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Positive Affective Style Covaries with Stimulated IL-6 and IL-10 Production in a Middle-Aged Community Sample

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Abstract

An emerging literature indicates that dispositional positive affect (PA) may play a protective role in health and render individuals less susceptible to inflammatory diseases. In this regard, it has been suggested that PA is associated with diminished activation of innate immune pathways. To explore this possibility, we examined relationships between trait positive emotional style, as assessed by the *Positive and Negative Affect Schedule*, and monocyte-derived lipopolysaccharide-induced production of the pro- and anti-inflammatory cytokines, interleukin (IL)-6, IL-1 β , TNF- α , and IL-10, among 146 healthy adults aged 30–54. After controlling for demographic factors and other covariates (age, gender, race, body mass index and white blood cell count), hierarchical regression analyses revealed an inverse association between trait PA and stimulated production of IL-6 ($\Delta R^2 = .03$, $b = -.18$, $p < .04$) and IL-10 ($\Delta R^2 = .09$; $b = -.32$, $p < .01$), with the latter association obtained only in men. No association was observed between trait PA and stimulated IL-1 β or TNF- α . Additionally, trait negative affect was unrelated to any of the stimulated cytokine levels. These initial findings suggest that individuals higher in trait positive emotional style show decreased in vitro production of the early inflammatory mediators IL-6 and IL-10 in response to stimulation with endotoxin which may confer protection against the emergence and progression of inflammatory diseases. Further exploration of this potential psychophysiological pathway is warranted.

It is well documented that psychological factors can influence the onset and progression of inflammatory diseases, including upper respiratory infection, atherosclerosis, rheumatoid arthritis, and asthma (Cohen et al., 2003; Everson-Rose & Lewis, 2005; Wright et al., 2005; Zautra et al., 1994). Most literature has focused on the detrimental impact of negative emotions on disease susceptibility and the course of illness. In contrast, an emerging literature suggests that dispositional positive affect (PA) may play a protective role in health, perhaps by rendering individuals less vulnerable to inflammatory disease. For example, a recent experimental study found that individuals who characterize themselves as happy, pleased, relaxed, and lively are less susceptible to upper respiratory infection (common cold virus) when compared with participants with less happy dispositions (Cohen et al., 2003). Moreover, no relationship between negative emotional style and infection was observed, nor could these findings be

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attributed to other factors including age, sex, education, negative affect, or virus-specific antibody status before challenge.

Pathways linking PA to inflammatory disease susceptibility remain unclear; however, possibilities include both behavioral and immune mechanisms. Behaviorally, PA has been linked to a number of healthy lifestyle choices that affect immune function (Kiecolt-Glaser & Glaser, 1988), including better sleep quality and exercise (Bardwell et al., 1999; Cohen et al., 2003; Myers & Diener, 1995). Recent attention has also focused on the possibility that dispositional PA is related to aspects of innate immune function that may influence host susceptibility to inflammation (see review by Marsland et al., 2007). In this regard, the viral challenge study conducted by Cohen and colleagues found higher PA to be associated with less production of the pro-inflammatory cytokine interleukin (IL) – 6 in nasal secretions in response to infection, with IL-6 partially mediating the association of PA and upper respiratory disease (Doyle et al., 2006). These findings provide initial evidence that dispositional PA is related to a diminished local inflammatory response, as measured by the production of the IL-6 and thus may decrease susceptibility to infectious disease.

An inflammatory response begins when monocytes/macrophages are activated by pathogens or tissue damage to release pro-inflammatory cytokines, including IL-6, IL-1 β , and TNF- α . Pro-inflammatory cytokines, in turn, stimulate the recruitment and activation of leukocytes to the site of injury, and the systemic release of acute phase proteins (Black & Garbutt, 2002), such as C-reactive protein and fibrinogen. The magnitude of pro-inflammatory cytokine response to immune activation is critical; insufficient response may leave the organism more vulnerable to infection, and excessive response can increase risk for inflammatory diseases. A number of mechanisms suppress macrophage activation and prevent the excessive production of pro-inflammatory cytokines, including the local release of anti-inflammatory mediators, such as IL-10, by activated immune cells. It remains to be determined whether PA covaries with production of this anti-inflammatory mediator.

