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Peer victimization predicts heightened inflammatory reactivity to social stress in cognitively vulnerable adolescents

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Background: During adolescence, peer victimization is a potent type of social stressor that can confer enduring risk for poor mental and physical health. Given recent research implicating inflammation in promoting a variety of serious mental and physical health problems, this study examined the role that peer victimization and cognitive vulnerability (i.e. negative cognitive styles and hopelessness) play in shaping adolescents' pro-inflammatory cytokine responses to an acute social stressor. **Methods:** Adolescent girls at risk for psychopathology (n = 157; M_{age} = 14.73 years; SD = 1.38) were exposed to a laboratory-based social stressor before and after which we assessed salivary levels of three key pro-inflammatory cytokines – interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α). **Results:** As hypothesized, adolescents with greater peer victimization exposure exhibited greater increases in IL-6 and IL1-β in response to the laboratory-based social stressor. Moreover, for all three cytokines individually, as well as for a combined latent factor of inflammation, peer victimization predicted enhanced inflammatory responding most strongly for adolescents with high levels of hopelessness. **Conclusions:** The findings reveal a biological pathway by which peer victimization may interact with cognitive vulnerability to influence health in adolescence. **Keywords:** Peer victimization; cytokines; social stress; hopelessness; adolescence.

Introduction

Being threatened, humiliated, gossiped about, or subtly excluded represent some of life's most unpleasant and painful experiences. Such experiences of peer victimization may be particularly harmful and have lasting effects on health when they occur during adolescence, given that during this developmental period youth develop a strong natural motivation to be accepted by peers. To better understand mechanisms that may underlie these effects, we drew from recent research in psychoneuroimmunology and human social genomics (Miller, Chen, & Parker 2011; Slavich & Cole, 2013) and examined whether experiences of peer victimization influence inflammatory reactivity to social stress in cognitively vulnerable adolescents who are at elevated risk for developing mental and physical health problems over the life span.

Peer victimization and adolescent inflammatory responses to social stress

Adolescence is a period of increased sensitivity to peers, which makes being the target of peer victimization a potent type of social stressor during this time (Somerville, 2013). Decades of research in developmental psychology have demonstrated that youth exposed to peer victimization are at elevated risk for developing mental health problems, including symptoms of anxiety, depression, loneliness, and – in the more serious instances – suicidality (Giletta et al., 2015; Reijntjes, Kamphuis, Prinzie, & Telch 2010), as well as physical health problems, such as sleep disruption (Herge, La Greca, & Chan 2016), fatigue, and loss of appetite (Gini & Pozzoli, 2013; Nixon, Linkie, Coleman, & Fitch 2011). These consequences of victimization persist well beyond the adolescent years, with effects lasting up to several decades (McDougall & Vaillancourt, 2015).

Recently, increasing interest has been focused on elucidating biological pathways that may explain the long-lasting effects of peer victimization on mental and physical health. This research has revealed that youth exposed to peer victimization have higher levels of low-grade systemic inflammation in adulthood (Copeland et al., 2014; Takizawa, Danese, Maughan, & Arseneault 2015). Given the health consequences of elevated inflammation, the immune system may play a key role in channeling the negative effects of peer victimization. One possibility proposed by Social Signal Transduction Theory of Depression is that social stressors get biologically embedded in the body in part by sensitizing the brain and immune system to future social threats (Slavich & Cole, 2013; Slavich & Irwin, 2014). Stressors that

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threaten the social self not only may upregulate acute inflammatory responses but also may lead to neuroinflammatory sensitization, which potentiates a person's inflammatory reactivity to subsequent social stressors and thus confers heightened risk for systemic inflammation and subsequent inflammation-related health problems. Supporting this hypothesis, children raised in abusive family contexts exhibit greater inflammatory responses to laboratory-based social stressors and following recent life stressors (Carpenter et al., 2010; Miller & Chen, 2010). Given adolescents' enhanced sensitivity to peers (Somerville, 2013), peer victimization may be particularly powerful in sensitizing inflammatory responses, thus accentuating the way in which the immune system responds to subsequent social threats. This study represents the first effort to test this hypothesis.

Moderating role of cognitive vulnerability factors

Notably, not all youth are equally affected by peer victimization. The extent to which peer victimization influences adolescent development depends to a significant extent on individual differences in cognitive processes, such as how adolescents perceive and appraise these experiences. For example, adolescents who tend to blame themselves for being victimized, consider these experiences as being stable and uncontrollable, or have pessimistic expectations about their future are at greater risk for developing health problems when exposed to peer victimization (Perren, Ettekal, & Ladd 2013; Prinstein, Cheah, & Guyer 2005; Van Dyk & Nelson, 2014). Cognitive processes may also affect youth's inflammatory reactivity to social stress. Indeed, a key tenant of Social Signal Transduction Theory of Depression is that individuals' perceptions of social threat trigger the neural and physiological responses that upregulate pro-inflammatory gene expression and affect health (Slavich & Irwin, 2014). Thus, according to this theory, differences in cognitive processes are essential for understanding which individuals are more likely to mount stronger inflammatory responses to social stressors. Despite having a clear theoretical model of these dynamics, though, surprisingly little research has investigated how cognitive factors influence inflammatory responses to stress, alone or in combination with a history of social stress.

