Role of inflammatory liability in modifying the relationship between stressful life events and depressive symptomology

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Abstract

There is a large literature documenting a robust association between major stressful life events and depression and depressive symptoms. While inflammation has been suggested as a potential biological mechanism linking stressful life exposures and depression, this link remains unclear. In this paper, we used data from the National Longitudinal Study of Adolescent to Adult Health (Add Health) to test the role of inflammatory liability in moderating the link between stressful life events and depressive symptomology. We found preliminary evidence that the increase in depressive symptoms associated with greater cumulative stressful life events is steeper for individuals with a gene expression profile of increase inflammatory liability.

Introduction

Stressful life events are considered as stimuli or life changes that are accompanied by taxing demands and elicit stress response (Schwarzer & Luszczynska, 2012). Life events such as the death of family or close friends, loss of a job, or end of a romantic relationship are typically included in such research, and have been documented as reliable predictors of depressive symptoms and the onset of major depressive disorder (Kessler, 1997). This relationship has been documented across severity, duration, and life course stage of the stressful experience (Hammen, 2005), controlling for important confounders such as genetics (Kendler, Karkowski, & Prescott, 1999)

There is evidence that stressful life events are associated with inflammation. Previous research has linked adverse childhood events to circulating levels of Il-6 and C-reactive protein (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Danese, Pariante, Caspi, Taylor, & Poulton, 2007). The association between stressful life events and inflammation is not restricted to early life, but has been documented among adults as well (Miller et al., 2008).

Relatedly, inflammatory response has been established as an important contributor to the pathophysiology of depression (Slavich & Irwin, 2014). Inflammatory response may be a risk factor for depression, putting individuals who are exposed to greater stressors at greater risk. Several longitudinal studies have linked levels of inflammation to subsequent development of depression (Au, Smith, Gariépy, & Schmitz, 2015; Gimeno et al., 2009). However, the relationship between stressful life events and depression as moderated by inflammatory

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liability is still unknown. Why do some individuals who experience stressful life events experience elevated depressive symptoms, while others do not? We examine the moderating role of inflammatory liability. We define inflammatory liability as peripheral inflammation that serves as a risk factor in shaping who will suffer from particular social stressors, and measure this using gene expression profiles of inflammation. In this paper, we used data from the National Longitudinal Study of Adolescent to Adult Health (Add Health) to test the role of inflammatory liability in moderating the link between stressful life events and depressive symptomology.

Data and Methods

Sample

We use data from the National Longitudinal Study of Adolescent to Adult Health (Add Health). Add Health is a nationally representative study of US adolescents in grades 7-12 at Wave I in 1994-1995, with four additional subsequent follow up interview waves. At the most recent data collection, Wave V in 2016-2018, respondents were aged 32-42. The Wave V sample is split into three random samples, each corresponding to a different time period of data collection. We use here survey and gene expression data from Sample 1 (n~3,800 survey, 1,350 RNA) collected in 2016-2017.

Depressive symptoms

In the preliminary analyses presented here, we use Wave V self-report of depressive symptoms experienced in the last week. This is a four-item abridged CES-D, with frequency of feeling "unable to shake off the blues", "depressed", "sad", and "happy" (reverse coded). For each feeling, respondents are able to select one of four responses – never/rarely, sometimes, a lot of the time, and most of the time, assigned values from zero to three. Responses are summed across measures, for a depressive symptom score ranging from zero to 12. In future analyses, we plan to examine repeated measures of depressive symptoms at Waves I, III, IV, and V.

Stressful life events

At each wave, respondents were asked about their lifetime or recent experience of life stage specific stressful events. This includes parental and sibling death, friend or family suicide, victimization, abuse, relationship dissolution, child death, job loss, financial hardship, and eviction. We plan to examine life course exposure to stressful life events in future analyses. For preliminary analyses presented here, we use a cumulative measure of stressful life events constructed as the sum across all waves.

Gene Expression

Following the Wave V survey, respondents were scheduled for an in-home biomarker data collection examination. During the examinations, fully trained field interviewers/phlebotomists collected biological data and specimens following standard protocols. Venous blood was collected via conventional phlebotomy. We used the PAXgene® Blood RNA System which consists of a blood collection tube (PAXgene® Blood RNA Tube 2.5 mL) and nucleic acid purification kit (PAXgene® Blood RNA Kit).

