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Depressive Symptoms Enhance Stress-induced Inflammatory Responses

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Abstract

Depression is a risk factor for morbidity and mortality, and immune dysregulation may be partially responsible for this link. Proinflammatory cytokines such as interleukin 6 (IL-6) are reliable predictors of quality of life, morbidity, and many causes of mortality. The current study evaluated relationships between depressive symptoms, as assessed by the CES-D, and stress-induced inflammation. The participants, 138 healthy adults, were evaluated at rest, and after a standardized laboratory speech and mental arithmetic stressor. Compared with individuals with fewer depressive symptoms, those with more depressive symptoms produced more IL-6 in response to the stressor, as well as significantly higher levels of IL-6 both 45 minutes and 2 hours after the stressor. These findings add to our emerging understanding of the complex interactions among stress, depression, and immune dysregulation, and provide one potential pathway to explain relationships between depressive symptoms and disease.

1. Introduction

Depression is a risk factor for morbidity and mortality (Rovner et al., 1991; Wulsin, Vaillant, & Wells, 1999). Both major depression and subthreshold depressive symptoms have been linked to many diseases of older adulthood (Bush et al., 2001; Frasure-Smith et al., 2009; Pan et al., 2011; Satin, Linden, & Phillips, 2009; Wouts et al., 2008). Immune dysregulation may partially contribute to these links. Inflammation is a key immunological mechanism that promotes many age-related diseases including diabetes, certain cancers, cardiovascular disorders, frailty and mortality (Maggio, Guralnik, Longo, & Ferrucci, 2006).

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In this study, we examined how depressive symptoms interact with acute stress to induce proinflammatory cytokine production.

Acute stress produces transient increases in systemic inflammation. Stress-induced elevations in inflammation have been detected among medical students preparing for an academic exam, individuals giving an oral presentation, and couples engaging in a marital disagreement (Heinz et al., 2003; Kiecolt-Glaser et al., 2005; Maes et al., 1998). Standardized experimental performance tasks, such as the Trier Social Stress Test (TSST), promote reliable elevations in interleukin-6 (IL-6) (Carpenter et al., 2010; Pace et al., 2006; Steptoe, Hamer, & Chida, 2007). These stress-induced inflammatory responses may vary in magnitude between individuals.

Prior stress and depression may enhance stress-induced inflammatory rises by sensitizing the inflammatory response to stress (Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003). For example, rats that were previously exposed to inescapable tailshock produced larger inflammatory responses to bacterial endotoxin than controls that were not shocked (Johnson et al., 2002). Studies in humans provide preliminary evidence that depression may promote greater stress-induced increases in circulating IL-6. In a study comparing 14 males with a history of early life stress and major depression with 14 controls, major depression patients with early life stress produced a more pronounced plasma IL-6 response to the TSST than controls (Pace et al., 2006). In another study 16 women with a lifetime history of depression showed greater IL-6 increases after giving birth than 50 women without a history of depression (Maes, Ombelet, De Jongh, Kenis, & Bosmans, 2001). These findings provide initial evidence that major depression may enhance systemic inflammation. However, sample size was limited in both studies, and we do not know if these findings extend to those with depressive symptoms more generally.

Minor elevations in depressive symptoms are associated with higher baseline levels of proinflammatory cytokine production (Lutgendorf et al., 1999). Furthermore, in a community sample of older adults, those with more depressive symptoms had a greater IL-6 increase after an annual influenza vaccination compared to those with fewer symptoms, suggesting that even modest elevations in depressive symptoms may sensitize the inflammatory response (Glaser et al., 2003). The current study sought to extend work demonstrating that those with major depression have more pronounced IL-6 elevations in response to a stressor by examining whether stress-induced IL-6 responses are exaggerated among individuals with more depressive symptoms compared with fewer depressive symptoms.

2. Methods

2.1 Subjects

The study data were drawn from the baseline sample of a clinical trial addressing the potential benefits of fish oil. Participants were recruited through advertisements, brochures, and media announcements in the local community. Screening exclusions included a prior history of cancer (except basal or squamous cell), diabetes, chronic obstructive pulmonary disease, autoimmune disease, evidence of liver or kidney failure, symptomatic ischemic heart disease, GERD, ulcerative colitis, smoking status, excessively high triglycerides or LDL cholesterol, more than 3 hours a week of vigorous physical exercise, and a body mass index (BMI) above 40. Individuals could not participate if they were taking medications for depression, anxiety, cholesterol, or blood pressure. The Ohio State Biomedical Research Review Committee approved the project; all subjects gave written informed consent prior to participation.