To address these issues, this study focused on two cognitive factors that are highly relevant for understanding individual differences in responses to stressful events: negative cognitive style and hopelessness. Individuals with negative cognitive styles tend to attribute negative events to internal, stable, and global causes. Moreover, they draw negative self-referential conclusions ('Something is wrong with me') and believe that such events will have dramatic future consequences. Hopeless individuals have pessimistic expectations about their future and believe that nothing can be done to change it. Both negative cognitive styles and hopelessness act as cognitive vulnerabilities for internalizing psychopathology, especially in the presence of stressful life events (Dixon, Heppner, Burnett, & Lips 1993; Gibb & Coles, 2005). Some indirect evidence also links these cognitions to inflammation. For instance, pessimism – a construct highly related to hopelessness – and lack of hope when facing a social stressor are associated with elevated levels of systemic inflammation and greater acute inflammatory responses (Aschbacher et al., 2012; Roy et al., 2010). However, no studies to date have examined whether these cognitive vulnerabilities moderate the effect of peer victimization on stress-induced inflammatory responses.

The present study

In this study, we tested whether a history of peer victimization during adolescence sensitizes inflammatory responses to social stress and whether these effects are moderated by cognitive vulnerability. Adolescent girls at high risk for psychopathology were exposed to a standardized laboratory-based social stressor before and after which pro-inflammatory cytokines were assessed from saliva. Mounting evidence provides support for the validity and utility of salivary cytokines (see Online Appendix S1 for more details). Similarly to serum cytokines, salivary cytokines have been shown to respond to acute stress (Slavish, Graham-Engeland, Smyth, & Engeland 2015), and these responses are associated with emotional and physiological stress reactivity (e.g. Izawa et al., 2013). Moreover, existing work indicates that cytokines in the oral cavity may reach other body parts, highlighting their potential to influence health. Most importantly, salivary cytokine activity can be detected by the brain via afferent nerves (Romeo, Tio, Rahman, Chiappelli, & Taylor 2001), in turn altering neural activity (O'Connor, Irwin, & Wellisch 2009) and eventually contributing to the development of psychopathological symptoms (Keller, El-Sheikh, Vaughn, & Granger 2010). Thus, although salivary cytokine levels do not necessarily reflect cytokines levels in serum (Riis et al., 2014), they are important given their reactivity to stress, ability to influence neural function, and possible utility in predicting poor health outcomes.

We hypothesized that girls more frequently exposed to peer victimization would show greater inflammatory responses to the laboratory-based social stressor. Moreover, we hypothesized that these effects would be strongest for more cognitively vulnerable girls, as indexed by their levels of negative cognitive styles or hopelessness. Given past evidence that peer victimization in adolescence predicts greater systemic inflammation in adulthood (Copeland et al., 2014), we also explored associations with

levels of baseline (prestress) pro-inflammatory cytokines.

We specifically tested these hypotheses among adolescent girls with a history of mental health concerns because this population of youth may be particularly vulnerable to the effects of peer victimization on inflammatory responses. For example, girls are more sensitive and reactive to social stressors than boys (Guyer, McClure-Tone, Shiffrin, Pine, & Nelson 2009), and initial evidence indicates that women display stronger pro-inflammatory responses to acute stressors than do men (Bekhbat & Neigh, 2017). Moreover, it is well-known that psychopathological symptoms increase the risk for being victimized (Reijntjes et al., 2010), and youth with a history of mental health difficulties exhibit more cognitive vulnerabilities and exacerbated physiological responses to social stress (Lopez-Duran, Kovacs, & George 2009).

Method

Participants

Participants were 157 adolescent girls (M_{age} = 14.73 years; *SD* = 1.38) at high risk for psychopathology. Most participants were born in the United States (93%), and they all lived in the southeast of the country. The sample was ethnically diverse, with most girls identifying themselves as Caucasian (65%), 24.2% as African-American, 1.9% as Latina, and 8.9% as mixed ethnicity or being from other ethnic minorities. Recruitment occurred from a wide range of referral sources, including local inpatient units, outpatient facilities and practices, local advertisements, and mass emails to university employees. Eligibility criteria included the following: (a) being a girl, (b) between 12 and 16 years old, (c) with a history of mental health concerns in the 2 years prior the study, and (d) who has a primary caregiver available to take part in the study. Eligibility was determined via telephone screening interviews with the adolescent's primary caregiver using items from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997) to assess adolescents' prior mental health. A history of mental health concerns was defined as having a diagnosis, significant psychiatric symptoms (e.g. mood disorders), or having received treatment. Adolescents with active psychosis, mental retardation, or any pervasive developmental disorder were considered ineligible (see Appendix S1 for more details).

Procedure and ethical considerations

Participants were invited to a laboratory session together with their primary caregiver and a close same-aged female friend. Upon arrival at the laboratory, the primary caregivers gave informed consent, and both the participants and their friends provided their assent. During the laboratory session, participants took part in a number of different tasks. Relevant for the purpose of this study, first, adolescents and their friends individually completed a series of self-report measures. Approximately 3 hr from the beginning of the visit, participants underwent an in vivo social stressor, a modified version of the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer 1993). Specifically, participants were told to pretend to audition for a reality show about how adolescents make friends and interact with other teens. After 1 min of preparation, they were asked to give a 3-min audition speech while they were oriented toward a camera connected to a closed-circuit feedback screen displaying their own live image. A young adult male, introduced as a judge, was present during the speech, ostensibly evaluating the quality of the performance. These procedures were used to enhance the social-evaluative nature of the task. Similar laboratory stressors tasks involving social evaluation and threatening individuals' social identity are commonly used to induce physiological responses, including inflammatory responses (Marsland, Walsh, Lockwood, & John-Henderson 2017; Slavish et al., 2015). To avoid possible social buffering effects due to the presence of supportive others (Gunnar & Hostinar, 2015), adolescents' caregiver and friend were not present during the social stressor. Saliva samples were collected just before (prestress) and 40 min after (poststress) the speech. This timeframe was chosen based on existing work suggesting that cytokines may peak sooner in saliva than blood (Slavish et al., 2015), with 40 min poststress allowing a sufficient time to capture stress reactivity (Newton et al., 2017). After the speech, participants competed additional self-report measures. All procedures were approved by the university human subjects committee.

