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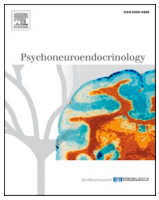

Positive and negative emotion are associated with generalized transcriptional activation in immune cells

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ABSTRACT

Alterations in immune system gene expression have been implicated in psychopathology, but it remains unclear whether similar associations occur for intraindividual variations in emotion. The present study examined whether positive emotion and negative emotion were related to expression of pro-inflammatory and antiviral genes in circulating leukocytes from a community sample of 90 adolescents (M_{age} = 16.3 years, SD = 0.7; 51.1% female). Adolescents reported their positive emotion and negative emotion and provided blood samples twice, five weeks apart. Using a multilevel analytic framework, we found that within-individual increases in positive emotion were associated with reduced expression of both pro-inflammatory and Type I interferon (IFN) response genes, even after adjusting for demographic and biological covariates, and for leukocyte subset abundance. By contrast, increases in negative emotion were related to higher expression of pro-inflammatory and Type I IFN genes. When tested in the same model, only associations with positive emotion emerged as significant, and increases in overall emotional valence were associated with both lower pro-inflammatory and antiviral gene expression. These results are distinct from the previously observed Conserved Transcriptional Response to Adversity (CTRA) gene regulation pattern characterized by reciprocal changes in pro-inflammatory and antiviral gene expression and may reflect alterations in generalized immunologic activation. These findings highlight one biological pathway by which emotion may potentially impact health and physiological function in the context of the immune system, and future studies can investigate whether fostering positive emotion may promote adolescent health through changes in the immune system.

1. Introduction

The immune system has been implicated in mental health and depressive symptoms, such that individuals with poorer mental health tend to have greater systemic inflammation as indicated by circulating protein inflammatory markers and upregulated expression of pro-inflammatory genes in circulating immune cells (Chiang et al., 2019; Frank et al., 2021; Moisan et al., 2021; Slavich and Irwin, 2014). Further, higher chronic and acute levels of inflammation have been prospectively related to depression (Gimeno et al., 2009; Iob et al., 2020; Steptoe et al., 2015). Neural and endocrine signals (e.g., glucocorticoids, catecholamines) can act on leukocytes to modify immune function, and greater pro-inflammatory gene expression has been related to both lower levels of indicators of positive mental health (i.e., psychological flourishing, mental well-being; Fredrickson et al., 2015) and higher levels of psychopathology (i.e., depression, post-traumatic stress disorder; Cole, 2019; Slavich and Irwin, 2014). Despite these associations, it remains unclear how ephemeral (e.g., daily) positive and negative

Abbreviations: IFN, Type I interferon.

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emotional states relate to immune system function. Such associations may be particularly important during adolescence, when youth show greater emotional intensity compared to adults and younger children and are still developing strategies for emotion regulation (e.g., Bailen et al., 2019; Larson et al., 2002; Maciejewski et al., 2015). Given the importance of emotion regulation for psychological well-being (Sheppes et al., 2015), the present study tested whether positive emotional states and negative emotional states over the past week were related to pro-inflammatory and antiviral molecular gene expression in a community sample of adolescents (i.e., youth not recruited based on clinical diagnosis).

Emotion and inflammation are bidirectionally related (Irwin and Cole, 2011). Inflammation can elicit sickness behaviors (e.g., social withdrawal; feeling fatigued, lonely, and sad) that promote rest and recovery (Eisenberger et al., 2017). Emotion and activation of emotion-related neural regions (e.g., amygdala, anterior insula, anterior cingulate cortex) can also elicit a cascade of biological processes including activation of the hypothalamic-pituitary-adrenal gland axis and the autonomic nervous system, which together modulate immune system activity (Irwin and Cole, 2011). Emotions have distinct biological correlates that can promote their functional purposes, and induction of discrete emotions can elicit autonomic activity and heighten inflammation (Dickerson et al., 2004; Shiota et al., 2011). It has been posited that difficulty with emotion regulation is related to greater systemic inflammation by contributing to more intense and long-lasting negative emotion (Cole, 2014; Renna, 2021). Much research has examined chronic negative emotion and associations between emotion and inflammation in clinical populations with mood disorders (Michopoulos et al., 2017) or with medical conditions (Duivis et al., 2011; Renna et al., 2020). Less is known about whether variations in state emotion in daily life also relate to differences in inflammation and immune function.

