed whether the results were unique to interpersonal stress, both as a predictor variable (ICA versus noninterpersonal CA) and outcome (interpersonal versus noninterpersonal dependent stress). Aligning with predictions, MGPS did not significantly interact with noninterpersonal CA to predict adolescent interpersonal dependent stress in the initial model, ß = −.02, $p = .816$. Furthermore, as hypothesized, there was no significant interaction between MGPS and ICA in predicting noninterpersonal dependent stress, ß = −.02, $p = .821$.

Exploratory tests of gender moderation

Although not initially hypothesized, we also conducted exploratory analyses involving gender moderation. Although biological sex was used in covariate analyses, for these tests, we focused on gender, given research suggesting greater risk for depression and stress generation in girls (e.g., Hammen, 1991; Rudolph et al., 2000). Thus, we excluded adolescents endorsing nonbinary gender ($n = 3$, 2 in the White sample) from our analyses. We tested gender as a moderator of the association between ICA

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

Table 4. Results for separate regression models predicting interpersonal dependent stress from the interactions between individual SNPs and interpersonal childhood adversity

		G × IP Childhood Adversity		
	b	*SE*	*p*	*B-H p*
CRHR1				
rs4792887	.15	.11	.174	0.290
rs110402	.10	.05	.026	0.058
rs242941	.11	.05	.021	0.058
rs242939	.20	.07	.005	0.025
rs1876828	−.01	.12	.930	0.930
NR3C1				
rs41423247	−.29	.13	.029	0.058
rs10482605	−.03	.05	.597	0.794
rs10052957	.12	.12	.292	0.417
NR3C2				
rs5522	.18	.06	.003	0.025
FKBP5				
rs1360780	.05	.06	.349	0.436

Note: Analyses conducted in Caucasian subsample ($n = 192$). B-H p = Benjamini-Hochberg corrected p value (Benjamini & Hochberg, 1995). Covariates included gender, age, and pubertal development.

and dependent interpersonal stress, MGPS and dependent interpersonal stress, and a 3-way interaction with ICA, MGPS, and gender predicting dependent interpersonal stress. Models including the MGPS variable were conducted in the White sample, and models with no genetic variable were conducted in the full sample. All models were nonsignificant, suggesting no support for gender moderation.

Sensitivity tests

We conducted exploratory analyses to test whether our significant findings were largely driven by single SNPs within the genetic profile. For these sensitivity analyses, we first tested G×E effects for each MGPS SNP in interaction with ICA to predict dependent interpersonal stress. We controlled for the main effects of covariates (i.e., gender, age, pubertal development) and tested covariate interactions for cases in which the single SNP interactions reached significance. We then further assessed the effects of individual SNPs by conducting *n – 1* analyses, removing individual SNPs from the original 10 SNP genetic profile one at a time and re-running our original model with these revised 9-SNP MGPSs (Vrshek-Schallhorn et al., 2015). Results (presented in Table 4) suggested that several SNPs reached nominal significance in their interaction with ICA (*CRHR1* rs242939, *CRHR1* rs242941, *CRHR1* rs110402, *NR3C1* rs41423247, and *NR3C2* rs5522). However, after FDR corrections, only two SNPs remained significant (*NR3C2* rs5522 and *CRHR1* rs243939; Benjamini-Hochberg adjusted p-values = .025). These ICA interactions with *NR3C2* rs5522 and *CRHR1* rs243939 remained significant after controlling for covariate interactions, $p = .002$ and $p = .033$, respectively. In the *n - 1* analyses, re-running analyses with 9-SNP MGPS profiles after removing each SNP individually, all G×E effects remained significant ($ps \leq .024$), suggesting that it is the cumulative influence of these SNPs within the profile, rather than an individual SNP with large effects.

Analyses with Full Sample

Analyses were re-run in the full sample, which included adolescents from all racial groups. Given that the majority of the sample reported European heritage (80%), these results should be interpreted more cautiously; note that there was insufficient power to examine any other racial group individually. These findings paralleled those from the White youth sample. MGPS moderated the association between ICA and interpersonal dependent stress, interaction term ß = .13, $p = .045$. Results were near-identical in the robust model, ß = .14, $p = .040$. Simple slope patterns were consistent with those from the White sample. As in the White sample, MGPS did not significantly moderate the relationship between ICA and independent stress or noninterpersonal dependent stress. No moderation effects were found for the association between noninterpersonal CA and interpersonal dependent stress.

Discussion

The current study examined the interaction between ICA and HPA axis-related genetic variation in predicting interpersonal stress generation. Our findings supported study hypotheses; first, aligning with previous findings (e.g., Chan et al., 2014; Hernandez et al., 2016), we found that ICA significantly predicted greater adolescent interpersonal dependent stress (but not noninterpersonal dependent) stress. The association between ICA and independent stress was marginally significant, which suggests that some of the effects may be attributable to continuity in high-stress environments, rather than stress generation alone. However, we found that the association between ICA and interpersonal dependent stress was qualified by its significant moderation by HPA axis-related genetic variation. Importantly, HPA axis-related MGPS G×E did not predict independent stress, which suggests that these effects contribute to generation of stress and not overall stress exposure. These results are consistent with the stress generation model (Hammen, 2006) and prior findings supporting the role of genetic factors and CA in stress generation (Harkness et al., 2015; Starr et al., 2012, 2013). Further, results were exclusive to *interpersonal* stress: MGPS did not moderate the association between noninterpersonal CA and interpersonal dependent stress, nor was there an interaction between ICA and MGPS in predicting noninterpersonal dependent stress.