Measures

Pro-inflammatory cytokines. To measure inflammatory responses to the social stressor, three pro-inflammatory cytokines were assessed – namely, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These cytokines were selected a priori because of their reactivity to social stressors as well as their involvement in the acute phase immune response and in the development of poor physical and mental health symptoms (Slavich & Irwin, 2014; Slavish et al., 2015; see Appendix S1 for more details). Cytokines levels were assessed via saliva samples, which have been shown to be valid for assessing cytokine reactivity while avoiding more invasive procedures like venipuncture (Slavish et al., 2015). Saliva samples were collected using a SalivaBio Oral Swab (Salimetrics, State College, PA). Samples were subsequently stored at −25°C until analysis. The immunoassays were conducted using a Bio-Plex 200 (Bio-Rad, Hercules, CA) at the UNC Cytokine and Biomarker Analysis Facility. All assays were performed according to the guideline recommendations of the manufacturer (R&D Systems, Minneapolis, MN) using high-sensitivity multiplex immunoassay kits, which have a mean minimal detectable dose of 0.29 pg/ml for TNF-α, 0.08 pg/ml for IL-1β, and 0.14 pg/ml for IL-6. As reported by the manufacturer, the mean intra-assay coefficients of variation are 5.2% for IL-6 and 5.3% for IL-1β and TNF-α, and the mean inter-assay coefficients of variation are 9.6% for IL-6 and TNF-α, and 12.8% for IL-1β. A logarithmic transformation was applied to all cytokine values to correct for skewness. After transforming the data, an extreme outlier was identified (6 *SD*s from the mean, for IL-1β at poststress); thus, this value was winsorized to the highest value in the distribution within 3 *SD*s.[1]

Peer victimization. Adolescents' close friends who accompanied them to the laboratory visit completed the Revised Peer Experiences Questionnaire (RPEQ; Prinstein, Boergers, & Vernberg 2001; see Appendix S1 for more details). This measure included 13 items assessing different forms of peer victimization (i.e. overt, relational, and reputational). Adolescents' best friends reported on a scale from 1 ('never') to 5 ('a few times a week') how often in the past year each experience occurred to their friend. For the primary analyses, a total peer victimization score was computed by averaging across the 13 items, with higher scores indicating higher levels of peer victimization (Cronbach's α = .91). For supplemental analyses, three subscales of peer victimization were derived: overt, relational, and reputational victimization (see Appendix S1, including Online Table S1). To correct for skewness, a

logarithmic transformation was applied to the total peer victimization score as well as all the subscales.

Negative cognitive style. Adolescents completed the Adolescent Cognitive Style Questionnaire (ACSQ; Hankin & Abramson, 2002). This measure assesses inferential style about causes, consequences, and the self in response to hypothetical scenarios describing negative situations that may commonly occur to adolescents. For each scenario, participants rated on a scale from 1 to 7 to what extent they attributed the negative event to internal (vs. external), stable (vs. unstable), and global (vs. specific) causes. Furthermore, they rated to what extent they thought the negative event (a) would have had future negative consequences and (b) implied that their self was flawed. Given the focus of this study on social stress, only five scenarios describing interpersonal situations (e.g. 'You want to go to a big party, but nobody invites you') were administered. Adolescent inferential styles about causes, consequences, and the self were highly correlated (r = .72–.76; p < .001); thus, consistent with past research (Auerbach, Ho, & Kim 2014), an overall measure of negative cognitive style was computed by averaging adolescents' responses to all items, with higher scores indicating higher negative cognitive style (Cronbach's α = .92).

Hopelessness. Adolescents completed the Hopelessness Scale for Children (HSC; Kazdin, Rodgers, & Colbus 1986). This measure includes 17 items assessing youth expectations about their future (e.g. 'I might as well give up because I can't make things better for myself'). Adolescents were asked to indicate whether each item was true or false for them. Nine positive items were reverse coded, and responses to all 17 items were summed in an overall measure of hopelessness, with higher scores indicating higher levels of hopelessness (Cronbach's α = .77).

Covariates. To account for individual differences in basic demographic characteristics, the primary analyses adjusted for ethnicity and age. Depressive symptoms were also included as a covariate, given the known associations with cognitive vulnerability as well as inflammation, including inflammatory responses to acute stressors (Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser 2013; see Table S2). Moreover, supplemental analyses were conducted adjusting for additional variables that have been previously linked to inflammation (Slavish et al., 2015), including socioeconomic status (SES), family-related stress, body mass index (BMI), recent illness, same-day caffeine intake, smoking, birth control, and medication use (see Appendix S1 for more details).