Although previous research has not assessed how emotion relates to gene regulation in the immune system, both positive emotion and negative emotion have been related to protein measures of systemic inflammation—another index of immune system function—among adults. Acute negative emotional states elicit increases in circulating pro-inflammatory cytokines (Dickerson et al., 2004; Duivis et al., 2011; Howren et al., 2009; Miller and Blackwell, 2006; Moons et al., 2010; Renna, 2021), and people with chronic negative emotion tend to have greater systemic inflammation as measured by circulating cytokine levels (Ai et al., 2005; Duivis et al., 2011; Messay et al., 2012; Miller et al., 2005; Moons and Shields, 2015; Pitsavos et al., 2006; Suarez, 2003). In turn, persistent positive emotion has been related to attenuated acute inflammatory responses to threat (Prather et al., 2007; Robles et al., 2009; Steptoe et al., 2005) as well as low systemic pro-inflammatory cytokines both cross-sectionally and prospectively (Brouwers et al., 2013; Deverts et al., 2010; Fancourt and Steptoe, 2020; Ironson et al., 2018; Moreno et al., 2016; Ong et al., 2018; Panagi et al., 2019; Stellar et al., 2015). It is important to assess positive emotion in addition to negative emotion because positive emotion and negative emotion have unique functions and effects on health, and emotions can elicit unique patterns of physiological activation in order to promote these functions (Fredrickson, 2004; Pressman and Cohen, 2005). Furthermore, prior research has suggested that greater positive emotion is related to lower levels of systemic inflammation even after accounting for mental health (Stellar et al., 2015). Taken together, these findings suggest that emotion is related to immune system function, but further research is needed regarding the mechanisms by which emotion may relate to circulating protein.

Genomic activity is another upstream measure of immune system function that has been related to health. Despite being part of the same biological pathway, circulating protein measures of systemic inflammation often do not align with measures of genomic activity within circulating leukocytes (as the latter are generally not the source of the former). Therefore, additional research is needed regarding whether state emotion relates to gene regulation in circulating immune cells. Furthermore, it remains unclear how emotion relates to antiviral activity, another facet of the immune system relevant to chronic disease but difficult to assess using circulating plasma markers due to the very low abundance of innate antiviral cytokines (e.g., Type I interferons; IFNs) under normal physiological conditions. In times of stress, gene regulatory resources tend to be martialed toward promoting inflammatory responses and away from antiviral responses in a gene regulatory pattern known as the Conserved Transcriptional Response to Adversity (CTRA), which is mediated by sympathetic nervous system signaling (Cole, 2009; Powell et al., 2013; Sloan et al., 2007).

Indeed, profiles of heightened pro-inflammatory gene expression and attenuated Type I IFN gene expression have been observed in a wide range of chronically threatening life circumstances such as socioeconomic disadvantage, stress, bereavement, and early life deprivation (Boyle et al., 2019; Chiang et al., 2019; Cole, 2019; Cole et al., 2012, 2015; Miller et al., 2014). Perceived threat is often accompanied by heightened negative emotion and decreased positive emotion. Therefore, positive and negative emotion may differentially elicit similar genomic profiles. Higher positive well-being has been associated with lower CTRA profiles (Fredrickson et al., 2013, 2015), and high positive emotion has been previously related to greater resistance to viral infection (Cohen et al., 2006), although research has not related CTRA profiles to state emotion. These observations underscore the need to expand analyses of the immunologic correlates of intraindividual emotional states beyond the realm of inflammation alone.

To identify how intraindividual variations in emotional state relate to immune system activity, the present study tested whether positive and negative emotional states over the past week were related to leukocyte expression of pro-inflammatory and Type I IFN response genes. Associations were tested in a community sample of 90 adolescents; because adolescents experience heightened emotional intensity and more negative emotional experiences compared to adults and children (Bailen et al., 2019), affective states may be particularly related to biological pathways during this period, despite the majority of research regarding emotion and immune system activity being examined in adults. By studying these associations during adolescence, we can develop a better understanding of the immune consequences of emotional states before they accumulate to contribute to health problems in adulthood. Furthermore, given greater emotional intensity and variability among adolescents, reports likely index state rather than trait emotion for this sample, which was of primary interest for these analyses. Adolescents completed reports of emotion and provided blood samples at two time points five weeks apart as part of a larger behavioral investigation (Tashjian et al., 2020).

We developed two distinct predictions regarding associations between emotional states and pro-inflammatory versus Type I IFN gene expression. In line with findings relating higher positive emotion and lower negative emotion to lower systemic inflammation (e.g., Duivis et al., 2011; Stellar et al., 2015), we predicted that higher positive emotion and lower negative emotion would be related to lower pro-inflammatory gene expression. Based on previous findings from CTRA research relating experienced well-being to profiles of lower pro-inflammatory gene expression and higher antiviral gene expression (e.g., Fredrickson et al., 2013, 2015), as well as research linking positive emotions to host resistance to viral infection (Cohen et al., 2006), we hypothesized that higher positive emotion and lower negative emotion would be related to higher antiviral activity. Separate models were tested for positive and negative emotion because valence is one important dimension of emotion according to the circumplex model (Yik et al., 2011). Finally, although positive emotion and negative emotion are generally thought to have unique effects on health (Fredrickson, 2004; Pressman and Cohen, 2005), there are competing theories regarding whether emotional valence is best measured using a bipolar univariate measure of emotion (i.e., overall valence) or a bivariate measure, separately assessing positive emotion and negative emotion (Mattek et al., 2017). Therefore, we tested two sets of models to assess valence:

models including positive and negative emotion as simultaneous predictors to test the unique effects of each emotion (i.e., bivariate approach), and models including a difference between positive and negative emotion to determine a single metric for overall emotional valence (i.e., univariate approach).