While previous studies have shown that genetic risk intensifies interpersonal stress generation (Harkness et al., 2015; Starr et al., 2012, 2013), the present study extends previous findings in several key ways. This is the first study to apply a multilocus genetic risk approach in examining stress generation. Previous research focused on G×Es involving a specific serotonergic genetic variant (5-HTTLPR) linked with stress reactivity; the MGPS approach considers the cumulative, polygenic effect of several genes linked to a specific biological system (Aliev, Latendresse, Bacanu, Neale, & Dick, 2014; Caspi et al., 2010; Dick et al., 2015). Further, HPA axis-related genetic risk has never been examined in relation to stress generation. Recent work has shown that HPA axis dysregulation following laboratory stress predicts stress generation (Morris et al., 2014). Our findings indicate that genetic risk linked to HPA axis functioning may interact with environmental stress, namely ICA, to promote stress generation. Given that few studies have examined HPA axis functioning in relation to stress generation, an important future research direction would be to examine

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

physiological mechanisms that might underpin this process. For example, CA has been shown to alter specific indices of diurnal HPA axis regulation (e.g., latent trait cortisol, cortisol awakening response; Chen, Stroud, Vrshek-Schallhorn, Doane, & Granger, 2017; Starr et al., 2017; Stroud, Chen, Doane, & Granger, 2016); it would be interesting to examine how these are, in turn, related to daily interpersonal behaviors which may culminate in stress generation.

In addition, our results provide further evidence of ICA as a specific environmental risk factor predicting interpersonal stress generation, as moderated by MGPS. Findings align with prior research that identified interpersonal stress, including ICA, as a particularly powerful candidate environment for the prediction of depression among genetically vulnerable youth (Feurer et al., 2017; Starr & Huang, 2018; Vrshek-Schallhorn et al., 2015). Several previous studies have examined specific types of adversities that fall into the interpersonal domain (e.g., parent–child conflict, childhood emotional abuse; Chan, Doan, & Tompson, 2014; Hernandez et al., 2016) as predictors of interpersonal stress generation, but this study was the first to explicitly classify CA by its interpersonal nature in the context of stress generation. Importantly, many of the previous studies examining the link between CA and stress generation focus on maltreatment, often occurring specifically in early childhood (e.g., Harkness et al., 2015; Hernandez et al., 2016; Liu et al., 2013). In contrast, the CA reported within this study largely reflect more commonplace stressors (e.g., parental divorce or separation, family conflicts) that occur over the course of childhood. These results suggest that genetic moderation of stress generation does not exclusively occur following very severe CA, and they are in line with previous research suggesting that the downstream effects of CA are not specific to childhood maltreatment (e.g., Felitti et al., 1998; Green et al., 2010; Hazel et al., 2008), potentially indicating that results are directly relevant to a broader portion of the population.

Further, our results suggest that the cascading effects of ICA may have particular relevance to the interpersonal domain, especially for those with HPA axis-related genetic risk, resulting in negative outcomes such as interpersonal stress generation. It may be that ICAs serve as acute threats that powerfully influence HPA axis functioning. Stress response systems are exquisitely sensitive to social threat, with interpersonal stressors reliably predicting HPA axis activation (Miller, Chen, & Zhou, 2007; Stroud et al., 2016). Our results build upon this past research, demonstrating that youth with high HPA axis-related genetic risk may be especially sensitive to ICA. Given that social relationships in childhood are particularly important (McLaughlin, 2016; Sroufe, 2000), ICAs that occur during this stage may lead to repeated or sustained HPA axis activation and consequent long-term alterations in HPA axis activity, especially for adolescents who are at genetic risk for HPA axis dysfunction. Moreover, ICAs and associated stress sensitization may be particularly relevant to social development. For example, attachment theory (Bowlby, 1982) suggests that early relationships and interpersonal interactions serve as models for future relationships and interpersonal patterns. Internalized expectations from prior negative interpersonal experiences have been linked to greater interpersonal conflict within relationships (Downey, Freitas, Michaelis, & Khouri, 1998). Furthermore, ICAs have been shown to predict chronic interpersonal difficulties (e.g., Salwen et al., 2014). Thus, social disruptions due to ICA may contribute to impairments in interpersonal functioning, such as interpersonal stress generation. Further, within our ICA construct, there may be specific dimensions of interpersonal adversities that may be more potent predictors of social disruptions and later stress generation. For example, research indicates that maladaptive family functioning (e.g., parental mental illness, neglect, physical or sexual abuse) strongly predicts later psychopathology (Green et al., 2010). It may be that stressful or highly conflictual family environments in particular, especially during key developmental periods, may increase vulnerability, posing more potent threats to attachment bonds and cognitions and expectations about interpersonal behavior (e.g., Dodge, Bates, & Pettit, 1990; Styron & Janoff-Bulman, 1997). Future studies on HPA axis-related biological mechanisms should investigate whether effects are unique to the interpersonal realm and examine whether specific dimensions of ICA increase vulnerability for interpersonal stress generation.