The goal of the following study is to further explore the relationship between trait levels of PA and susceptibility to inflammation by examining whether trait positive emotional style is associated with the capacity of immune cells to produce the cytokines IL-1 β , IL-6, TNF- α , and IL-10 following in vitro stimulation with lipopolysaccharide (LPS) among a community sample of relatively healthy mid-life volunteers. Consistent with Cohen et al (2003), we define PA as feelings that reflect a level of pleasurable engagement with the environment (Clark et al., 1989). Based on existing findings, we expect dispositional PA to be inversely associated with production of pro-inflammatory cytokines, potentially resulting in decreased susceptibility to inflammatory conditions. We also explore the relationship between PA and the production of the anti-inflammatory cytokine, IL-10.

Methods

Participants

Participants were 146 community volunteers (57.5% male, 95.2% Caucasian) between the ages of 30 and 54, enrolled in the Adult Health and Behavior (AHAB) project, a registry of behavioral and biological measurements from community volunteers recruited by mass mail solicitation in Allegheny County, Pennsylvania. All eligible participants reported being in good general health (including no history of myocardial infarction, asthma, cancer treatment in the past year, or psychotic illness). In addition, participants were free from symptoms of current or recent infection. Individuals taking cardiovascular (except antihypertensives and lipid lowering medications), psychotropic, weight-loss or otherwise immune altering drugs were excluded. Informed consent was acquired in compliance with the Institutional Review Board at the University of Pittsburgh.

Procedure

Participants were asked to fast for 8 hours, avoid strenuous physical activity for 12 hours and abstain from alcohol consumption for 24 hours prior to a blood draw for the determination of cytokine production. The blood draw was performed after participants completed a structured medical history interview, and had height and weight recorded. At a separate session scheduled 2-4 weeks later, participants completed a battery of computer-administered psychosocial and health behavior measures. Positive and negative affective style was assessed using the *Positive and Negative Affect Schedule* (PANAS; Watson et al., 1988). The PANAS is a 20-item measure consisting of 10 positive and 10 negative adjectives previously found to load onto dimensions of positive and negative affect. Participants were asked to rate themselves on a Likert scale ranging from 1 (*very slightly or not at all*) to 5 (*extremely*) to what extent each positive or negative affective adjective described how they feel “generally” or “on average.” The PANAS has been shown to be a reliable measure of dispositional affective style (Cronbach coefficient $\alpha = .88$; Watson et al., 1988). Health practices, assessed as possible pathways linking psychosocial parameters to inflammation, included smoking status (current smoker versus ex/non-smoker), sleep quality (Pittsburgh Quality Sleep Index; PSQI; Buysse et al., 1989), and exercise (kilocalories/week; Paffenbarger Physical Activity Questionnaire; Paffenbarger et al., 1993).

Stimulated cytokine production

Whole blood stimulation assay: Whole blood was collected in citrate-treated vacutainer tubes and stimulated with LPS (serotype 026:B6, Sigma) at a final concentration of 2.5 ug/ml under sterile conditions and incubated at 37°C with 5.0% CO₂ for 24 hours. The tubes were then centrifuged at 1000g for 10 minutes and the plasma was frozen at -80°C until the completion of the study.

Samples were assayed in one batch using a multiplex analysis system. Multiplex bead kits (Biosource, Camarillo, CA), based on the principle of solid phase sandwich immunoassays, were employed and stimulated levels of IL-6, IL-1 β , and TNF- α were determined using Bio-Plex Manager Software (Bio-rad Corporation, Hercules, CA), interpolating from the standard curve (Logistic-5PL curve fit). As a result of plasma dilution, levels of IL-10 were too low to be reliably detected by these methods. Thus, stimulated levels of IL-10 were assessed by enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN). All presented IL-10 data is based on the results of these ELISAs. Pooled plasma controls were included on all plates to determine assay reliability. Inter- and intra- assay coefficients of variability were less than 10%. Stimulated cytokine production was quantified by subtracting cytokine levels in unstimulated samples from the stimulated levels. A complete blood count was also performed to determine the absolute numbers of white blood cells (WBC) in peripheral circulation.