2. Method

The present results come from a secondary analysis of data collected as part of a previously published randomized controlled intervention study with three conditions (see Tashjian et al., 2020 for full details). All analyses control for intervention condition (experimental condition and active control condition versus control condition) to avoid any potential confounding of the effects of emotion that are targeted in this analysis.

2.1. Participants and Procedures

This study involved a community sample of 90 racially and socioeconomically diverse adolescents (M_{age} = 16.28 years, SD = 0.73, range 14–17; 51.1% female) who were recruited from local high schools in Los Angeles to complete a prosocial intervention (Table 1). There were no exclusion criteria regarding psychopathology. Participants were randomly assigned to one of three conditions and received text messages every other day for four weeks asking them to do one of the following: to describe their day, complete a kind act for themselves, or complete a kind act for someone else (see Tashjian et al., 2020 for full details). Recruitment continued until there were 30 participants with valid blood data per condition. The present analyses do not focus on the effects of this intervention but experimental condition is included as a covariate in all analyses.

This study involved one laboratory visit at baseline and a second visit five weeks later, one week post-intervention, both between 8:00 a.m.–12:00 p.m. At each laboratory visit, participants completed a survey regarding emotion and provided blood samples. As part of the first survey, participants reported their age and sex, and research assistants measured their height and weight to calculate body mass index (BMI). One parent accompanied the child during the visit and reported family income and each parent's highest level of education, which was averaged across both parents when possible.

Table 1
Descriptive statistics for demographic variables.

Variable	*N*	%/M (SD)
Age	90	16.28 (0.73)
Female	46	51.11%
Family Annual Income	83	$100505 ($75353)
Mother's Education	84	7.04 (2.15)
Father's Education	84	6.63 (2.48)
Race/Ethnicity		
Hispanic/Latino	36	40.00%
European American	28	31.11%
African American	19	21.11%
Asian American	9	10.00%
Middle Eastern	8	8.89%
Native American	5	5.56%
Other	9	10.00%
Biracial	21	23.33%
Sick (Pre-Intervention)	14	15.56%
Sick (Post-Intervention)	10	11.11%

Note: Participants could select multiple racial/ethnic backgrounds, such that the percentages sum to over 100%. Participants' parents reported highest level of education of the participant's mother and father using the following scale: 1 =Elementary school only, 2 =Elementary and middle school only, 3 =Middle school completion, 4 =High school diploma / GED, 5 =Some high school, 6 =Some college, 7 =Associates degree (2-year degree), 8 = 4-year college degree, 9 =Master's degree, 10 = Doctorate, Medical, or Law Degree. Values for mother's education and father's education were averaged when possible.

Participants self-reported positive and negative emotion using the positive emotion and negative emotion subscale of the Affect Adjective Scale (Diener et al., 1985). Participants rated the extent to which they experienced four positive emotions (i.e., happy, joyful, fun/enjoyment, pleased) and five negative emotions (i.e., frustrated, depressed/blue, unhappy, angry/hostile, worried/anxious) in the past week on a scale ranging from 0 (not at all) to 6 (extremely much). Items showed high inter-item reliability (Cronbach's αs = 0.85 and 0.91 for positive emotion; Cronbach's αs = 0.89 and 0.84 for negative emotion), and items were averaged with higher scores indicating higher positive emotion and higher negative emotion, respectively.

Blood samples were collected by a phlebotomist at each laboratory visit. Participants reported whether they felt sick (0 = not sick, 1 = sick) and the degree to which they were experiencing nasal congestion, muscle aches, upset stomach, hot/cold spells, poor appetite, and coughing/sore throat using a five-point Likert scale (1 = not at all, 2 = slight, 3 = mild, 4 = moderate, 5 = severe). A minority of participants were sick (n = 14, 15.6% at first visit; n = 10; 11.1% at second visit), and participants reported low levels of symptoms (M = 1.36, SD = 0.38, range 1–2.5 at first visit; M = 1.29, SD = 0.33, range 1–2.3 at second visit). No participants had ever smoked cigarettes, and few reported ever drinking alcohol (7.8%).

Pro-inflammatory and Type I IFN gene expression were assayed as previously described (Rahal et al., 2021). Briefly, RNA was extracted from peripheral blood mononuclear cells (RNeasy; Qiagen), checked for suitable mass (> 50 ng by NanoDrop One spectrophotometry; achieved M = 5042 ± SD 2219 ng) and integrity (RNA integrity number > 3 by Agilent TapeStation capillary electrophoresis; M = 7.9 ± SD 0.6) and assayed by RNA sequencing in the UCLA Neuroscience Genomics Core Laboratory using Lexogen QuantSeq 3′ FWD cDNA library synthesis and multiplex DNA sequencing on an Illumina HiSeq 4000 instrument with single-strand 65-nt sequence reads (all following the manufacturer's standard protocol). Analyses targeted over 10 million sequence reads per sample (achieved mean 10.5 million), each of which was mapped to the RefSeq human genome sequence using the STAR aligner (achieved average 93% mapping rate) to generate transcript counts per million total transcripts (TPM; Dobin et al., 2013). Six samples failed endpoint quality control analyses, leaving 174 samples in analyses. TPM values were normalized based on 11 standard reference genes (Eisenberg and Levanon, 2013), floored at 1 normalized TPM to reduce spurious variability, log2-transformed to reduce heteroscedasticity, and z-score standardized within gene.