2.2. Procedure

When participants arrived at the Clinical Research Center (a hospital research unit) at 7:45 a.m., a catheter was inserted in their arm. Once they had eaten a standardized breakfast (after fasting since midnight) and completed questionnaires (approximately 25 minutes after catheter insertion), they sat quietly in a chair for 20 minutes. At the end this relaxation period, blood was drawn to assess baseline IL-6 levels.

Next, subjects participated in the Trier Social Stress Test, a well validated stressor (Kirschbaum, Pirke, & Hellhammer, 1993). Participants were told they would deliver a speech in front of a committee of behavioral experts, and were briefly brought into the room to view the committee before they prepared the speech. Then, in another room, they spent 10 minutes preparing a speech about why they were the best candidate for a job. After that, a research assistant escorted them to a room where they saw a microphone, video camera, and an audience panel of 2 individuals wearing white laboratory coats. While seated, participants gave their 5-minute speech and then performed mental arithmetic serial subtraction tasks for 5 minutes in front of this panel. Then, 45 minutes post-stressor, another blood sample was drawn, followed by another blood draw 2 hours after the stressor.

2.3 Measures

The Center for Epidemiological Studies Depression Scale (CES-D) was used as a measure of depressive symptoms. It has been used extensively as a brief measure of depressive symptomatology (Basco, Krebaum, & Rush, 1997; Radloff, 1977). Studies have shown acceptable test-retest reliability and excellent construct validity (Basco et al., 1997).

We assessed major depression with the Structured Clinical Interview for DSM-IV, nonpatient version (SCID-NP) (First, Spitzer, & Williams, 1995) Inter-rater reliability for SCID-NP diagnoses were calculated using randomly selected audiotapes for 20% of the participants. This substantial interrater agreement was confirmed with McNemar's test for marginal proportions ($p>0.99$ for all diagnoses).

The Childhood Trauma Questionnaire provided data on early childhood abuse and neglect. Widely used, it has excellent normative data for its 5 scales: Physical, Sexual, and Emotional Abuse, and Physical and Emotional Neglect (Bernstein & Fink, 1998). We adopted the Walker cuts (Walker et al., 1999) to make categorical cut-offs (with sensitivity and specificity >.85 for each scale). Then, we created a categorical indicator variable representing any maltreatment (exceeding ≥ CTQ cut point threshold)(Walker et al., 1999).

We used the **Beck Anxiety Inventory** to assess both cognitive and physiological symptoms (Beck, Epstein, Brown, & Steer, 1988). This scale has been shown to have sound psychometric properties such as factorial validity, internal consistency, and test-retest stability.

Whole blood was drawn into a BD vacutainer serum tube (Becton-Dickinson, New Jersey) and allowed to clot at room temperature for 30 minutes. Serum tubes were then centrifuged for 10 minutes at 2700rpm. Serum was stored at -86OC until assayed in duplicate levels for IL-6 cytokine using MSD 96-well Multispot Custom Cytokine Kits (Meso Scale Discovery, Maryland) . Plates were read using an MSD Sector Imager 2400. A four parameter logistic fit standard curve was derived using the MSD Software and IL-6 concentrations were extrapolated from the standard curve. The IL-6 sensitivity was 0.26 pg/ml. The CV for intra-assay precision had a range of 5.64-6.70%. The CV for inter-assay precision had a range of 5.16-10.2%.

2.4 Analytic Method

All analyses were run using mixed models regression and restricted maximum likelihood estimation. IL-6 was log transformed before analysis. We adjusted for key potential confounds including age, BMI, and sex. We examined residuals from all analyses to confirm that they were distributed normally.

We hypothesized that individuals who had more depressive symptoms would have greater increased IL-6 in response to the stressor than those with fewer depressive symptoms. We ran a repeated measures analysis with depressive symptoms modeled as a continuous variable to test this hypothesis. There was considerable variability in correlations over the three segments. Hence, we employed an unstructured within-subjects covariance matrix for all repeated measures analyses. The Kenward-Roger option was used to correct the degrees of freedom in the model, which brought Type I errors rates back to the nominal level. All tests used a two-sided, α=0.05 significance level.

3. Results

Table 1 reports descriptive information for the participants. Table 2 summarizes the results of the repeated measures analysis that assessed whether changes in IL-6 over time differed depending on depressive symptoms.