Statistical Analyses

All analyses were performed using SPSS for windows (version 14.0). Stimulated pro-inflammatory cytokine levels, circulating WBC counts, body mass index (BMI), trait negative affective style (NA) scores, physical activity, and PSQI scores were log transformed prior to analysis to better approximate normal distributions. A square-root transformation was employed for stimulated IL-10 cytokine levels. Pearson Product-Moment and point-biserial correlations were performed to examine relationships among demographic variables, medication use, menopausal status, health behaviors, psychosocial characteristics, and stimulated levels of IL-6, IL-1 β , TNF- α , and IL-10. Based on these initial findings, hierarchical linear regressions were performed examining whether PA predicted stimulated cytokine levels after adjustment for prominent covariates (age, gender, race, BMI) and WBC count. Stimulated cytokine levels were adjusted for WBC count in regression analyses to control for

interindividual variability in cell numbers that could potentially account for a relationship between PA and cytokine production.

Results

Means and standard deviations for demographic variables, psychosocial characteristics and cytokine production are presented in Table 1. As expected, when compared with unstimulated samples, whole blood stimulation with LPS induced an increase in the levels of all 4 inflammatory mediators. Correlational analyses showed that men produced higher levels of stimulated IL-6, TNF- α , and IL-10 than women (p 's<.04). Stimulated cytokine levels were unrelated to medication usage with the exception of higher TNF-alpha levels among those using antihypertensives ($n=6$) ($r=.17$, $p<.05$). Additionally, stimulated levels of IL-1 β , but not the other cytokines, were lower among women currently taking hormones ($n=6$) ($r=.29$, $p<.03$). Menopausal status was unrelated to stimulated cytokine production. Stimulated cytokine levels were unrelated to self-reported health behaviors, with the exception of IL-1 β which was associated with less physical activity ($r=-.18$, $p<.05$) and more sleep problems ($r=.21$, $p<.02$). In addition, being a current smoker was associated with higher levels of stimulated IL-6 ($r=.24$, $p<.01$) and IL-10 ($r=.20$, $p<.02$) production. As expected, pro-inflammatory cytokine responses were significantly correlated with one another ($p<.001$). Stimulated IL-10 production was positively correlated with IL-6 ($r=.27$, $p<.001$) and inversely correlated with IL-1 β ($r=-.20$, $p<.02$) and TNF- α ($r=-.18$, $p<.03$).

The Role of Positive Affective Style

Initial correlational analyses revealed negative associations between PA and stimulated levels of IL-6 ($r=-.23$, $p<.01$) and IL-10 ($r=-.24$, $p<.01$); however, PA was unrelated to IL-1 β and TNF- α . There were no significant correlations between NA and levels of stimulated cytokines. Next, we assessed several control variables that might account for the observed relationships between PA and cytokine production. Higher levels of PA were associated with being female ($r=.26$, $p<.01$), older ($r=.20$, $p<.02$), more physically active and reporting fewer sleep disturbances (p 's<.01). No associations between levels of PA and current smoking status, menopausal status, or medication use were observed.

Hierarchical regression analyses including standard controls (age, gender, race, BMI, and WBC count) were employed to further examine the associations between PA and stimulated production of IL-6 and IL-10. After entering covariates in the first step, the negative relationship between PA and IL-6 production persisted [$F(6, 139)=5.63$, $p<.001$; $\Delta R^2=.03$; $b=-.18$, $p<.04$]. Figure 1 summarizes this association between PA and stimulated IL-6 production. To further illustrate this association, we categorized positive affective style scores into three groups as close in size as possible, 19-34 (mean=28.4; SD=5.2); 35-38 (mean=36.6; SD=1.0); 39-48 (mean=41.2; SD=3.0). Figure 1 displays mean stimulated levels of IL-6 among the 3 groups. In a separate model, a negative relationship between PA and IL-10 production [$F(6, 139)=4.95$, $p<.001$; $\Delta R^2=.04$; $b=-.21$, $p<.02$] also persisted. The full regression models are presented in Tables 2 and 3.