In addition, these effects may more specifically put youth at greater risk of generating interpersonal (but not noninterpersonal) stress. Notably, there were relatively few noninterpersonal dependent events in our sample. Although the lack of prediction of noninterpersonal stress may be a consequence of restricted range, it may also imply that the fusion of ICA and genetic risk specifically leads to interpersonal dysfunction. While CA may lead to interpersonal stress generation through a number of mechanisms, one of particular relevance may be stress sensitization. According to the stress sensitization hypothesis (Post, 1992), CA is linked with a lower threshold for depressive onset following future stressful events, such that depressed youth with CA histories report lower levels of recent stress than do depressed youth with no CA history (Hammen, Henry, & Daley, 2000; La Rocque, Harkness, & Bagby, 2014; Monroe & Harkness, 2005; Shih, Eberhart, Hammen, & Brennan, 2006). Likewise, CA amplifies the relationship between proximal stressors and depression, again suggesting greater stress reactivity (Kim et al., 2014; McLaughlin et al., 2010; Shapero et al., 2014; Starr et al., 2017). Further, HPA axis-related genetic risk has also been shown to moderate stress sensitivity following CA, suggesting that genetic vulnerabilities may also increase risk for stress sensitization (Starr et al., 2014). Research has also found that HPA axis-related genetic variation interacts with CA to predict alterations in threat-related amygdala function, which has been implicated in reactivity to stress and linked to greater psychological vulnerability to subsequent life stress (Di Iorio et al., 2017; Swartz, Knodt, Radtke, & Hariri, 2015). HPA axis MGPS has also been shown to interact with environmental stress to predict differences in diurnal cortisol regulation, an alteration in HPA axis functioning that may also contribute to stress reactivity (Starr et al., 2019). Increases in stress reactivity, along with potential alterations in neural circuitry and other indices relating to HPA axis functioning, may bias perceptions of social threats in these situations and affect stress responses, resulting in further stress experienced and contributing to interpersonal stress generation. For instance, for someone who is hyper-responsive to stress, a perceived slight may rapidly escalate into a conflict and subsequent friendship dissolution, culminating more readily into a significant stressor. Supporting this model, several variables related to stress reactivity directly predict stress generation, including neuroticism and rejection sensitivity (Hernandez et al., 2016; Uliaszek et al., 2012). For example, one recent study found that CA predicted greater rejection sensitivity, which, in turn, led to greater interpersonal stress generation (Hernandez et al., 2016). These results suggest that CA produces increased reactivity within interpersonal relationships, which contributes to greater self-generated interpersonal stress. Thus, heightened sensitivity and associated negative interpersonal

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

processes following CA may increase the likelihood of interpersonal stress generation.

Further research is necessary to understand potential interpersonal mechanisms involved. For example, CA is related to a range of interpersonal risk processes, such as insecure attachment, ineffective interpersonal stress responses (e.g., involuntary engagement/ disengagement with stressors), and excessive reassurance seeking (e.g., Massing-Schaffer, Liu, Kraines, Choi, & Alloy, 2015; Mickelson, Kessler, & Shaver, 1997; Shih, Abela, & Starrs, 2009; Troop-Gordon, Sugimura, & Rudolph, 2017). These interpersonal risk processes have also been linked to interpersonal stress generation (Flynn & Rudolph, 2011; Shih et al., 2009; Starr et al., 2013). Future research should examine how the interaction of ICA and HPA axis-related genetic risk might create a marked vulnerability for these negative interpersonal processes and later interpersonal stress generation.

While we focus on interpersonal stress generation as an outcome, it is also important to consider downstream effects that may follow. A wealth of literature links interpersonal dysfunction (including interpersonal stress generation) to later depression (Hames et al., 2013; Joiner & Timmons, 2002; Liu & Alloy, 2010; Rudolph et al., 2000). Thus, another avenue for future research may be to examine whether processes highlighted in our study are a probable factor in propagating depression, such that increased interpersonal stress generation predicts later increases in depressive symptoms. Moreover, there is evidence to suggest that HPA axis-related genetic risk may moderate this relationship, as HPA axis MGPS has been shown to increase reactivity to acute interpersonal stressors, predicting stronger associations between interpersonal stress and depressive symptoms in youth (Feurer et al., 2017). As such, it would be interesting to examine how the increased self-generated interpersonal stress might bridge ICA with later emotional outcomes among youth at high genetic risk. Longitudinal research examining these questions may be an important future direction.

Furthermore, our results suggested that at very low levels of ICA (i.e., no ICA reported), high HPA axis-related MGPS was marginally associated with *lower* interpersonal dependent stress. This pattern is consistent with differential susceptibility models, which propose that genetic factors that leave adolescents more susceptible to negative outcomes in negative, stressful environments may actually also predispose them to thrive in positive, supportive environments (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009). Prior studies (e.g., Feurer et al., 2017; Starr & Huang, 2018) have found evidence for the differential susceptibility model using HPA axis-related MGPS in predicting depressive outcomes. Given this converging set of findings, further work examining potential differential susceptibility effects for interpersonal stress generation is needed. For example, our ability to detect this pattern may potentially have been limited by the environmental measures in our study, as low ICA may not necessarily reflect a true positive context; rather, it may better capture the *absence* of a negative environment. It could be the case that a differential susceptibility pattern would be more evident using a measure that encapsulates the extent to which the environment was warm, nurturing, and supportive.

Adolescence provided an ideal developmental period for our research questions, given the changes in reactivity to stress, increased rates of disorders (e.g., depression) associated with stress generation and CA, shifts in biological functioning, and pronounced increases in stressful life events during this time (Avenevoli et al., 2015; Gunnar et al., 2009; Romeo, 2013; Rudolph, 2002). An important remaining question is whether effects replicate across other age groups. Stress generation processes occur across development and are not solely relevant to adolescence (Alloy, Liu, & Bender, 2010). Research suggests that there are changes in HPA axis activity across development, including increases in basal cortisol from childhood into adulthood (Gunnar & Vazquez, 2006). These shifts may have implications for stress reactivity and stress generation processes, particularly for those who are more genetically vulnerable to stress system dysregulation. Furthermore, twin study research indicates that G×E effects may also change with age, as the relative influence of environmental versus genetic factors vary over time (e.g., Rice, Harold, & Thapar, 2002; Tully, Iacono, & McGue, 2010). Thus, the extent to which HPA axis-related genetic variation modulates the effects of CA on stress generation processes may vary across development. Longitudinal studies examining whether these HPA axis-related G×E effects on stress generation and related processes shift with age are needed.