Analytic strategy

Two main sets of analyses were performed. First, consistent with most prior work on inflammatory activity (Marsland et al., 2017), reactivity to the laboratory-based social stressor was examined separately for each pro-inflammatory cytokine. These analyses allow comparing results from this study to previous findings and offer important information about the specificity of each inflammatory marker. To examine changes in cytokine levels in response to the social stressor, a series of latent change score models was conducted using a structural equation modeling (*SEM*) approach (McArdle, 2009; see Online Figure S1 for more details). Unconditional models were initially estimated followed by three conditional models for each cytokine. Model 1 included the main effects of total peer victimization, negative cognitive style, and hopelessness on both prestress cytokines and the cytokine change scores. In Models 2 and 3, the moderating role of cognitive vulnerabilities was examined by adding the interaction effects between total peer victimization and negative cognitive style (Model 2) or hopelessness (Model 3), respectively.

Second, the three pro-inflammatory cytokines were used as indicators to create a latent factor of inflammation (see Appendix S1 for more details). Although rarely used in the inflammation literature, this approach has a number of advantages, including accounting for measurement error (Burt & Obradović, 2013) and creating a more reliable inflammatory phenotype. In these models, changes in the inflammatory phenotype were defined by a second-order latent factor (i.e. Δ latent change score; see Figure 1; Burt & Obradović, 2013; McArdle, 2009). Paralleling analyses for each cytokine, first an unconditional latent change score model was estimated; subsequently, three conditional models were estimated, examining the main effects of peer victimization and cognitive vulnerabilities (Model 1) and their interaction effects (Models 2 and 3), respectively.

All analyses adjusted for three primary covariates: age, ethnicity, and depressive symptoms. The proportion of missing data was minimal (Table 1), so listwise deletion was used to handle missing data on the exogenous variables. Full information maximum-likelihood estimation with robust standard errors was used to handle missing data on the endogenous variables. Continuous predictors were centered before analyses. Significant interactions were probed by computing simple slopes and regions of significance. Analyses were conducted in Mplus version 7.11 (Muthén & Muthén, 1998–2012).

Results

Descriptive statistics and bivariate correlations among the main study variables are presented in Tables 1 and S2, respectively.

Latent change score models by pro-inflammatory cytokine

Changes in cytokines in response to the social stressor. Three unconditional latent change score models were conducted to examine mean changes and individual differences in cytokine responses to the social stressor. For all cytokines, a nonsignificant mean for the latent change score was observed (IL-6: b = .03, 95% CI = [−0.02, 0.08], p = .254; IL-1β: b = .02, 95% CI = [−0.02, 0.07], p = .34; TNF-α: b = −.03, 95% CI = [−0.08, 0.03], p = .302), indicating no mean changes in cytokine levels from pre- to poststressor. However, significant variation was found in the mean scores (IL-6: b = .09, 95% CI = [0.06, 0.12], p < .001; IL-1β: b = .08, 95% CI = [0.05, 0.12], p < .001; TNF-α: b = .10, 95% CI = [0.07, 0.13], p < .001), suggesting inter-individual differences in within-person changes responses to the social stressor.

Predicting cytokine responses to the social stressor. Table 2 presents estimates from the conditional latent change score models predicting changes in pro-inflammatory cytokines in response to the social stressor, separately for each cytokine. In Model 1, peer victimization significantly predicted changes in IL-6 and IL-1β. That is, after accounting for covariates and for participants' prestress cytokines, girls with higher levels of peer victimization