2.2. Analytic Plan

Multilevel model analyses quantified associations between ratings of positive emotion and negative emotion and average expression of a prespecified set of 19 pro-inflammatory genes and a set of 34 Type I IFN indicator genes as an indicator of antiviral gene expression (Fredrickson et al., 2015). Positive emotion and negative emotion were tested as separate predictors in preliminary analyses, and pro-inflammatory and antiviral gene expression were tested as outcomes in separate models. Analyses were then conducted to determine whether positive emotion and negative emotion were independently related to leukocyte gene expression (i.e., including both positive and negative emotion in the same analytic model). Finally, analyses of primary interest tested whether overall emotional valence was associated with pro-inflammatory and antiviral gene expression by testing the difference of positive and negative emotion (i.e., Positive Emotion – Negative Emotion) as a predictor. For this difference, positive values indicated higher overall positive emotion, negative values indicated higher overall negative emotion, and values of 0 indicated an equal degree of positive and negative emotion. To examine within-person differences in emotion and emotional valence, average levels of positive emotion, negative emotion, and overall valence were calculated for each participant. Reports of positive emotion, negative emotion, and overall valence at each

time point were centered at the participant's mean, such that positive values indicated reports that were higher than the participant's mean. The person-centered value was included in models to index the within-person effect (i.e., state emotion) while controlling for the average level across the two time points, which accounted for the between-person effect.

Preliminary models assessed whether the study protocol affected gene expression by testing the Intervention Condition × Time interaction as a predictor of pro-inflammatory and antiviral gene expression. All effects were consistently nonsignificant, *ps* > .05, suggesting that there were no systematic differences in pro-inflammatory and antiviral gene expression related to engaging in the study protocol (Supplemental Table S1). However, when examining main effects for study condition and time, we observed that participants assigned to the active control condition (completing kind acts for oneself) had lower levels of inflammatory gene expression than participants in the passive control condition (completing daily reports), potentially due to involvement in a study or non-random assignment at baseline ($B = -0.16$, $SE = 0.07$, $p = .021$). As an exploratory analysis, we tested associations limited to baseline data (i.e., before participants began the study protocol) and found that there was already a significant difference in pro-inflammatory gene expression ($B = -0.24$, $SE = 0.09$, $p = .008$). No associations emerged between intervention condition and antiviral gene expression, *ps* > .4, and there was no main effect of time on antiviral or pro-inflammatory gene expression, *ps* > .19. Based on these findings, we controlled for intervention condition (active control and experimental conditions compared to baseline) in addition to indicator gene (repeated measure) in all analyses. An identical pattern of results emerged in fully unadjusted models without intervention condition as a covariate.

Models were then tested again adjusting for age (grand-mean centered), sex (0 = female, 1 = male), self-reported potential illness (0 = not sick, 1 = sick), BMI (grand-mean centered), and race/ethnicity (indicator variables for Asian American, African American, Hispanic/Latino, Native American, Middle Eastern, vs. reference group European American [sample majority group]). All analyses were repeated using a continuous measure of mean symptom severity as a covariate rather than the dichotomous self-reported sickness item, and we observed the same pattern of results. Ancillary adjusted analyses additionally controlled for mRNA markers of major leukocyte subsets to control for the potential heterogeneity in leukocyte subset distributions (*CD3D, CD19, CD4, CD8A, FCGR3A, NCAM1, CD14*), although a consistent pattern of results emerged irrespective of covariates. Primary analyses omitted the potentially relevant confounders of family income and parent education due to missing data ($n = 7$ and 6, respectively). However, secondary analyses were conducted to include these covariates and yielded substantively identical results.

Analyses were conducted using SAS v9.4 PROC MIXED, specifying a random subject-specific intercept. Multilevel models of within-person differences require at least two time points (Allison, 2005; McMahon et al., 2006). All models used maximum likelihood. There was no missing data on gene expression, emotion, and most covariates with two exceptions: income and parents' education. Post-hoc power analyses were conducted for each model using Monte Carlo simulations with 1000 replications. These models used the resulting parameter estimates with the current sample size (180 observations across 90 participants), adjusting for the family-wise correction. Power analyses indicated that we had over 89% power to detect associations between emotion and gene expression. We had three families of analyses: associations between positive emotion, negative emotion, and overall emotional valence and leukocyte activity. Antiviral and pro-inflammatory gene expression were tested as two different indices of leukocyte activity, so tests of associations for positive emotion and negative emotion were corrected for two analyses each (α = .025 based on Bonferroni correction). Overall emotional valence was tested in two models using a bivariate approach (positive and negative emotion tested simultaneously) and a univariate approach (positive emotion – negative emotion). Therefore, we corrected for four models for emotional valence (α = .0125). Exploratory analyses examined differences in associations by arousal, another dimension of emotion.