This study featured several important limitations. First, the sample size was small by typical G×E standards, which has been associated with concerns over statistical power and robustness. Of note, our effect of R^2 of .04 is somewhat larger than those typically associated with predictions of complex behavioral phenotypes and could be anomalous to this sample (Bogdan, Baranger, & Agrawal, 2018); replication is paramount. We used the MGPS approach, which appears to yield greater predictive validity than single polymorphisms examined in isolation and allow for theoretically-driven hypotheses about intermediate phenotypes (e.g., Pagliaccio et al., 2014; Vrshek-Schallhorn et al., 2015), but GWAS-based approaches that map genetic risk using the entire human genome offer additional computational benefits (Bogdan et al., 2018). Our study findings were preserved after conservative control of covariates and covariate interactions and sample racial stratification, which we believe supports that the sample was adequately powered for these analyses. Of note, we controlled for past and current depressive symptoms, given their established association with stress generation; however, given that computation of the CA variables involved aggregation across all relevant CA events, we were prevented from testing whether depressive symptoms temporally preceded these events. Given the smaller sample size and the novelty of these findings, however, replication is important. Further, because this study did not use GWAS-based genotyping, we were unable to conduct competitive significance testing in order to assess the performance of this MGPS in comparison with MGPSs derived from randomly drawn SNPs (Di Iorio et al., 2017), which will be an interesting next step for future studies. Additionally, in our analyses featuring noninterpersonal events (both for CA and dependent stress), reported interpersonal events outnumbered noninterpersonal ones; these differences in frequency may have limited power for these specific analyses.

The study also featured a cross-sectional sample. One problem this raises is bias that occurs with retrospective reports, especially in the assessment of adversities occurring many years prior to the interview. Further, information about CA was obtained from parents. This means that reported events may have been described from the parent's perspective, and any experiences that occurred outside of the parent's awareness may not have been included in their report. There may also have been instances in which parents were reluctant to report specific events they had perpetrated or were at fault for in some way. Future research would benefit

https://doi.org/10.1017/S0954579419001123 Published online by Cambridge University Press

from longitudinal tracking of CA across childhood and incorporating multisource data (e.g., cross-checking with multiple reporters, child protection services records).

These limitations notwithstanding, this study highlights the interaction between ICA and HPA axis-related genetic risk in adolescent interpersonal stress generation and sheds light on the complex processes involved in stress generation, contributing to the growing literature on G×Es using HPA axis MGPSs. Future studies should consider their use in multilevel analyses to help further elucidate the many pathways that contribute to this and other stress-related outcomes.

Acknowledgments. The authors thank Y. Irina Li, Zoey A. Shaw, and Fanny Mlawer for data collection management, as well as the participating families for generously volunteering their time. We are also grateful to Sheree Toth for her comments on an earlier draft of this manuscript. The authors acknowledge the University of Wisconsin Biotechnology Center DNA Sequencing Facility for providing genotyping facilities and services.

Financial Support. Study funding was provided by the University of Rochester.

References

Aliev, F., Latendresse, S. J., Bacanu, S.-A., Neale, M. C., & Dick, D. M. (2014). Testing for measured gene-environment interaction: Problems with the use of cross-product terms and a regression model reparameterization solution. *Behavior Genetics*, *44*, 165–181.

Alloy, L. B., Liu, R. T., & Bender, R. E. (2010). Stress generation research in depression: A commentary. *International Journal of Cognitive Therapy*, *3*, 380–388.

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., … Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience*, *256*, 174–186. doi:10.1007/s00406-005-0624-4

Arnau-Soler, A., Macdonald-Dunlop, E., Adams, M. J., Clarke, T. K., MacIntyre, D. J., Milburn, K., … Thomson, P. A. (2019). Genome-wide by environment interaction studies of depressive symptoms and psychosocial stress in UK Biobank and Generation Scotland. *Translational Psychiatry*, *9*, 14. doi: 10.1038/s41398-018-0360-y

Avenevoli, S., Swendsen, J., He, J.-P., Burstein, M., & Merikangas, K. R. (2015). Major depression in the National Comorbidity Survey–Adolescent Supplement: Prevalence, correlates, and treatment. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*, 37–44.e32. doi: https://doi.org/10.1016/j.jaac.2014.10.010

Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). For better and for worse. *Current Directions in Psychological Science*, *16*, 300–304. doi:10.1111/j.1467-8721.2007.00525.x

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*, 885–908.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B* (*Methodological*), *57*, 289–300.

Bogdan, R., Baranger, D. A. A., & Agrawal, A. (2018). Polygenic risk scores in clinical psychology: Bridging genomic risk to individual differences. *Annual Review of Clinical Psychology*, *14*, 119–157. doi:10.1146/annurev-clinpsy-050817-084847

Bowlby, J. (1982). Attachment and loss: Retrospect and prospect. *American Journal of Orthopsychiatry*, *52*, 664–678.

Brown, G. W., & Harris, T. (2012). *Social origins of depression: A study of psychiatric disorder in women*. London: Routledge.

Buchmann, A. F., Holz, N., Boecker, R., Blomeyer, D., Rietschel, M., Witt, S. H., … Laucht, M. (2014). Moderating role of FKBP5 genotype in the impact of childhood adversity on cortisol stress response during adulthood. *European Neuropsychopharmacology*, *24*, 837–845. doi:10.1016/j.euroneuro.2013.12.001

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*, *167*, 509–527. doi:10.1176/appi.ajp.2010.09101452

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., … Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*, 386–389. doi:10.1126/science.1083968

Chan, P. T., Doan, S. N., & Tompson, M. C. (2014). Stress generation in a developmental context: The role of youth depressive symptoms, maternal depression, the parent–child relationship, and family stress. *Journal of Family Psychology*, *28*, 32–41. doi:10.1037/a0035277

Chen, F. R., Stroud, C. B., Vrshek-Schallhorn, S., Doane, L. D., & Granger, D. A. (2017). Individual differences in early adolescents' latent trait cortisol: Interaction of early adversity and 5-HTTLPR. *Biological Psychology*, *129*, 8–15. doi:10.1016/j.biopsycho.2017.07.017

Cicchetti, D., & Rogosch, F. A. (2012). Neuroendocrine regulation and emotional adaptation in the context of child maltreatment. *Monographs of the Society for Research in Child Development*, *77*, 87–95. doi:doi:10.1111/j.1540-5834.2011.00666.x

