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Acute deviations from long-term trait depressive symptoms predict systemic inflammatory activity

Nicolas Rohleder *, Gregory E. Miller

Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC, Canada V6T 1Z4

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Abstract

Objective. Depressive symptoms increase morbidity and mortality from coronary heart disease and systemic inflammation has been proposed as the underlying mechanism. While higher levels of inflammatory mediators have been found in dysphoric individuals, it is not known whether long-term or short-term mood changes are responsible for this phenomenon.

Methods. A sample of 65 young women provided weekly web-based self-ratings of depressive mood over a period of 20 weeks using the CES-D, and systemic inflammation was assessed by measuring plasma interleukin-6 (IL-6) and C-reactive protein (CRP) before and after the observation period. CES-D ratings were used to develop state and trait indicators of depressed mood and evaluate their relationship with inflammatory mediators.

Results. Hierarchical linear regressions controlling for baseline inflammation, age, and BMI revealed that trait levels of depressive symptoms were not associated with IL-6 ($\beta = 0.09$; n.s.) and CRP ($\beta = 0.01$; n.s.) concentrations after the observation period. In contrast, state levels of depressive symptoms were associated with changes in IL-6, but not CRP, particularly when they were indexed as the disparity between a person's trait level of symptoms and her CES-D score just prior to IL-6 assessment ($\beta = 0.35$; $p = 0.03$).

Conclusion. These results lead us to conclude that in young women, state, rather than trait depressed mood stimulates peripheral inflammation as measured by IL-6. This pattern suggests that in this age group, fast-reacting inflammatory mediators such as IL-6 probably respond to short-term changes, for example, in stress hormones or stress hormone sensitivity, rather than long-term dysregulations of allostatic mechanisms.
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1. Introduction

Symptoms of depression not only diminish a person's quality of life, but they also increase the risk for various physical diseases. The most prominent example is coronary heart disease. Depressive symptoms after myocardial infarction increase the risk for further cardiac events and thereby lower survival rates (Carney et al., 1988, 2004; Frasure-Smith et al., 1993; Lesperance et al., 2002). Depressive symptoms also predict cardiac events in initially healthy individuals (for a meta-analyses see Rugulies, 2002), and are associated with worse outcomes in patients with diabetes (Lustman et al., 2000; de Groot et al., 2001), inflammatory bowel disease (Mittermaier et al., 2004), and rheumatoid arthritis (Zautra et al., 2004, 2007).

Since inflammation is a pathogenic mechanism in all of the above conditions (Danesh, 1999; Libby and Ridker, 2006; Hotamisligil, 2006), research has focused on inflammatory processes as mediators between depressive symptoms and disease outcomes (for a summary see: Irwin, 2002; Miller and Blackwell, 2006; Irwin and Miller, 2007). Recent studies have shown that depressive symptoms are associated with increased concentrations of inflammatory mediators such as interleukin-6 (IL-6) and C-reactive protein (CRP). Increased concentrations of

* Corresponding author. Fax: +1 604 822 6923.
E-mail address: nicolasrohleder@mac.com (N. Rohleder).

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inflammatory mediators have for example been found in patients with clinical depression (Miller et al., 2002; Danner et al., 2003; Ford and Erlinger, 2004), interestingly even in remitted major depressive disorder (Kling et al., 2007). This association of depressed mood and inflammation is not limited to clinical depression. Instead, sub-clinical depressive symptoms as assessed by self-rating scales have been related to higher plasma concentrations of inflammatory mediators as well (Dentino et al., 1999; Kop et al., 2002; Glaser et al., 2003; Panagiotakos et al., 2004; Empana et al., 2005; Miller et al., 2005a; for a review see Shimbo et al., 2005).

In all studies relating depressed mood with inflammation, results are based on single, one-time assessments of depressive symptoms. However, depression has both trait and state components, with the trait component reflecting a person's general tendencies to experience symptoms, and the state part more variable and short-term feelings of sadness, anhedonia, fatigue, etc. Any single measure of depressive symptoms will therefore reflect both trait and state influences, which are impossible to disentangle with a single, one-time measure of depressed mood.

Thus, it remains unclear whether trait or state components of depression, or an interaction of both, contributes to inflammation and hence to somatic disease. A discrimination between trait or state effects of depression on systemic inflammation would be important, because of different implications for treatment opportunities on the one hand, and theories about underlying mechanisms on the other hand. Should trait depression turn out to be associated with inflammation, negative effects on somatic health could be more difficult to treat, but if state depression would be associated with inflammation, it might be easier to therapeutically control its adverse effects, and effects might be less severe because the duration would probably be shorter.

In terms of mechanisms, association of state depressed mood with inflammation would point to mediation by fast reacting stress hormones, such as catecholamines, or changes in the ability of glucocorticoids to suppress cellular inflammatory responses. In fact, there are data in support of acute effects of mental states on peripheral inflammation. Several studies have shown that acute psychosocial stress as operationalized by laboratory stress tasks can lead to increased concentrations of inflammatory mediators in plasma (Miller et al., 2005b; von Kanel et al., 2006; Edwards et al., 2006; for a summary see Steptoe et al., 2007). It is unclear at present which tissues are the main sources of stress-induced inflammatory mediator increases (Miller et al., 2005b). Although there is evidence that noradrenergic activation of the transcription factor nuclear factor (NF)-κB in peripheral mononuclear cells links stress and peripheral inflammation (Bierhaus et al., 2003; Pace et al., 2006), it could also be similar mechanisms stimulating cytokine release from adipose tissues, which has been shown to be a significant source of circulating IL-6 (Yudkin et al., 2000).