3. Results

Sample characteristics are given in Table 1. Participants on average reported moderately high levels of positive emotion above the scale midpoint and low levels of negative emotion, in line with prior studies (Armenta et al., 2020; Walsh et al., 2022). Across study visits, the two reports of positive emotion and of negative emotion were highly correlated; $r(88) = 0.62$ and.65, respectively, both *ps* < .001. As expected, positive and negative emotion were highly negatively related to one another at each visit; $r(88) = -0.61$ and − 0.55 at the respective visits, *ps* < .001 (Table 2).

3.1. Pro-Inflammatory gene expression

As hypothesized, increases in positive emotion were associated with lower pro-inflammatory gene expression, $B = -0.11$, $SE = 0.03$, $p = .0005$, 95% Confidence Interval (CI) [− 0.17, − 0.05], and increases in negative emotion were associated with higher pro-inflammatory gene expression, $B = -0.10$, $SE = 0.04$, $p = .009$, 95% CI [0.02, 0.17]. Both associations remained significant when controlling for demographic covariates (Tables 3–4) and when analyses additionally controlled for 7 mRNA indicators of major immune cell subsets (T cells, B cells, NK cells, monocytes; Supplemental Tables S1-S2). When both positive and negative emotion were tested as simultaneous predictors of pro-inflammatory gene expression, a unique association emerged for increases in positive emotion, $B = -0.09$, $SE = 0.03$, $p = .010$, 95% CI [− 0.16, − 0.02], but not negative emotion, $B = 0.05$, $SE = 0.04$, $p = .208$, 95% CI [− 0.03, 0.13] (Supplemental Table S3). In line with our results implying that pro-inflammatory gene expression tracks with the covariance of positive and negative emotion, we found a robust association of pro-inflammatory gene expression with increases in general emotional valence using a univariate approach (i.e., positive emotion – negative emotion), $B = -0.07$, $SE = 0.02$, $p = .0003$, 95% CI [− 0.11, − 0.03]. This result suggested that overall more positive emotional valence is related to reduced pro-inflammatory gene expression. Again, this association remained significant after adjusting for covariates (Supplemental Table S4).

3.2. Antiviral gene expression

Contrary to our hypothesis, increases in positive emotion were associated with lower antiviral gene expression, $B = -0.12$, $SE = 0.02$, $p < .0001$, 95% CI [− 0.16, − 0.08], and increases in negative emotion were associated with higher antiviral gene expression, $B = 0.09$, $SE = 0.03$, $p = .0002$, 95% CI [0.04, 0.14]. Again, associations remained significant when controlling for demographic covariates (Tables 3–4) and additionally controlling for major immune cell subsets (Supplemental Tables S1-S2). In simultaneous analyses of negative and positive

Table 2
Descriptive statistics and correlations between emotion ratings at both study visits.

Variable	*M*	*SD*	*Min*	*Max*	1.	2.	3.	4.
Positive Emotion Time 1	3.81	1.35	0.50	6.00	—			
Positive Emotion Time 2	3.93	1.40	0.25	6.00	0.62	—		
Negative Emotion Time 1	2.07	1.34	0.00	5.40	-0.61	-0.32	—	
Negative Emotion Time 2	1.42	1.07	0.00	4.00	-0.55	-0.55	0.65	—

Note: All *ps* < .0025.

Table 3
Pro-inflammatory and antiviral gene expression as a function of positive emotion.

.	Pro-Inflammatory Gene Expression				Antiviral Gene Expression			
	Unadjusted		Adjusted for Demographic Covariates		Unadjusted		Adjusted for Demographic Covariates	
	B	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Intercept	0.04	0.12	0.17	0.64	-0.04	0.15	-0.06	0.80
Person-Centered Positive Emotion	-0.11 * **	0.03	-0.12 * **	0.03	-0.12 * **	0.02	-0.12 * **	0.02
Mean Positive Emotion	0.00	0.02	0.00	0.02	0.00	0.03	0.01	0.03
Time	0.06	0.04	0.06	0.04	0.03	0.03	0.03	0.03
Experimental Condition	-0.09	0.07	-0.10	0.07	0.02	0.10	-0.02	0.08
Active Control Condition	-0.16 *	0.07	-0.16 *	0.07	0.07	0.10	0.04	0.08
Male	—	—	-0.06	0.06	—	—	-0.21 * *	0.07
Age	—	—	-0.02	0.04	—	—	-0.01	0.05
BMI	—	—	0.01	0.01	—	—	0.01 *	0.01
African American	—	—	0.05	0.08	—	—	-0.03	0.10
Hispanic/Latino	—	—	0.01	0.06	—	—	-0.10	0.07
Asian American	—	—	0.12	0.09	—	—	0.39 * *	0.12
Native American	—	—	-0.01	0.15	—	—	-0.09	0.18
Middle Eastern	—	—	0.23 *	0.09	—	—	-0.05	0.11

Note: BMI=Body mass index. Model 1 adjusted only for experimental condition and time point. Model 2 adjusted for person-characteristics (i.e., Age, Sex, BMI, and Race/Ethnicity). Time was dummy-coded (0 = pre-intervention, 1 = post-intervention; repeated measure). Condition was dummy-coded. Sex was dummy-coded (0 = female, 1 = male). Race/ethnicity was dummy-coded with European American as the reference group. Mean Positive Emotion, Age, and BMI were centered at the sample mean. Person-Centered Positive Emotion was centered at the participant mean.