Cicchetti, D., Rogosch, F. A., & Oshri, A. (2011). Interactive effects of corticotropin releasing hormone receptor 1, serotonin transporter linked polymorphic region, and child maltreatment on diurnal cortisol regulation and internalizing symptomatology. *Development and Psychopathology*, *23*, 1125–1138. doi:10.1017/s0954579411000599

Conway, C. C., Hammen, C., Brennan, P. A., Lind, P. A., & Najman, J. M. (2010). Interaction of chronic stress with serotonin transporter and catechol-O-methyltransferase polymorphisms in predicting youth depression. *Depression and Anxiety*, *27*, 737–745. doi:10.1002/da.20715

Culverhouse, R. C., Saccone, N. L., Horton, A. C., Ma, Y., Anstey, K. J., Banaschewski, T., … Bierut, L. J. (2018). Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. *Molecular Psychiatry*, *23*, 133–142. doi:10.1038/mp.2017.44

Derijk, R. H. (2009). Single nucleotide polymorphisms related to HPA axis reactivity. *Neuroimmunomodulation*, *16*, 340–352. doi:10.1159/000216192

de Vries, Y. A., Roest, A. M., Franzen, M., Munafo, M. R., & Bastiaansen, J. A. (2016). Citation bias and selective focus on positive findings in the literature on the serotonin transporter gene (5-HTTLPR), life stress and depression. *Psychological Medicine*, *46*, 2971–2979. doi:10.1017/s0033291716000805

Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., … Sher, K. J. (2015). Candidate gene-environment interaction research: reflections and recommendations. *Perspectives on Psychological Science*, *10*, 37–59. doi:10.1177/1745691614556682

Di Iorio, C. R., Carey, C. E., Michalski, L. J., Corral-Frias, N. S., Conley, E. D., Hariri, A. R., & Bogdan, R. (2017). Hypothalamic-pituitary-adrenal axis genetic variation and early stress moderates amygdala function. *Psychoneuroendocrinology*, *80*, 170–178. doi:10.1016/j.psyneuen.2017.03.016

Dodge, K. A., Bates, J. E., & Pettit, G. S. (1990). Mechanisms in the cycle of violence. *Science*, *250*, 1678–1683.

Downey, G., Freitas, A. L., Michaelis, B., & Khouri, H. (1998). The self-fulfilling prophecy in close relationships: Rejection sensitivity and rejection by romantic partners. *Journal of Personality and Social Psychology*, *75*, 545–560.

Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry*, *168*, 1041–1049. doi:10.1176/appi.ajp.2011.11020191

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., … Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*, *14*, 245–258.

Feurer, C., McGeary, J. E., Knopik, V. S., Brick, L. A., Palmer, R. H., & Gibb, B. E. (2017). HPA axis multilocus genetic profile score moderates the impact of interpersonal stress on prospective increases in depressive symptoms for offspring of depressed mothers. *Journal of Abnormal Psychology*, *126*, 1017–1028. doi:10.1037/abn0000316

Flynn, M., & Rudolph, K. D. (2011). Stress generation and adolescent depression: contribution of interpersonal stress responses. *Journal of Abnormal Child Psychology*, *39*, 1187–1198. doi:10.1007/s10802-011-9527-1

George, D., & Mallery, M. (2010). *SPSS for windows step by step: A simple guide and reference, 17.0 update* (10a ed.). Boston: Pearson.

Gerritsen, L., Milaneschi, Y., Vinkers, C. H., van Hemert, A. M., van Velzen, L., Schmaal, L., & Penninx, B. W. (2017). HPA axis genes, and their interaction with childhood maltreatment, are related to cortisol levels and stress-related phenotypes. *Neuropsychopharmacology*, *42*, 2446–2455. doi:10.1038/npp.2017.118

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. *Archives of General Psychiatry*, *67*, 113–123. doi:10.1001/archgenpsychiatry.2009.186

Guerry, J. D., & Hastings, P. D. (2011). In search of HPA axis dysregulation in child and adolescent depression. *Clinical Child and Family Psychology Review*, *14*, 135–160. doi:10.1007/s10567-011-0084-5

Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, *58*, 145–173. doi:10.1146/annurev.psych.58.110405.085605

Gunnar, M. R., & Vazquez, D. (2006). *Developmental psychopathology: Developmental Neuroscience* (Vol. *2*, pp. 533–577). Hoboken, NJ: Wiley.

Gunnar, M., Wewerka, S., Frenn, K., Long, J. D., & Griggs, C. (2009). Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: Normative changes and associations with puberty. *Development and Psychopathology*, *21*, 69–85. doi:10.1017/s0954579409000054

Hames, J. L., Hagan, C. R., & Joiner, T. E. (2013). Interpersonal processes in depression. *Annual Review of Clinical Psychology*, *9*, 355–377. doi:10.1146/annurev-clinpsy-050212-185553

Hammen, C. (1991). Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology*, *100*, 555–561.

Hammen, C. (2006). Stress generation in depression: Reflections on origins, research, and future directions. *Journal of Clinical Psychology*, *62*, 1065–1082. doi:10.1002/jclp.20293

Hammen, C., Henry, R., & Daley, S. E. (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology*, *68*, 782–787.

Hankin, B. L. (2005). Childhood maltreatment and psychopathology: Prospective tests of attachment, cognitive vulnerability, and stress as mediating processes. *Cognitive Therapy and Research*, *29*, 645–671. doi:10.1007/s10608-005-9631-z

Harkness, K. L., Bagby, R. M., Stewart, J. G., Larocque, C. L., Mazurka, R., Strauss, J. S., … Kennedy, J. L. (2015). Childhood emotional and sexual maltreatment moderate the relation of the serotonin transporter gene to stress generation. *Journal of Abnormal Psychology*, *124*, 275–287. doi:10.1037/abn0000034

Harkness, K. L., Lumley, M. N., & Truss, A. E. (2008). Stress generation in adolescent depression: The moderating role of child abuse and neglect. *Journal of Abnormal Child Psychology*, *36*, 421–432. doi:10.1007/s10802-007-9188-2

Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*: Guilford Publications.