For transcriptome profiling, we selected a subsample (n=1,350) from respondents who provided PAXgene specimens in Sample 1. Transcriptome profiling by Illumina HT- 12 bead arrays was done using 100 ng of total RNA. RNA was extracted under RNAse-free/PCR clean BSL2 conditions using automated nucleic acid extraction systems (Qiagen QIAcube). RNA concentration and purity were assessed by spectrophotometry (Nanodrop ND1000) and RNA integrity was assessed using an Agilent Bioanalalyzer (Agilent, Palo Alto CA). In samples with suitable RNA mass and integrity,genome-wide transcriptional profiles was obtained using target cRNA synthesis (Ambion TotalPrep) and hybridization to Illumina Human HT-12 bead arrays in the UCLA Neuroscience Genomics Core Laboratory following the manufacturer's standard protocol (Illumina, San Diego CA). Raw hybridization fluorescence intensity data was assessed for quality using standard endpoint quality assurance procedures. Samples passing endpoint quality assurance metrics were quantile normalized to provide the benchmark working dataset.

Inflammatory Liability

In this preliminary analysis, we construct a measure of inflammatory liability by selecting transcription sites that were identified as part of the conserved transcriptional response to adversity (CTRA) (Steve W. Cole et al., 2007; Steven W. Cole, 2013; Irwin & Cole, 2011). Briefly, the CTRA is a 53-gene panel with up-regulation of inflammatory pathways and down regulation of anti-inflammatory and antiviral pathways among socially isolated and among low socioeconomic status individuals. We selected the 18 transcription sites involved in inflammation, and construct a measure of inflammatory liability as the arithmetic mean of transcription across these sites for each individual where higher values indicate greater liability.

In future analysis, we plan to employ additional strategies to identify relevant gene expression profiles. First, we will draw from genome wide association studies (GWAS) to identify genes involved in inflammation. Second, we will use a data-driven machine learning approach to identify gene expression patterns that are correlated with stressful life events.

Analysis

We estimate Poisson regression models for the number of depressive symptoms at Wave V, controlling for sex, age, and race/ethnicity. To test whether the relationship between stressful life events and depressive symptoms varies by inflammatory liability, we include an interaction term for stressful life events and the inflammatory gene expression profile.

Preliminary Results

On average, at Wave V Add Health respondents reported two depressive symptoms on the twelve-point scale.

In Table 2, incidence-rate ratios are presented from Poisson regression. Men reported lower depressive symptoms compared to women, and depressive symptoms increased with age. In this preliminary sample, there were no significant race/ethnic differences in reports of depressive symptoms. Cumulative number of stressful life events was associated with increased depressive symptoms. There was no significant main effect of the inflammatory gene expression profile.

We explored the possibility of a moderating relationship between cumulative stressful life events and inflammatory liability in Table 3. We found preliminary evidence that the association between stressful life events and depressive symptoms is moderated by inflammatory liability, such that the increase in depressive symptoms associated with greater exposure to stressful events is heightened among those with greater inflammatory liability. This finding is more apparent in Figure 1, which plots the predicted number of depressive symptoms across exposure to cumulative stressful live events separately for individuals with low and high inflammatory liability. These results suggest that there are some people who experience stressful life events but, due perhaps in part to lower inflammatory liability, do not experience as great of an increase in depressive symptoms.

Future results will present discovery analyses of gene expression signatures for stressful life events linked to inflammatory processes and analysis of these signatures in moderating exposure to stressful life events and depressive symtoms.

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Table 1. Descriptive Statistics

Variable	Mean(SD)/%
Male	39%
Age	36.5 (1.75)
Race/ethnicity (NH white)	65%
NH Black	17%
Asian	4%
Other	1%
Hispanic	13%
Stressful life events	7.5 (5.5)
Inflammatory gene expression profile	2.46 (0.39)
NH Black	1000

Table 2. Poisson Regression Results for Depressive Symptoms

	IRR	SE	p-value
Male	0.780	0.043	0.000
Age	1.052	0.017	0.002
Race/ethnicity (NH white)			
NH Black	1.040	0.072	0.569
Asian	1.008	0.164	0.962
Other	0.999	0.253	0.998
Hispanic	0.946	0.077	0.501
Stressful life events	1.045	0.005	0.000
Inflammatory gene expression profile (standardized)	1.032	0.026	0.214
N		1000	