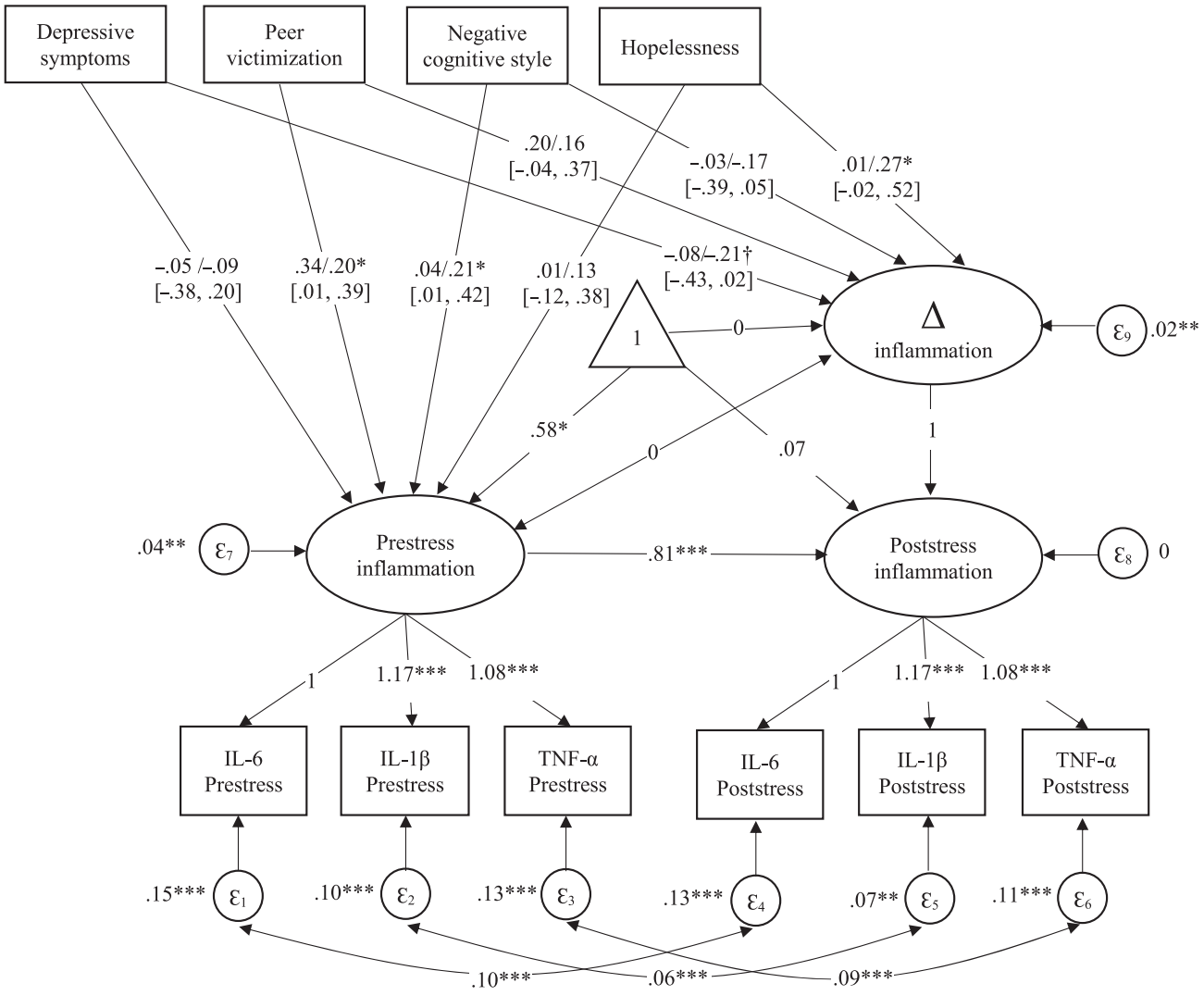

Figure 1 Conditional latent change score model with latent factor of inflammation. R^2 = .17, p = .034, for prestress inflammation. R^2 = .12, p = .105, for Δ inflammation. Unstandardized estimates are reported. Standardized estimates are shown after the slash, with 95% CI in square brackets

showed greater cytokine reactivity to the social stressor. Moreover, a main effect of hopelessness was revealed on changes in IL-1β.[2] Neither peer victimization nor cognitive vulnerability predicted changes in TNF-α. Significant main effects also emerged on prestress cytokines; peer victimization was associated with higher prestress TNF-α, and negative cognitive style with higher prestress IL-1β (Table S3).

In Models 2 and 3, the moderating role of cognitive vulnerabilities was examined. Across all models, no significant interactions were found between peer victimization and negative cognitive style, neither on cytokine changes (Table 2, Model 2) nor on prestress cytokines (Table S3). However, consistently across all cytokines, a significant interaction emerged between peer victimization and hopelessness on cytokine changes (Table 2, Model 3). Probing these interactions indicated that peer victimization was associated with increases in pro-inflammatory cytokines during the social stressor among adolescents with high, but not low, levels of hopelessness (Figures S2–S4). Hopelessness did not moderate the effects of peer victimization on prestress cytokine levels (Table S3).

Latent change score models with inflammatory phenotype

Results from the measurement models and the unconditional latent change score model with the inflammatory phenotype are discussed in Appendix S1 (see also Tables S4 and S5). In the first conditional model (Model 1), only hopelessness predicted changes in the inflammatory phenotype. Main effects of peer victimization and negative cognitive style on prestress inflammation were revealed, indicating that adolescents with a history of peer victimization and those with more negative cognitive styles had higher levels of inflammation before the social stressor (Figure 1).

In Model 2, negative cognitive style did not moderate the effects of peer victimization either on changes in inflammation (b = .10; β = .09, 95% CI = [−0.11, 0.30], p = .377; total R^2 = .13, p = .086) or on prestress inflammation (b = .01; β = .007, 95% CI = [−0.18, 0.20], p = .946; total R^2 = .17, p = .033). In Model 3, a significant interaction between peer victimization and hopelessness was revealed on the inflammation latent change factor (b = .13; β = .37, 95% CI = [0.22, 0.53], p < .001; total R^2 = .26, p = .002). Probing this interaction revealed that peer victimization was associated with greater increases in inflammation in response to the social stressor for youth exhibiting high (b = .57, 95% CI = [0.26, 0.87], p < .001), but not low (b = −.27, 95% CI = [−0.56, 0.03], p = .080), levels of hopelessness (Figure 2). Again, hopelessness did not moderate the effect of peer victimization on prestress inflammation (b = −.005; β = −.01, 95% CI = [−0.18, 0.16], p = .902; total R^2 = .17, p = .035).

Table 1 Descriptive statistics of main study variables

	N	Mean (*SD*)
Pro-inflammatory cytokines (pg/ml)		
IL-6		
Prestress	156	7.67 (12.71)
Poststress	155	7.90 (10.69)
IL-1β		
Prestress	157	584.55 (538.54)
Poststress	157	602.58 (602.98)
TNF-α		
Prestress	155	5.99 (5.98)
Poststress	149	5.61 (4.98)
Total peer victimization	155	1.56 (0.54)
Overt victimization	155	1.23 (0.44)
Relational victimization	153	1.60 (0.64)
Reputational victimization	155	1.78 (0.88)
Negative cognitive style	157	3.12 (1.14)
Hopelessness	157	3.92 (3.24)
Depressive symptoms	157	0.57 (0.44)

IL-6, interleukin-6; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α. Raw values are presented; yet, cytokines values and the peer victimization measures were log transformed before analysis.