Hazel, N. A., Hammen, C., Brennan, P. A., & Najman, J. (2008). Early childhood adversity and adolescent depression: The mediating role of continued stress. *Psychological Medicine*, *38*, 581–589. doi:10.1017/s0033291708002857

Heim, C., Bradley, B., Mletzko, T. C., Deveau, T. C., Musselman, D. L., Nemeroff, C. B., … Binder, E. B. (2009). Effect of childhood trauma on adult depression and neuroendocrine function: Sex-specific moderation by CRH receptor 1 gene. *Frontiers in Behavioral Neuroscience*, *3*. doi:10.3389/neuro.08.041.2009

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry*, *49*, 1023–1039.

Hernandez, E. M., Trout, Z. M., & Liu, R. T. (2016). Vulnerability-specific stress generation: Childhood emotional abuse and the mediating role of depressogenic interpersonal processes. *Child Abuse and Neglect*, *62*, 132–141. doi:10.1016/j.chiabu.2016.10.019

Huh, H. J., Kim, S. Y., Yu, J. J., & Chae, J. H. (2014). Childhood trauma and adult interpersonal relationship problems in patients with depression and anxiety disorders. *Annals of General Psychiatry*, *13*. doi: 10.1186/s12991-014-0026-y

Johnson, J. G., Cohen, P., Gould, M. S., Kasen, S., Brown, J., & Brook, J. S. (2002). Childhood adversities, interpersonal difficulties, and risk for suicide attempts during late adolescence and early adulthood. *Archives of General Psychiatry*, *59*, 741–749.

Joiner, T. E., & Timmons, K. A. (2002). Depression in its interpersonal context. *Handbook of depression*, *2*, 322–339.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry*, *68*, 444–454. doi:10.1001/archgenpsychiatry.2010.189

Kaufman, J., Birmaher, B., Brent, D., Rao, U. M. A., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*, 980–988. doi: http://dx.doi.org/10.1097/00004583-199707000-00021

Kendler, K. S., & Karkowski-Shuman, L. (1997). Stressful life events and genetic liability to major depression: Genetic control of exposure to the environment? *Psychological Medicine*, *27*, 539–547.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry*, *156*, 837–841. doi:10.1176/ajp.156.6.837

Kim, J. H., Martins, S. S., Shmulewitz, D., Santaella, J., Wall, M. M., Keyes, K. M., … Hasin, D. S. (2014). Childhood maltreatment, stressful life events, and alcohol craving in adult drinkers. *Alcoholism: Clinical and Experimental Research*, *38*, 2048–2055. doi:10.1111/acer.12473

Kuras, Y. I., Assaf, N., Thoma, M. V., Gianferante, D., Hanlin, L., Chen, X., … Rohleder, N. (2017). Blunted diurnal cortisol activity in healthy adults with childhood adversity. *Frontiers in Human Neuroscience*, *11*, 574. doi:10.3389/fnhum.2017.00574

Kushner, S. C., Bagby, R. M., & Harkness, K. L. (2017). Stress generation in adolescence: Contributions from five-factor model (FFM) personality traits and childhood maltreatment. *Personality Disorders: Theory, Research, and Treatment*, *8*, 150–161. doi:10.1037/per0000194

Lahey, B. B. (2009). Public health significance of neuroticism. *American Psychologist*, *64*, 241–256. doi:10.1037/a0015309

La Rocque, C. L., Harkness, K. L., & Bagby, R. M. (2014). The differential relation of childhood maltreatment to stress sensitization in adolescent and young adult depression. *Journal of Adolescence*, *37*, 871–882. doi:10.1016/j.adolescence.2014.05.012

Laucht, M., Treutlein, J., Blomeyer, D., Buchmann, A. F., Schmidt, M. H., Esser, G., … Banaschewski, T. (2013). Interactive effects of corticotropin-releasing hormone receptor 1 gene and childhood adversity on depressive symptoms in young adults: Findings from a longitudinal study. *European Neuropsychopharmacology*, *23*, 358–367. doi:10.1016/j.euroneuro.2012.06.002

Liu, R. T., & Alloy, L. B. (2010). Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. *Clinical Psychology Review*, *30*, 582–593. doi:10.1016/j.cpr.2010.04.010

Liu, R. T., Choi, J. Y., Boland, E. M., Mastin, B. M., & Alloy, L. B. (2013). Childhood abuse and stress generation: The mediational effect of depressogenic cognitive styles. *Psychiatry Research*, *206*, 217–222. doi:10.1016/j.psychres.2012.12.001

Luijk, M. P., Velders, F. P., Tharner, A., van Ijzendoorn, M. H., Bakermans-Kranenburg, M. J., Jaddoe, V. W., … Tiemeier, H. (2010). FKBP5 and resistant attachment predict cortisol reactivity in infants: Gene-environment interaction. *Psychoneuroendocrinology*, *35*, 1454–1461. doi:10.1016/j.psyneuen.2010.04.012

Mahon, P. B., Zandi, P. P., Potash, J. B., Nestadt, G., & Wand, G. S. (2013). Genetic association of FKBP5 and CRHR1 with cortisol response to acute psychosocial stress in healthy adults. *Psychopharmacology*, *227*, 231–241. doi:10.1007/s00213-012-2956-x

Manuck, S. B., & McCaffery, J. M. (2014). Gene-environment interaction. *Annual Review of Psychology*, *65*, 41–70. doi:10.1146/annurev-psych-010213-115100

Massing-Schaffer, M., Liu, R. T., Kraines, M. A., Choi, J. Y., & Alloy, L. B. (2015). Elucidating the relation between childhood emotional abuse and depressive symptoms in adulthood: The mediating role of maladaptive interpersonal processes. *Personality and Individual Differences*, *74*, 106–111. doi:10.1016/j.paid.2014.09.045

Masten, A. S., Best, K. M., & Garmezy, N. (1990). Resilience and development: Contributions from the study of children who overcome adversity. *Development and Psychopathology*, *2*, 425–444. doi:10.1017/S0954579400005812

Masten, A. S., Hubbard, J. J., Gest, S. D., Tellegen, A., Garmezy, N., & Ramirez, M. (1999). Competence in the context of adversity: Pathways to resilience and maladaptation from childhood to late adolescence. *Development and Psychopathology*, *11*, 143–169.