Initial hierarchical regression analyses indicated a gender by PA interaction on analysis of IL-10 and IL-6 production. This effect was explored by including the gender by PA interaction term in the final step of the regression model. A significant gender $\times$ PA interaction was observed on analysis of IL-10 production [$F(7, 138)=5.21$, $p<.001$; $\Delta R^2=.03$; $b=1.45$, $p<.02$], with PA predicting lower IL-10 levels among men only. Though in the same direction, a gender $\times$ PA interaction for stimulated IL-6 failed to meet statistical significance.

Discussion

This study provides preliminary evidence of a modest association between dispositional PA and LPS-stimulated production of the pro- and anti-inflammatory cytokines IL-6 and IL-10 in a nonpatient sample of community volunteers. Consistent with an emerging literature showing PA associated with better objective health (Pressman & Cohen, 2005), we found that PA was inversely associated with stimulated production of IL-6, a measure of inflammatory potential. This association persisted after controlling for age, gender, race, BMI, and WBC count and replicates the in vivo relationship between positive emotional style and lower IL-6 levels recently observed in the nasal secretions of healthy individuals experimentally challenged with a rhinovirus (Doyle et al., 2006).

Consistent with the findings of Doyle and colleagues, we failed to find PA associated with the production of other pro-inflammatory cytokines. Although it is possible that PA has an immunomodulatory effect specific to IL-6 production, a more likely explanation for our failure to find consistent associations between PA and IL-1 β or TNF- α is the kinetics of cytokine responses to endotoxin. Specifically, the expression of TNF- α peaks at 2 hours and IL-1 β at 6 hours following LPS stimulation (Oliver et al., 1993). In contrast, stimulated IL-6 levels gradually increase across a 24 hour period (Oliver et al., 1993). These differences in cytokine response kinetics may favor detection of IL-6 (and incidentally IL-10) rather than IL-1 β or TNF- α following 24 hours of incubation with LPS.

The current findings did reveal a novel inverse relationship between PA and production of the anti-inflammatory cytokine IL-10. At first glance, the direction of this association was surprising; however, recent evidence indicates that IL-6 stimulates IL-10 production in vitro (Steensberg et al., 2003), providing a local feedback loop to limit the pro-inflammatory response. This is supported by observations that atherogenic plaques, which show high levels of pro-inflammatory cytokines, also show high levels of IL-10 (Ambrosius et al., 2006; Jatta et al., 2005). By taking a snapshot at one point in time, it is not possible in this study to examine the kinetics of the individual cytokine responses. Further research is warranted to explore whether the IL-6 response precedes the IL-10 response to stimulation.

Interestingly, exploratory findings revealed stronger associations between PA and lower stimulated IL-6 and IL-10 production among men than women. As these findings were not predicted, they should be considered preliminary and interpreted only with caution. That said, it is intriguing to speculate that gender differences in stimulated cytokine production may contribute to the observed gender disparities in inflammatory disease susceptibility. Further exploration of gender differences in the relationship between PA and cytokine production and the role they may place in sex differences in susceptibility to inflammatory diseases is indicated.

There are a number of limitations of the current study. First, the cross-sectional nature of the study design limits our ability to make causal inferences regarding relationships between PA and inflammatory mediators. Indeed, peripheral pro-inflammatory cytokines have been shown to have mood altering effects (Capuron et al., 2001), with higher stimulated production of IL-6 predicting a subsequent reduction in positive mood (Janicki-Deverts et al., 2006). However, reverse causality is an unlikely explanation for the current findings because the immune cells were stimulated ex vivo and we observed no relationship between stimulated production and in vivo circulating levels of IL-6 ($r = -.002$, $p > .97$). It is possible that an unmeasured third factor could account for the present findings although patients on medications most likely to affect immune function were excluded. Another limitation is the measurement of both PA and stimulated cytokine levels at a single point in time. Although both parameters are known to be relatively stable (De Craen et al., 2005; Watson et al., 1988), multiple assessments over time would provide a more reliable indicator of interindividual variability.