Table 4
Pro-inflammatory and antiviral gene expression as a function of negative emotion.

.	Pro-Inflammatory Gene Expression				Antiviral Gene Expression			
	Unadjusted		Adjusted for Demographic Covariates		Unadjusted		Adjusted for Demographic Covariates	
	B	*SE*	*B*	*SE*	*B*	*SE*	*B*	*SE*
Intercept	-0.02	0.10	0.10	0.63	-0.16	0.12	-0.10	0.80
Person-Centered Negative Emotion	0.10 * *	0.04	0.10 * *	0.04	0.09 * **	0.03	0.09 * **	0.03
Mean Negative Emotion	0.03	0.03	0.03	0.03	0.05	0.04	0.02	0.03
Time	0.11 *	0.04	0.11 *	0.04	0.07 *	0.03	0.07 *	0.03
Experimental Condition	-0.08	0.07	-0.08	0.07	0.04	0.10	-0.01	0.08
Active Control Condition	-0.16	0.07	-0.16	0.07	0.07	0.10	0.05	0.08
Male	—	—	-0.04	0.06	—	—	-0.19 * *	0.07
Age	—	—	-0.02	0.04	—	—	-0.01	0.05
BMI	—	—	0.01	0.01	—	—	0.01 *	0.01
African American	—	—	0.06	0.08	—	—	-0.02	0.10
Hispanic/Latino	—	—	0.01	0.06	—	—	-0.10	0.07
Asian American	—	—	0.13	0.09	—	—	0.40 * **	0.12
Native American	—	—	0.02	0.15	—	—	-0.07	0.18
Middle Eastern	—	—	0.24 * *	0.09	—	—	-0.04	0.11

Note: BMI=Body mass index. Model 1 adjusted only for experimental condition and time point. Model 2 adjusted for person-characteristics (i.e., Age, Sex, BMI, and Race/Ethnicity). Time was dummy-coded (0 = pre-intervention, 1 = post-intervention; repeated measure). Condition was dummy-coded. Sex was dummy-coded (0 = female, 1 = male). Race/ethnicity was dummy-coded with European American as the reference group. Mean Negative Emotion, Age, and BMI were centered at the sample mean. Person-Centered Positive Emotion was centered at the participant mean.

emotion, a unique association emerged between increases in positive emotion and lower antiviral gene expression (i.e., controlling for negative emotion, $B = -0.10$, $SE = 0.02$, $p < .0001$, 95% CI [−0.15, −0.06]) but not negative emotion when controlling for positive emotion ($B = 0.04$, $SE = 0.03$, $p = .131$, 95% CI [−0.01, 0.10]; Supplemental Table S5). Again, we found that overall emotional valence using a univariate approach (i.e., positive emotion – negative emotion) was associated with Type I IFN gene expression; $B = -0.08$, $SE = 0.01$, $p < .0001$, 95% CI [− 0.10, − 0.05]. Similar to results for pro-inflammatory gene expression, more positive emotional valence was associated with reduced antiviral gene expression, and this association remained significant in adjusted analyses (Supplemental Table S6).

3.3. Exploratory analyses

In ancillary analyses that did not control for systematic effects of time (e.g., habituation of negative emotional state on the day of blood sampling), similar results emerged for positive emotion and overall valence but not for negative emotion (Supplemental Table S8). We used the 12-Point Affect Circumplex model of Core Affect to identify high arousal versus low arousal emotions (Yik et al., 2011). All positive emotion items were considered high arousal. We tested three-level models with items nested within time points within adolescents and included Emotion × Arousal (0 = Low [depressed/blue, unhappy], 1 = High [frustrated, angry/hostile, worried/anxious]) interactions to test whether associations between negative emotion and gene expression differed by emotional arousal. We found no evidence of such an interaction, $ps > .5$ (Supplemental Tables S9-S10).

4. Discussion

Results in the present study link intraindividual variation in positive emotional valence to reduced expression of both pro-inflammatory gene transcripts and Type I IFN antiviral gene transcripts in an analysis of circulating immune cells from a community sample of adolescents (i.e., not selected for either presence or absence of psychopathology). Complementary patterns of results were observed for measures of positive emotion and negative emotion. In addition to testing associations for

positive and negative emotion separately, analyses tested both univariate and bivariate approaches to measuring emotional valence. Significant effects emerged for overall emotional valence (i.e., univariate approach), and unique effects emerged for positive emotion but not negative emotion for both antiviral and pro-inflammatory gene expression when assessing both positive and negative emotion simultaneously (i.e., bivariate approach). These analyses suggest that either the univariate approach or a focus on positive emotion specifically may be most useful in future research examining associations between emotion and leukocyte gene expression, as opposed to focusing on negative emotion alone.