Table 3. Poisson Regression Results for Depressive Symptoms Moderated by Inflammatory Liability

	IRR	SE	p-value
Male	0.790	0.044	0.000
Age	1.052	0.017	0.002
Race/ethnicity (NH white)			
NH Black	1.045	0.073	0.525
Asian	1.025	0.167	0.880
Other	0.967	0.245	0.894
Hispanic	0.942	0.077	0.465
Stressful life events	1.044	0.005	0.000
Inflammatory gene expression profile (standardized)	0.912	0.044	0.055
Stressful life events x inflammatory profile	1.014	0.005	0.002
N		1000	

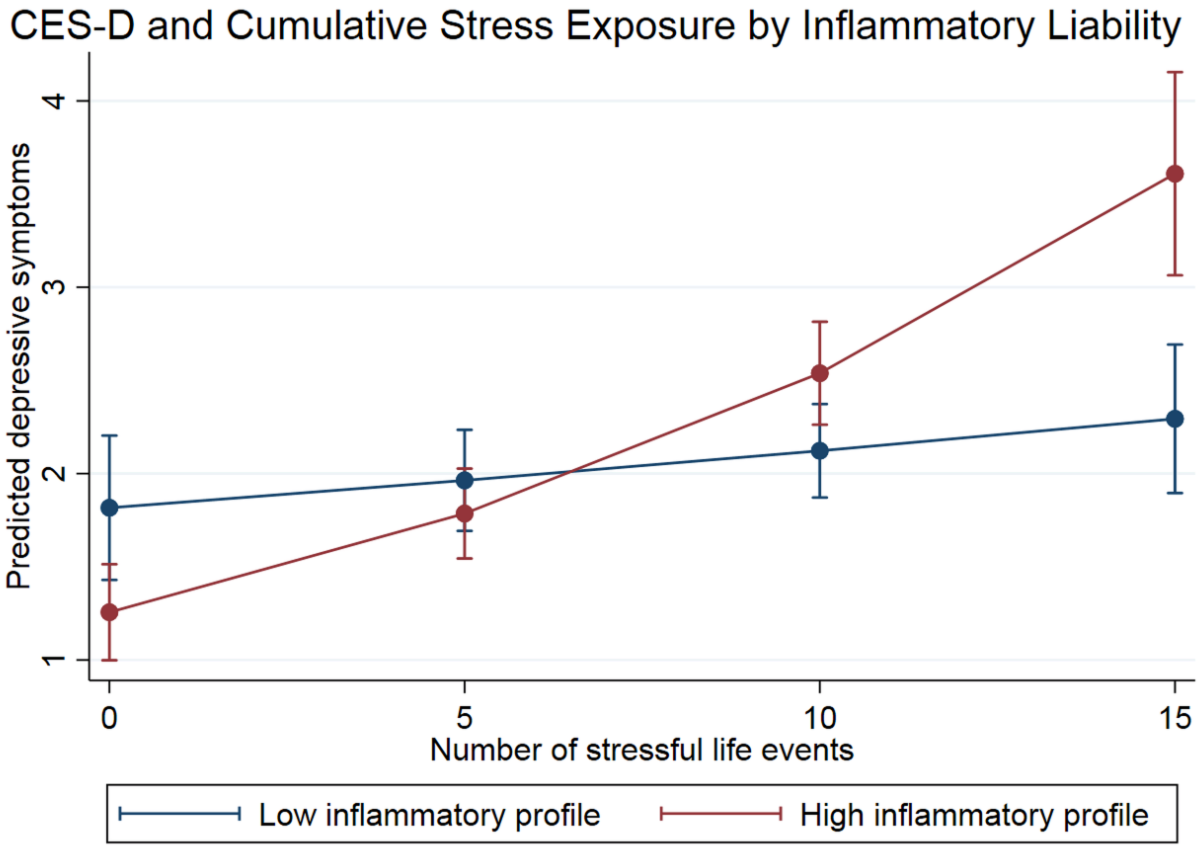

Figure 1. Depressive symptoms by exposure to cumulative stressful life events by inflammatory gene expression profile. Low/high inflammatory gene expression profiles are defined as two standard deviations below/above the mean.