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44.

McLaughlin, K. A. (2016). Future directions in childhood adversity and youth psychopathology. *Journal of Clinical Child and Adolescent Psychology*, *45*, 361–382. doi:10.1080/15374416.2015.1110823

McLaughlin, K. A., Conron, K. J., Koenen, K. C., & Gilman, S. E. (2010). Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: A test of the stress sensitization hypothesis in a population-based sample of adults. *Psychological Medicine*, *40*, 1647–1658. doi:10.1017/S0033291709992121

Mickelson, K. D., Kessler, R. C., & Shaver, P. R. (1997). Adult attachment in a nationally representative sample. *Journal of Personality and Social Psychology*, *73*, 1092–1106.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological bulletin*, *133*, 25–45.

Monroe, S. M., & Harkness, K. L. (2005). Life stress, the "kindling" hypothesis, and the recurrence of depression: Considerations from a life stress perspective. *Psychological Review*, *112*, 417–445. doi:10.1037/0033-295x.112.2.417

Morris, M. C., Kouros, C. D., Hellman, N., Rao, U., & Garber, J. (2014). Two prospective studies of changes in stress generation across depressive episodes in adolescents and emerging adults. *Development and Psychopathology*, *26*, 1385–1400. doi:10.1017/s0954579414001096

Musliner, K. L., Seifuddin, F., Judy, J. A., Pirooznia, M., Goes, F. S., & Zandi, P. P. (2015). Polygenic risk, stressful life events and depressive symptoms in older adults: A polygenic score analysis. *Psychological Medicine*, *45*, 1709–1720. doi:10.1017/S0033291714002839

Nikolova, Y. S., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology*, *36*, 1940–1947. doi:10.1038/npp.2011.82

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2014). Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology*, *39*, 1245–1253. doi:10.1038/npp.2013.327

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2015). Amygdala functional connectivity, HPA axis genetic variation, and life stress in children and relations to anxiety and emotion regulation. *Journal of Abnormal Psychology*, *124*, 817–833. doi:10.1037/abn0000094

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, *17*, 117–133.

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin*, *84*, 309–322. doi:10.1037/0033-2909.84.2.309

Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry*, *149*, 999–1010.

Rao, U. M. A., Daley, S. E., & Hammen, C. (2000). Relationship between depression and substance use disorders in adolescent women during the transition to adulthood. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*, 215–222. doi: http://dx.doi.org/10.1097/00004583-200002000-00022

Rice, F., Harold, G. T., & Thapar, A. (2002). Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *Journal of Child Psychology and Psychiatry*, *43*, 1039–1051. doi:10.1111/1469-7610.00231

Romeo, R. D. (2013). The teenage brain: The stress response and the adolescent brain. *Current Directions in Psychological Science*, *22*, 140–145. doi:10.1177/0963721413475445

Roy, A., Gorodetsky, E., Yuan, Q., Goldman, D., & Enoch, M. A. (2010). Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology*, *35*, 1674–1683. doi:10.1038/npp.2009.236

Rudolph, K. D. (2002). Gender differences in emotional responses to interpersonal stress during adolescence. *Journal of Adolescent Health*, *30*, 3–13.

Rudolph, K. D., Hammen, C., Burge, D., Lindberg, N., Herzberg, D., & Daley, S. E. (2000). Toward an interpersonal life-stress model of depression: The developmental context of stress generation. *Development and Psychopathology*, *12*, 215–234.

Salwen, J. K., Hymowitz, G. F., Vivian, D., & O'Leary, K. D. (2014). Childhood abuse, adult interpersonal abuse, and depression in individuals with extreme obesity. *Child Abuse and Neglect*, *38*, 425–433. doi:10.1016/j.chiabu.2013.12.005

Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype greater than environment effects. *Child Development*, *54*, 424–435.

Shapero, B. G., Black, S. K., Liu, R. T., Klugman, J., Bender, R. E., Abramson, L. Y., & Alloy, L. B. (2014). Stressful life events and depression symptoms: The effect of childhood emotional abuse on stress reactivity. *Journal of Clinical Psychology*, *70*, 209–223. doi:10.1002/jclp.22011

Sheikh, H. I., Kryski, K. R., Smith, H. J., Hayden, E. P., & Singh, S. M. (2013). Corticotropin-releasing hormone system polymorphisms are associated with children's cortisol reactivity. *Neuroscience*, *229*, 1–11. doi:10.1016/j.neuroscience.2012.10.056

Shih, J. H., Abela, J. R., & Starrs, C. (2009). Cognitive and interpersonal predictors of stress generation in children of affectively ill parents. *Journal of Abnormal Child Psychology*, *37*, 195–208. doi:10.1007/s10802-008-9267-z

Shih, J. H., Eberhart, N. K., Hammen, C. L., & Brennan, P. A. (2006). Differential exposure and reactivity to interpersonal stress predict sex differences in adolescent depression. *Journal of Clinical Child and Adolescent Psychology*, *35*, 103–115. doi:10.1207/s15374424jccp3501_9

Spangler, G., Johann, M., Ronai, Z., & Zimmermann, P. (2009). Genetic and environmental influence on attachment disorganization. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *50*, 952–961.