All observed effects were independent of demographic factors and variations in the relative abundance of major leukocyte subsets within the circulating white blood cell pool. Controlling for systematic effects of time had no effect on the association of gene expression with positive affect or with overall emotional valence, but it did enhance the associations between greater negative affect with greater pro-inflammatory and antiviral gene expression. This valence-specific effect may be due to removal of confounded changes in study procedure-related affect (i.e., a reduction in negative affect recorded during follow-up relative to initial study visit). Future studies can further assess associations between intraindividual variations in negative emotion and gene expression in individuals who have not completed a behavioral intervention.

The pattern of gene regulatory results observed is notably distinct from the CTRA profile previously identified in the context of chronically adverse life circumstances (and inversely related to eudaimonic well-being) which involves a complementary upregulation of pro-inflammatory genes and downregulation of Type I IFN expression (Cole, 2019; Fredrickson et al., 2013). By contrast, the present data link positive emotional valence to simultaneous down-regulation of both pro-inflammatory genes (broadly consistent with CTRA) and Type I IFN antiviral genes (inconsistent with CTRA). This difference may have emerged because eudaimonia and hedonia are two distinct aspects of positive well-being, and the items used to measure positive emotion in the PANAS focus on high-arousal pleasure and consequently may be assessing hedonia rather than eudaimonia (Pressman et al., 2019). Furthermore, CTRA gene expression tends to be more weakly related to hedonia than eudaimonia (Fredrickson et al., 2015). Exploratory analyses suggested that associations did not differ by emotional valence. The emotion measure was not capable of distinguishing effects of high versus low arousal from effects of emotional valence (all positive emotion items reflected high arousal, whereas negative emotions included both low and high arousal items). As such, future studies can use a dimensional model to disentangle effects of arousal and valence (e.g., by including emotion items with more varied arousal, or directly measuring arousal physiology).

This signature of coordinated change in pro-inflammatory and antiviral gene expression is most consistent with a reduction in immunologic activation (i.e., generalized transcriptional activity across all immune response systems; Murphy et al., 2017) in association with positive emotional valence, rather than redeployment of transcriptional resources from pro-inflammatory to innate antiviral effector activities as seen in the CTRA. These results suggest that variations in positive and negative emotional states may have immunoregulatory impacts that are distinct from the CTRA gene regulation program previously identified in the context of chronically threatening, stressful, and adverse life circumstances (Cole, 2019). Future research will be required to confirm these initial observations regarding the distinct immunoregulatory effects of variation in daily emotional state versus the effects of chronic life adversity, but the present findings suggest a previously unappreciated complexity in the relationship between psychological processes and the biology of immune system function. These associations suggest that changes in state affect may contribute to mobilization of the immune system in youth and could thereby gradually confer propensity for disease risk in adulthood.

The present findings are consistent with previous research linking high positive emotion and low negative emotion to reduced levels of circulating inflammatory mediators (Chiang et al., 2019; Duivis et al., 2011; Fancourt and Steptoe, 2020; Gimeno et al., 2009; Iob et al., 2020; Panagi et al., 2019; Steptoe et al., 2015; Stellar et al., 2015) as well as studies documenting changes in immune cell activation (e.g., stimulated cell proliferation) in response to experimental mood inductions (Futterman et al., 1994). Links between positive emotion and reduced Type I IFN antiviral gene expression are inconsistent with previous data linking positive emotion to host resistance to respiratory virus infection (Cohen et al., 2006), but the latter results may stem from different mechanisms than the Type I IFN system examined here (e.g., adaptive immune responses rather than innate antiviral genes). Although the gene regulatory correlates of emotional valence do not exemplify the CTRA pattern of reciprocal pro-inflammatory and antiviral effects, they are similar to the simultaneous upregulation of pro-inflammatory and Type I IFN gene transcripts findings observed in studies of adolescents and young adults with a history of adverse childhood experiences (ACEs; Bower et al., 2020; MacCormack et al., 2021; Marie-Mitchell and Cole, 2021). It is possible that there is a shared mechanism relating both overall negative emotional valence and ACEs to greater immune system activity, and these results highlight the importance of assessing both profiles of gene expression (e.g., CTRA) as well as separate measures of antiviral and pro-inflammatory gene expression.