Supplementary analyses

Two sets of supplementary analyses were conducted to examine the robustness and consistency of these findings. First, latent change score models with the latent factor of inflammation (similar to the one displayed in Figure 1) were estimated while controlling for additional covariates (SES, family-related stress, BMI, recent illness, same-day caffeine intake, smoking, birth control, and medication use). Results from these models (Table S6) were highly consistent with those reported above, including a significant interaction effect between hopelessness and peer victimization on the inflammation latent change factor.

Second, latent change score models with the latent factor of inflammation were estimated separately for each victimization subtype (overt, relational, and reputational victimization). Again, results emerged to be consistent across all three victimization subtypes, with significant interaction effects between peer victimization and hopelessness on the inflammation latent change factor (Tables S7 and S8).[3]

Discussion

Although substantial research has demonstrated that experiences of peer victimization in adolescence pose enduring risk for mental and physical health (McDougall & Vaillancourt, 2015), we still have a relatively poor understanding of mechanisms that

Table 2 Prediction of latent change scores of cytokines by peer victimization and cognitive vulnerabilities

	ΔIL-6 (*N* = 155)			ΔIL-1β (*N* = 155)			ΔTNF-α (*N* = 153)		
Model and predictor	β	95% CI	*b*	β	95% CI	*b*	β	95% CI	*b*
Model 1: Main effects		R^2 = .14, p = .016			R^2 = .26, p < .001			R^2 = .23, p = .008	
Age	.01	[−0.12, 0.14]	.002	.08	[−0.04, 0.20]	.02	.03	[−0.12, 0.17]	.01
Ethnicity	.04	[−0.11, 0.19]	.03	.08	[−0.05, 0.22]	.05	.26**	[0.10, 0.41]	.17
Depressive symptoms	−.04	[−0.25, 0.18]	−.03	−.22**	[−0.35, −0.09]	−.15	−.08	[−0.24, 0.09]	−.06
Prestress cytokine levels	−.36***	[−0.52, −0.20]	−.24	−.43***	[−0.57, −0.30]	−.30	−.42***	[−0.61, −0.22]	−.30
Total peer victimization	.18*	[0.03, 0.32]	.39	.17**	[0.05, 0.29]	.37	−.04	[−0.17, 0.10]	−.08
Negative cognitive style	−.06	[−0.23, 0.12]	−.02	−.14†	[−0.29, 0.01]	−.04	−.02	[−0.19, 0.14]	−.01
Hopelessness	.09	[−0.10, 0.28]	.01	.26**	[0.09, 0.44]	.02	.12	[−0.03, 0.28]	.01
Model 2: Interaction effect		R^2 = .16, p = .007			R^2 = .26, p < .001			R^2 = .23, p = .008	
Total peer victimization × Negative cognitive style	.13	[−0.03, 0.29]	.26	.01	[−0.13, 0.14]	.01	.05	[−0.07, 0.17]	.11
Model 3: Interaction effect		R^2 = .17, p = .003			R^2 = .33, p < .001			R^2 = .27, p = .001	
Total peer victimization × Hopelessness	.17*	[0.03, 0.31]	.11	.26***	[0.14, 0.38]	.16	.20**	[0.08, 0.32]	.14

ΔIL-6, latent change score for interleukin-6; ΔIL-1β, latent change score for interleukin-1β; ΔTNF-α, latent change score for tumor necrosis factor-α. Ethnicity was coded as nonwhite=0 and white=1.
95% CI = 95% confidence intervals for standardized coefficients (βs).
†p < .10; *p < .05; **p < .01; ***p < .001.

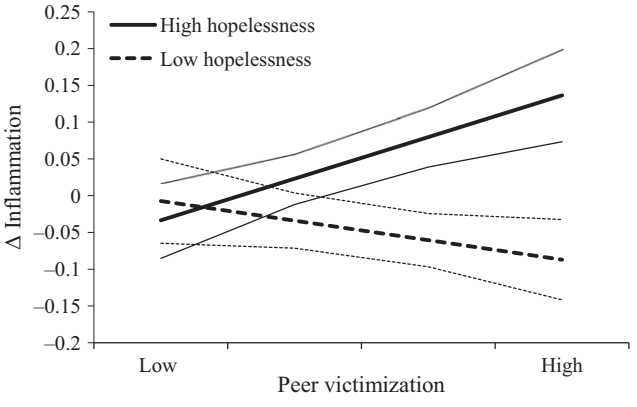

Figure 2 Interaction effect between peer victimization and hopelessness on acute inflammatory responses to the laboratory-based social stressor. Δ inflammation = latent change score for inflammation. 'Low' and 'High' peer victimization and hopelessness indicate scores one standard deviation below and above the mean, respectively. The thinner lines represent 95% confidence intervals. The lower and upper bounds of the regions of significance on hopelessness were −1.13 *SD* and 0.14 *SD* from the mean. These values indicate that peer victimization was associated with increases in inflammation among adolescents with hopelessness levels >0.14 *SD* from the mean, but with decreases in inflammation among adolescents with hopelessness levels lower than approximately 1 *SD* from the mean

underlie these effects. This study addressed this important issue by examining whether peer victimization is associated with acute inflammatory responses to social stress and whether individual differences in cognitive vulnerability moderate this effect. Results revealed that adolescents more frequently exposed to peer victimization exhibited greater inflammatory responses to a standardized laboratory-based social stressor, as indexed by the pro-inflammatory cytokines IL-6 and IL-1β, and that these effects were strongest for youth with high levels of hopelessness. A conjoint effect of peer victimization and hopelessness emerged when examining the three cytokines separately as well as combined, as a 'pro-inflammatory phenotype'. In addition, this effect was robust to several confounders (e.g. SES, BMI) and was consistent across the different peer victimization subtypes.