Overall, IL-6 increased in response to the Trier Social Stress Test. There was a significant interaction between depressive symptoms and time. Compared to those with fewer depressive symptoms, individuals with more depressive symptoms had a greater IL-6 response to the Trier Social Stress Test. Specifically, individuals with more depressive symptoms displayed greater increases in IL-6 from baseline to 45 minutes post-stressor and baseline to 2 hours post-stressor (Figure 1). Depressive symptoms were unrelated to baseline levels of IL-6. However, those who had more depressive symptoms had significantly higher IL-6 levels both 45 minutes post-stressor and 2 hours post-stressor than those with fewer depressive symptoms. We ran an additional analysis controlling for baseline levels of IL-6, and all significance levels remained the same. In sum, those who had more depressive symptoms had greater IL-6 increases in response to the stressor and higher levels of IL-6 after the stressor than those with fewer depressive symptoms.

In ancillary analyses, we adjusted for a history of maltreatment, menopausal status, and anxiety levels. None of these variables were associated with changes in IL-6, and the significance levels of all results remained the same. When we dichotomized BMI at 30, it was not significantly associated with changes in IL-6. Furthermore, it did not interact with depressive symptoms.

4. Discussion

Individuals with more depressive symptoms had larger stress-induced increases in IL-6 to a standardized laboratory speech and mental arithmetic stressor. They also had significantly higher levels of IL-6 after the stressor than those with fewer depressive symptoms. With a considerably larger sample, this study extends work linking major depression to greater stress-induced increases in IL-6 by demonstrating that those who have more depressive symptoms show an exaggerated IL-6 response to a laboratory stressor.

Depression has been linked to premature mortality among those with cancer, heart disease, stroke, and diabetes (Bush et al., 2001; Frasure-Smith et al., 2009; Pan et al., 2011; Satin et al., 2009; Wouts et al., 2008). Elevated inflammation is a risk factor for these diseases (De Martinis, Franceschi, Monti, & Ginaldi, 2006; Maggio et al., 2006). Accordingly, these

findings may provide one potential pathway to explain relationships between depressive symptoms and morbidity and premature morality.

Proinflammatory cytokines can act on the brain to induce sickness behaviors (Ahles et al., 2002; Bower, Ganz, Aziz, & Fahey, 2002; Luecken, Kraft, Appelhans, & Enders, 2009; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). Although there is ample evidence that depressive symptoms can elevate inflammation, there is also considerable evidence that inflammation contributes to depressive symptoms (Miller, Maletic, & Raison, 2009; Raison, Capuron, & Miller, 2006). The association between inflammation and depressive symptoms has been found in a variety of different populations (Alesci et al., 2005; Bouhuys, Flentge, Oldehinkel, & van den Berg, 2004; Miller, Stetler, Carney, Freedland, & Banks, 2002; Musselman et al., 2001). Minor elevations in depressive symptoms may be a catalyst for stress-induced inflammatory rises that subsequently promote more depressive symptoms through a feedback loop.

Mechanistically, both autonomic and neuroendocrine function may promote stress-induced inflammation. Norepinephrine enhances proinflammatory cytokines by inducing nuclear factor B (NF- B) transcription, an intracellular signaling molecule that regulates proinflammatory cytokine gene expression (Bierhaus et al., 2003; Straub & Härle, 2005). Furthermore, higher levels of parasympathetic activity can reduce inflammation via the cholinergic anti-inflammatory pathway that induces acetylcholine release (Tracey, 2009).

Our sample consisted of healthy adults. Accordingly, we do not know if these findings could be detected among those with chronic diseases. Furthermore, our sample was predominately college educated and white. Future studies that are more diverse are needed in order to ensure our findings generalize across different ethnic and socioeconomic groups. Finally, the type of stressor we used may have influenced the results. The stressor we imposed evokes negative self-evaluation (Kirschbaum et al., 1993), which may be particularly stressful for those with more depressive symptoms (Giesler, Josephs, & Swann Jr, 1996). In future work, it would be interesting to see if other types of acute stressors elicit similar inflammatory responses.

In sum, those with more depressive symptoms exhibited enhanced inflammation to a stressor compared with those with fewer depressive symptoms. Accordingly, depressive symptoms may enhance the stress response system in ways that promote excessive inflammation. These findings add to our emerging understanding of the complex interactions among stress, depression, and immune dysregulation.