Sroufe, L. A. (2000). Early relationships and the development of children. *Infant Mental Health Journal*, *21*, 67–74. doi:10.1002/(SICI)1097-0355(200001/04)21:1/2<67::AID-IMHJ8>3.0.CO;2-2

Starr, L. R., Dienes, K., Li, Y. I., & Shaw, Z. A. (2019). Chronic stress exposure, diurnal cortisol slope, and implications for mood and fatigue: Moderation by multilocus HPA-Axis genetic variation. *Psychoneuroendocrinology*, *100*, 156–163. doi: https://doi.org/10.1016/j.psyneuen.2018.10.003

Starr, L. R., Dienes, K., Stroud, C. B., Shaw, Z. A., Li, Y. I., Mlawer, F., & Huang, M. (2017). Childhood adversity moderates the influence of proximal episodic stress on the cortisol awakening response and depressive symptoms in adolescents. *Development and Psychopathology*, *29*, 1877–1893. doi:10.1017/s0954579417001468

Starr, L. R., Hammen, C., Brennan, P. A., & Najman, J. M. (2012). Serotonin transporter gene as a predictor of stress generation in depression. *Journal of Abnormal Psychology*, *121*, 810–818. doi:10.1037/a0027952

Starr, L. R., Hammen, C., Brennan, P. A., & Najman, J. M. (2013). Relational security moderates the effect of serotonin transporter gene polymorphism (5-HTTLPR) on stress generation and depression among adolescents. *Journal of Abnormal Child Psychology*, *41*, 379–388. doi:10.1007/s10802-012-9682-z

Starr, L. R., Hammen, C., Conway, C. C., Raposa, E., & Brennan, P. A. (2014). Sensitizing effect of early adversity on depressive reactions to later proximal stress: Moderation by polymorphisms in serotonin transporter and corticotropin releasing hormone receptor genes in a 20-year longitudinal study. *Development and Psychopathology*, *26*, 1241–1254. doi:10.1017/s0954579414000996

Starr, L. R., & Huang, M. (2019). HPA-axis multilocus genetic variation moderates associations between environmental stress and depressive symptoms among adolescents. *Development and Psychopathology*, *31*, 1339–1352. doi:10.1017/S0954579418000779.

Steinberg, S. J., & Davila, J. (*2008*). Romantic functioning and depressive symptoms among early adolescent girls: The moderating role of parental emotional availability. *Journal of Clinical Child and Adolescent Psychology*, *37*, 350–362.

Stroud, C. B., Chen, F. R., Doane, L. D., & Granger, D. A. (2016). Individual differences in early adolescents' latent trait cortisol (LTC): Relation to early adversity. *Developmental Psychobiology*, *58*, 700–713. doi:10.1002/dev.21410

Styron, T., & Janoff-Bulman, R. (1997). Childhood attachment and abuse: Long-term effects on adult attachment, depression, and conflict resolution. *Child Abuse and Neglect*, *21*, 1015–1023.

Sumner, J. A., McLaughlin, K. A., Walsh, K., Sheridan, M. A., & Koenen, K. C. (2014). CRHR1 genotype and history of maltreatment predict cortisol reactivity to stress in adolescents. *Psychoneuroendocrinology*, *43*, 71–80. doi:10.1016/j.psyneuen.2014.02.002

Swartz, J. R., Knodt, A. R., Radtke, S. R., & Hariri, A. R. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron*, *85*, 505–511. doi:10.1016/j.neuron.2014.12.055

Tarullo, A. R., & Gunnar, M. (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior*, *50*, 632–639. doi:10.1016/j.yhbeh.2006.06.010

Troop-Gordon, W., Sugimura, N., & Rudolph, K. D. (2017). Responses to interpersonal stress: Normative changes across childhood and the impact of peer victimization. *Child Development*, *88*, 640–657. doi:10.1111/cdev.12617

Tully, E. C., Iacono, W. G., & McGue, M. (2010). Changes in genetic and environmental influences on the development of nicotine dependence and major depressive disorder from middle adolescence to early adulthood. *Development and Psychopathology*, *22*, 831–848. doi:10.1017/S0954579410000490

Uhrlass, D. J., & Gibb, B. E. (2007). Childhood emotional maltreatment and the stress generation model of depression. *Journal of Social and Clinical Psychology*, *26*, 119–130. doi:10.1521/jscp.2007.26.1.119

Uliaszek, A. A., Zinbarg, R. E., Mineka, S., Craske, M. G., Griffith, J. W., Sutton, J. M., … Hammen, C. (2012). A longitudinal examination of stress generation in depressive and anxiety disorders. *Journal of Abnormal Psychology*, *121*, 4–15. doi:10.1037/a0025835

Vrshek-Schallhorn, S., Sapuram, V., & Avery, B. M. (2017). Letter to the editor: Bias in the measurement of bias. Letter regarding 'Citation bias and selective focus on positive findings in the literature on the serotonin transporter gene (5-HTTLPR), life stress and depression'. *Psychological Medicine*, *47*, 187–192. doi:10.1017/s0033291716002178

Vrshek-Schallhorn, S., Stroud, C. B., Mineka, S., Zinbarg, R. E., Adam, E. K., Redei, E. E., … Craske, M. G. (2015). Additive genetic risk from five serotonin system polymorphisms interacts with interpersonal stress to predict depression. *Journal of Abnormal Psychology*, *124*, 776–790. doi:10.1037/abn0000098

Xie, P., Kranzler, H. R., Poling, J., Stein, M. B., Anton, R. F., Farrer, L. A., & Gelernter, J. (2010). Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology*, *35*, 1684–1692. doi:10.1038/npp.2010.37

Zannas, A. S., & Binder, E. B. (2014). Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. *Genes, Brain and Behavior*, *13*, 25–37. doi:10.1111/gbb.12104