These findings are consistent with the formulation that adolescence is a developmental period marked by heightened sensitivity to peer interactions (Somerville, 2013), during which victimization and similar social stressors may impact how the adolescent immune system responds to subsequent social threats (Carpenter et al., 2010; Murphy, Slavich, Rohleder, & Miller 2013). Specifically, consistent with existing theoretical frameworks (Miller et al., 2011; Slavich & Irwin, 2014), the present data suggest that a history of peer victimization – particularly among cognitively vulnerable youth – is associated with increased inflammatory reactivity to social stress (Slavich & Irwin, 2014). As compared with their peers, when confronted with the same threatening social situations, adolescents with a history of peer victimization may display enhanced inflammatory responses. Notably, these adolescents also had higher levels of inflammation before the laboratory-based social stressor, as indicated by the significant effect of peer victimization on the inflammatory phenotype at baseline (prestress). This finding suggests that peer victimization may be related to enduring, not only reactive and transient, elevated levels of pro-inflammatory cytokines that, in turn, may result in low-grade systemic inflammation, as shown in prior work (e.g. Copeland et al., 2014). In the long term, these inflammatory responses can contribute to the development a number of mental and physical health concerns, including internalizing symptoms (Slavich & Irwin, 2014), sleep disturbances, and fatigue (Irwin & Cole, 2011), all of which have been previously associated with peer victimization (Herge et al., 2016; Reijntjes et al., 2010). Thus, sensitization of inflammatory reactivity may represent a potential mechanism through which adolescent peer victimization causes long-term changes in well-being.

This hypothesis is in line with other recent evidence linking peer victimization to a pattern of altered neurophysiological responses. For example, youth with a history of peer victimization have greater neural responses to social threats in brain regions that process social disconnection (e.g. dorsal anterior cingulate cortex; Rudolph, Miernicki, Troop-Gordon, Davis, & Telzer 2016). Interestingly, activation in these same brain regions is associated with inflammatory responses to social stressors (Slavich, Way, Eisenberger, & Taylor 2010). Moreover, peer victimization is associated with blunted hypothalamic–pituitary–adrenal (HPA) axis responses to social stress (Ouellet-Morin et al., 2011). Given the role of the HPA axis in regulating pro-inflammatory gene expression, this evidence suggests that the effects of peer victimization on inflammatory responses may be mediated at least, in part, by the HPA axis (Slavich & Cole, 2013).

A major contribution of this study pertains to the analysis of the conjoint effect of social-environmental and cognitive factors on inflammatory responses to social stress. Partial support was found for the study hypotheses, as hopelessness, but not negative cognitive styles, moderated the effects of peer victimization on stress-induced inflammation. What could explain this effect of hopelessness? Because hopelessness involves having negative expectations about the future and a sense of helplessness that strongly affect how individuals appraise life situations, one possibility is that adolescents who are high in hopelessness experience peer victimization and similar social stressors (including the laboratory stressor) as being particularly threatening and difficult to overcome. These subjective perceptions may facilitate the sensitization effects of peer victimization, thereby increasing sensitivity to new threatening social situations and activating the social signal

transduction pathways that eventually result in increased pro-inflammatory cytokine activity (Slavich & Cole, 2013). However, for victimized adolescents who are able to remain hopeful and hold optimistic beliefs about their future, exposure to the same situations may not result in increased inflammation. On the contrary, results suggest that among those participants with very low levels of hopelessness, peer victimization tended to be negatively associated with stress-induced inflammatory responses. Although this unexpected trend was not consistent across the inflammatory markers and should be taken with caution, it may suggest a process of habituation to stress – that is, an attenuated response as a result of repeated exposure to social stressors. This interpretation is consistent with prior work indicating that, in response to a repeated TSST, individuals with high levels of purpose in life (a construct strongly related to low hopelessness) show habituation rather than sensitization of inflammatory responses (Thoma et al., 2017). Thus, in the context of high levels of peer victimization, being hopeless may enhance inflammatory stress responses, whereas remaining hopeful despite a history of social difficulties may be helpful for buffering inflammatory responses to new social stressors. In sum, supporting research in developmental psychology, the present data demonstrate that the extent to which peer victimization poses health risks depends largely on adolescents' cognitions.

Contrary to hopelessness, negative cognitive styles did not emerge as a relevant factor in moderating the effects of peer victimization on inflammatory responses. One possible explanation is that negative cognitive styles reflect general tendencies in response to an *actual* negative event. Indeed, negative cognitive styles were assessed across hypothetical scenarios of actual negative social situations (e.g. 'You want to go to a big party, but nobody invites you'). However, the laboratory-based social stressor was a potentially negative social experience: adolescents could expect to fail but also to perform well. Because hopelessness reflects the tendency to expect the worst from the future, hopeless girls likely expected the laboratory-based social stressor to be a certain failure, but this was not necessarily the case for girls with negative cognitive styles. Hence, for hopeless girls with a history of peer victimization, but not for those with negative cognitive styles, the laboratory-based social stressor paralleled the kind of threatening experiences they had with peers in the past, leading to increased inflammatory responses.