Acknowledgments

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Highlights

Compared with individuals with fewer depressive symptoms, those with more depressive symptoms produced more IL-6 in response to a laboratory stressor, as well as significantly higher levels of IL-6 both 45 minutes and 2 hours after the stressor.

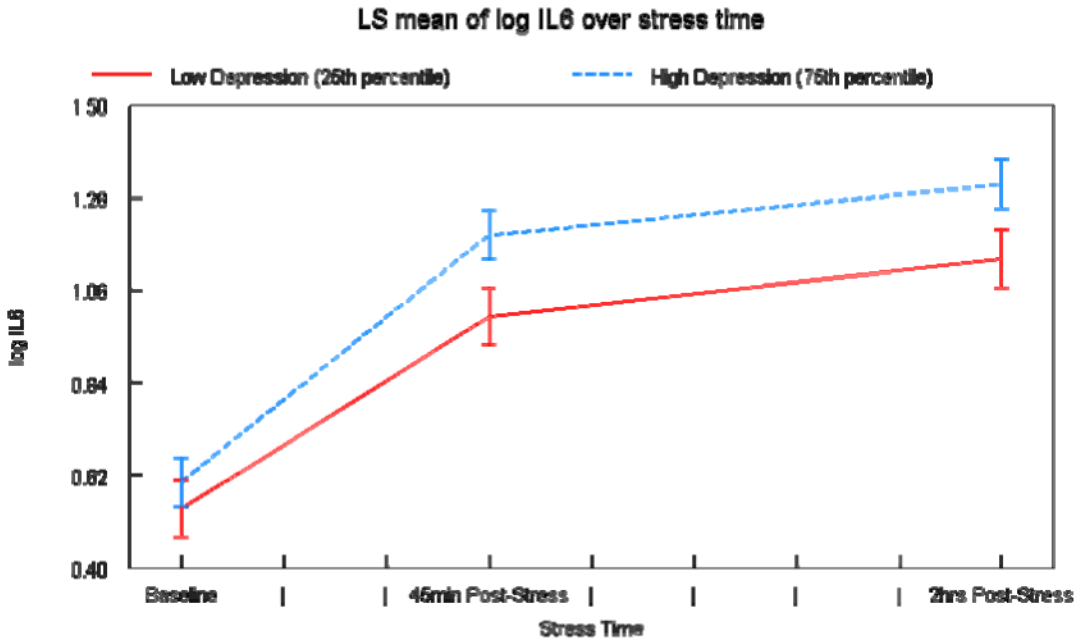

Figure 1.
Mean (± SEM) IL-6 across experimental periods in people with more and fewer depressive symptoms based on the 75th and 25th percentile scores on the CES-D. The 25% represents a score of "2" on the CES-D and the 75% represents a score of "10." These are both well below the clinical threshold for depression, which is "16."

Table 1

Sample Population Characteristics

	Total (N=138)		
Variable	***n***	***M***	***SD***
IL6		3.79	3.84
Log IL6		1.01	0.81
Age (yrs)		51.04	7.75
BMI (kg/m^2)		30.59	4.50
CESD		7.58	8.10
Current depression			
No	119		
Yes	4		
Race			
White	109		
Black	22		
Asian	4		
Native American	2		
Other	1		
Sex			
Female	93		
Male	45		
Menopause			
No	56		
Yes	45		
NA	37		
Marital Status			
Single	19		
Married	92		
Common Law	3		
Separated	3		
Divorced	16		
Widowed	5		
Education			
Some high school	7		
Some college	32		
College graduate	52		
Graduate/Professional	47		
Income			
< 25 K	11		
25 K- 50 K	34		
50 K- 75 K	35		
75 K- 100 K	26		

	Total (N=138)		
Variable	***n***	***M***	***SD***
> 100 K	24		
Prefer not to answer	8		

Table 2
Interleukin 6 across time based on CES-D scores

Effect	Time point	Log IL6	
		Estimate	p
CESD total score		0.008	0.240
Period	Baseline		
	Post stress 45 minutes	0.424	<0.001
	Post stress 2 hours	0.565	<0.001
CESD × Period	Baseline		
	Post stress 45 minutes	0.017	0.016
	Post stress 2 hours	0.014	0.035
Change per unit depression	Baseline	0.008	0.240
	Post stress 45 minutes	0.024	0.001
	Post stress 2 hours	0.022	0.002
Slope change per unit depression	Baseline to 45 minutes	0.017	0.016
across time points	Baseline to 2 hours	0.014	0.035
	45 minutes to 2 hours	−0.002	0.757