The mechanisms of the observed associations remain to be identified in future research. Associations between positive emotional valence and reduced pro-inflammatory gene expression are broadly consistent with the CTRA pattern, which is known to be mediated in large part by alterations in sympathetic nervous system activity and the effects of neurotransmitter signaling through beta-adrenergic receptor stimulation of pro-inflammatory transcription factors (Cole, 2019). However, the present results are not consistent with the known effects of the sympathetic nervous system (or HPA-axis/glucocorticoid system), which generally act to suppress Type I IFN activity and would thus be expected to link positive emotional valence (associated with low adrenergic/glucocorticoid activity) to increased antiviral activity. It is important to note that participants in the present study were a community sample of youth, with high levels of positive emotion and low levels of negative emotion, and results need to be replicated among youth with lower levels of positive emotion and higher levels of negative emotion who may be at higher risk for poorer health and psychopathology. Still, it is conceivable that the link between negative emotion and increased Type I IFN activity is a consequence of emotion-related changes in the activity of chronic viral infections within the body (e.g., Epstein-Barr Virus or Cytomegalovirus), which might stimulate innate antiviral responses if negative emotional states were associated with increased viral activity. Future research will be required to assess these hypotheses and map the biological pathways that connect variations in emotional state to variations in immune cell gene regulation. It seems likely that those emotion-related mechanisms will be at least in part distinct from those previously mapped for the CTRA.

4.1. Limitations

Although the present results provide preliminary evidence that emotional states are related to immune cell gene regulation, findings must be interpreted in the context of the study sample and design. Associations were tested in a community sample of adolescents (i.e., no inclusion or exclusion based on psychopathology or other illness), and future research among clinical and older samples will be required to confirm the health significance of these observations (e.g., for rates of viral infection and disease, inflammation-related disease, etc.) and whether findings generalize to other developmental periods. In addition to replicating findings in other populations, future research should assess how state versus trait emotion relates to gene expression in immune cells, potentially through use of electronic momentary assessment.

Furthermore, future studies can also measure different discrete emotions (e.g., sadness versus anger) given that discrete emotions can have unique effects on health (Barlow et al., 2019).

In line with the circumplex model (Yik et al., 2011), emotional valence and emotional arousal are two distinct and orthogonal dimensions of emotion. Although the Affect Adjective Scale includes items with varied valence, the emotion measure was not capable of distinguishing effects of high versus low arousal from effects of emotional valence (all positive emotion items reflected high arousal, whereas negative emotion included both low and high arousal items). Exploratory analyses suggested that associations did not differ by emotional valence, although future studies will be needed to disentangle effects of arousal and valence (e.g., by including emotion items with more varied arousal, or directly measuring arousal physiology). Future studies can also assess other dimensions of emotion including emotional variability, which is also heightened during adolescence (Maciejewski et al., 2015). Finally, this study focused on two well-established aspects of innate immune cell gene regulation (i.e., pro-inflammatory and Type 1 IFN antiviral genes); other aspects of immune cell gene regulation may also track with intraindividual variation in emotional state. Those effects remain to be identified in future research, with larger sample sizes needed to support reliable genome-wide discovery analyses.

Regarding study design, the study was observational and cannot determine whether emotion causally influences gene expression (e.g., via neural regulation of leukocyte transcription), whether alterations in gene expression causally influence emotion (e.g., via cytokine signaling to the brain), or whether both factors are jointly influenced by a third variable (e.g., changes in pathogen exposure or activity). Future research experimentally manipulating emotion and utilizing prospective designs will be required to determine directional associations between emotion and immune gene expression. Although emotional states may elicit differences in genomic profile similar to experiences of acute stress, it is also plausible that genomic profile may influence emotional well-being, in line with experimental research suggesting that acute inflammation can elicit negative emotion (Kuhlman et al., 2018).

Participants in this study also completed a behavioral intervention between the two laboratory visits, although preliminary models did not suggest that the behavioral intervention influenced gene expression. Time was covaried in analytic models to account for systematic effects of returning for a second blood draw on emotion. Future observational studies can collect blood samples and measure emotion at multiple time points without administration of a behavioral intervention. A higher number of participants and repeated samples could improve reliability of estimated associations. Analyses controlling for differences in mRNA markers of leukocyte subset abundance suggest that the observed effects do not stem from variations in the relative abundance of cell types within the white blood cell pool, but future research should verify this inference by direct measurement of leukocyte subset abundance (e.g., by flow cytometry).

5. Conclusions

Results from this study demonstrate that intraindividual variations in emotional valence (i.e., positive vs. negative emotional state) are associated with parallel reductions in expression of both pro-inflammatory and innate antiviral genes in circulating immune cells. These results are distinct from the reciprocal pattern observed in the CTRA, and may reflect reductions in generalized immunologic activation in the context of positive emotional states.

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CRediT authorship contribution statement

Danny Rahal: Conceptualization, Data curation, Formal analysis, Funding acquisition, Visualization, Writing – original draft. **Sarah M. Tashjian**: Funding acquisition, Writing – review & editing. **Maira Karan**: Writing – review & editing. **Naomi Eisenberger**: Writing – review & editing. **Adriana Galván**: Writing – review & editing. **Andrew J. Fuligni**: Funding acquisition, Writing – review & editing. **Paul D. Hastings**: Funding, Writing – review & editing. **Steve W. Cole**: Funding acquisition, Visualization, Writing – review & editing.

Declarations of interest

None.

Appendix A. Supporting information

Supplementary information associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106103.

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