Future work is needed to identify other psychological processes that may alter environmental effects on inflammatory responses. Based on depression research, this study examined negative cognitive styles and hopelessness; yet, individual differences in personality traits (e.g. neuroticism, rejection sensitivity) and self-esteem may also play a central role in affecting individuals' perceptions and eventually inflammatory responses. Social relationships should also be considered as possible moderating factors. Indeed, the negative consequences of peer victimization tend to be attenuated among adolescents with more supportive friends or parents (e.g. Hodges, Boivin, Vitaro, & Bukowski 1999), and friends may buffer physiological stress responses in adolescence (Gunnar & Hostinar, 2015). Furthermore, extensive work among adults shows that social support is associated with lower levels of systemic inflammation (Fagundes, Bennett, Derry, & Kiecolt-Glaser 2011) and may also reduce the link between stress and inflammatory responses (Mezuk, Roux, & Seeman 2010). Thus, further research is warranted to investigate whether positive social relationships can buffer the effects of peer victimization on inflammatory stress responses.

Findings from this study should be interpreted in light of a number of limitations. First, cytokines were measured in saliva rather than blood. Although an increasing number of studies have established validity for saliva assessments of cytokines (Slavish et al., 2015), blood remains the gold standard and, to date, the association between blood and saliva levels cytokines is still poorly understood. Second, the sample included only adolescent girls with a history of psychopathology, thus limiting the generalizability of the findings. Adolescence is a developmental period in which there is heightened sensitivity to peer difficulties, and several lines of research are consistent with the idea that girls and adolescents with a history of mental health problems may show more pronounced inflammatory responses to social stress as a result of a peer victimization. However, in adolescence, experiences of peer victimization are equally common across gender (Casper & Card, 2017), and they predict poor health for both boys and girls even after accounting for history of psychopathology (e.g. Reijntjes et al., 2010). Thus, there are reasons to expect that results from this study may extend to other populations of youth, including boys and low-risk adolescents, but replications of these findings in different populations are sorely needed. Finally, both peer victimization and inflammatory responses were assessed at a single time point. Longitudinal designs are needed to examine changes in stress-induced inflammatory responses over time as a function of peer victimization.

Despite these limitations, this study is the first to demonstrate that peer victimization in adolescence is associated with increased inflammatory reactivity to a subsequent laboratory-based social stressor, especially for youth exhibiting high levels of hopelessness. These findings are thus important as they elucidate a possible pathway by which peer victimization in cognitive vulnerable youth alters biological processes that in turn may affect mental and physical health over the life span.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Additional information on validity and utility of salivary cytokines, additional information on study sample, additional information on pro-inflammatory cytokines, additional information on peer victimization measure, exploratory factor analysis of peer victimization measure, additional information on study covariates, construction of latent factor of inflammation, results from measurement models of latent factor of inflammation, and results from unconditional latent change score model with latent factor of inflammation.

Figure S1. Unconditional latent change score model of cytokine reactivity.

Figure S2. Interaction effect between peer victimization and hopelessness on IL-6 changes in response to the laboratorybased social stressor.

Figure S3. Interaction effect between peer victimization and hopelessness on IL-1β changes in response to the laboratory-based social stressor.

Figure S4. Interaction effect between peer victimization and hopelessness on TNF-α changes in response to the laboratory-based social stressor.

Table S1. Factor loadings from exploratory factor analysis of peer victimization measure.

Table S2. Bivariate correlations among main study variables.

Table S3. Prediction of prestress cytokines.

Table S4. Model fit indices and model fit comparisons of measurement models of latent factor of inflammation.

Table S5. Model fit indices for latent change score models with latent factor of inflammation.

Table S6. Results from conditional latent change score model with latent factor of inflammation adjusting for additional covariates.

Table S7. Prediction of second-order latent change score of inflammation separately by peer victimization subtype.

Table S8. Prediction of prestress inflammation latent factor separately by peer victimization subtype.

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Key points

- Peer victimization in adolescence confers risk for subsequent poor mental and physical health, especially among cognitively vulnerable youth.
- Little is known about why peer victimization has deleterious and enduring consequences.
- This study showed that among high-risk adolescent girls, peer victimization predicted pro-inflammatory cytokine reactivity to a laboratory-based social stressor.
- Hopelessness moderated the effect of peer victimization, with high hopeless girls displaying the strongest inflammatory responses to the laboratory-based social stressor.
- Future peer victimization research should pay increased attention to the immune system functioning, as it may represent a pathway by which peer victimization influences health, particularly among adolescents with high cognitive vulnerability.

Notes

1. An additional eight cytokine values (for IL-6 and IL-1β at prestress, and for TNF-α at pre- and poststress) were found to range between 3 and 3.5 *SD*s from the mean. We opted not to winsorize these values, given that they did not deviate excessively from the other values in the distribution. Thus, in the analyses presented here, only the one extreme value (6 *SD*s from the mean) was winsorized. Notably, this approach did not change the rank ordering of the individuals. Moreover, additional analyses using all winsorized values showed identical results.

2. The (opposite) effects of hopelessness and depressive symptoms on changes in IL-1β emerged only when both predictors were simultaneously included in the model. Neither hopelessness nor depressive symptoms predicted changes in IL-1β when the other predictor was not accounted for. The same findings emerged in the latent change score model with the latent factor of inflammation. However, all other models yielded the same results when no covariates were included (age, ethnicity, and depressive symptoms).

3. For all three victimization subtypes, significant interactions with hopelessness were found even when accounting for the main effects of the other two victimization subtypes.

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