Finally, it should be noted that the clinical significance of individual differences in the stimulated production of cytokines remains to be determined. Indeed, initial evidence has linked greater stimulation of pro-inflammatory cytokine production to both positive and negative health outcomes. For instance, production of pro-inflammatory cytokines has been associated with faster wound healing (Marucha, 1998), a process that relies on local inflammatory processes. In contrast, a recent study showed higher LPS activation of monocytes to predict future risk of heart failure among individuals who are post myocardial infarction (Sato et al., 2006). Further investigation into the predictive and clinical utility of this in vitro measure is necessary to interpret these differences.

This study provides initial evidence that positive emotional style is inversely associated with the potential for monocytes to produce IL-6 and IL-10, raising the possibility that there is a meaningful distribution of differences in cytokine production that may form a physiological basis for associations between trait PA and risk of inflammatory disease. Further exploration of this potential pathophysiological pathway is warranted.

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Figure 1.
Positive emotional style and stimulated IL-6 after controlling for covariates (age, gender, race, BMI and WBC count)

Demographic and health characteristics and cytokine production levels of the sample (n=146, except where noted)

Variable	Mean (SD) or %
Gender	57.5% male
Age (years)	45.2 (6.2)
Race	95.2% white, 4.8% other
BMI (kg/m ²)	26.6 (5.1)
% taking medication	13.6%
% current smokers	13.7%
% taking anti-hypertensive medication	4.1%
% taking lipid-lowering medication	7.5%
% taking reproductive hormones	9.7%
Menopausal Status	64.5% pre-menopausal, 35.5% other ^d
PSQI sleep score ^a	4.7 (2.3)
Physical Activity (kcal/week)	2603 (1872)
Positive Affective Style	35.7 (6.7)
Negative Affective Style	14.1 (4.7)
White Blood Cells ($\times 10^6/L$)	5817 (1609)
IL-6 production (pg/ml)	68867 (19728)
IL-1 β production (pg/ml) ^b	30901 (12143)
TNF- α production (pg/ml) ^c	53014 (2116)
IL-10 production (pg/ml)	501 (294)

^an= 143;
^bn= 139;
^cn= 144
^d“Other”= peri-menopausal (n=12); post-menopausal (n= 4); hysterectomy (n=1); hysterectomy with hormone replacement therapy (n= 5)

Table 2
Positive affective style predicts stimulated IL-6 production

Predictor	B	SE B	β	t	p-value
Step 1 ^a					
Gender	-.196	.047	-.333	-4.176	.000
Age	.000	.004	.000	.004	.997
Race	.094	.108	.069	.877	.382
BMI	.000	.005	-.006	-.077	.939
WBC count	.425	.196	.173	2.174	.031
Step 2					
Positive Affect	-.008	.004	-.180	-2.156	.033

^aFor step1 equation adjusted $R^2=.14$, $\Delta R^2=.14$, $p<.001$; for step 2 adjusted $R^2=.16$, $\Delta R^2=.03$, $p=.033$

Table 3
Positive affective style predicts stimulated IL-10 production

Predictor	B	SE B	β	t	p-value
Step 1 ^a					
Gender	-4.196	1.093	-.311	-3.839	.000
Age	.003	.089	.002	.029	.977
Race	-.356	2.509	-.011	-.142	.887
BMI	-.100	.108	-.076	-.919	.360
WBC count	-12.980	4.557	-.230	-2.848	.005
Step 2					
Positive Affect	-.207	.085	-.207	-2.445	.016

^aFor step1 equation adjusted $R^2=.11$, $\Delta R^2=.11$, $p<.001$; for step 2 adjusted $R^2=.14$, $\Delta R^2=.04$, $p=.016$