Association of trait depressive symptoms with inflammation would point to either long-term dysregulations of stress systems, possibly taking the form of allostatic load (McEwen, 1998; McEwen and Stellar, 1993), or common underlying genetic differences, which might predispose individuals to depressive as well as inflammatory phenotypes. The possibility of such connections between depression and coronary heart disease has been reviewed by McCaffery et al. (2006), however, as the authors note there are few data available on common genetic vulnerabilities to depression and inflammation (McCaffery et al., 2006).

The goal of the present study was to sort out whether state or trait components of depressed mood are associated with markers of systemic inflammation. This differentiation can only be achieved by assessing depressive symptoms on multiple occasions over longer periods of time. Therefore, we assessed depressive symptoms weekly over a period of 5–6 months using a web-based version of the CES-D, and measured the inflammatory mediators IL-6 and C-reactive protein (CRP) at the beginning and the end of this period. We reasoned that if trait depressed mood is what contributes to inflammation, average symptom severity over 5–6 months should predict IL-6 and CRP. But if the state component of depressed mood is what instigates inflammation, then only symptoms measured in close temporal proximity to IL-6 and CRP should be predictive. We were uncertain about whether these state effects would be absolute or relative in nature. If they are absolute, then higher scores on the CES-D proximal to assessment should relate to greater IL-6 and CRP, regardless of trait levels. But if they are relative in nature, raw scores on the CES-D will be unrelated to inflammation; what will matter is how far above or below their usual level of symptoms people are.

2. Methods

2.1. Participants

Data for this article were collected as part of a larger research project in which young women visited our research center every 5–6 months over the span of 2.5 years. Adolescent females were recruited from the larger Vancouver, British Columbia community through advertisements in schools, newspapers, and magazines. Young women were eligible for the study if they were (1) between the ages of 15 and 19, (2) fluent in the English language, (3) free of acute and chronic medical conditions, (4) without a lifetime history of major psychiatric disorders, and (5) at high risk for developing an initial episode of major depression. High risk was defined as having a first-degree relative with a history of depression, or as scoring in the top quartile of the sample distribution on one of two indices of cognitive vulnerability, the Dysfunctional Attitudes Scale (Weissmann and Beck, 1978) or the Adolescent Cognitive Style Questionnaire (Alloy et al., 1999).

The current article focuses on a subgroup of $n = 74$ young women who agreed to provide weekly web-based depression ratings over a period of 20 weeks. This period occurred between scheduled visits to our laboratory, during which their plasma IL-6 and CRP concentrations were assessed. Nine women had to be excluded because at least one of their plasma IL-6 measurements revealed a concentration greater than 3 pg/ml, suggestive of an infectious episode. The final sample of $n = 65$ women had a mean age of 18.6 years (SD = 1.4; range = 16.1–20.9) and a mean body

mass index (BMI) of 21.33 kg/m^2 (SD = 2.21; range = 16.95–26.83). Forty-three percent of the women self-identified of East Asian descent, 43% as Caucasian, and the remaining 14% described themselves as East Indian, African, Aboriginal, or other. Participants came from homes where mothers had an average of 14.6 years of education and fathers had an average of 15.6 years of education, and 64% of parents had at least a 2-year college diploma. Eighty-three percent of the participants came from a family in which their parents were currently married or common-law. This project was approved by the Research Ethics Board of the University of British Columbia. Written consent was obtained from all participants 18 years or older; for those who were younger, a parent or guardian provided consent, and participants provided written assent.

2.2. Procedures

Laboratory visits always occurred between 0900 h and 1200 h to control for diurnal variations. During visits, participants were interviewed regarding somatic health and life stress, filled out a battery of self-report scales, and provided venous blood samples for assessment of biological parameters, including circulating IL-6 (see below). After participants had completed their second visit to the center, we asked them to provide weekly ratings of depressive symptoms for a 5- to 6-month period between the two visits. This could either be done by logging onto a specifically designed web site and completing a short form of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) online, or by filling out a paper form of the CES-D and mailing it in every week. At the end of the observation period, they came to the laboratory for a regularly scheduled session, during which blood was again collected for IL-6.

To facilitate weekly assessments, we used a 10-item short form of the CES-D as described previously (Andresen et al., 1994). Each item asks for the frequency of specific feelings or behaviors during the past week, which are rated between 0 "not at all" and 3 "most or all of the time (5–7 days)", hence sum scores range between 0 and 30. Internal consistency in our sample was $\alpha = 0.71$. On average, the women in the study completed 13/20 weekly CES-D ratings (SD = 4.0). Further analysis suggest that this value reflects the influence of a few non-compliant participants, because almost 3/4 of the sample (74%) completed 12 or more of their scheduled web entries. Regardless, compliance with the web diary was unrelated to peripheral inflammation (IL-6: $r = 0.17$; $p = 0.17$; CRP: $r = 0.14$; $p = 0.27$) and trait ($r = -0.14$; $p = 0.27$) as well as state depressed mood (relative: $r = 0.01$; $p = 0.95$; absolute: $r = 0.01$; $p = 0.97$).

2.3. Peripheral inflammatory activity

To assess systemic inflammatory activity, venous blood was drawn from an antecubital vein into serum separator Vacutainer tubes (Becton–Dickinson, Mississauga, Canada). Blood was allowed to clot for 30 min and then centrifuged for 10 min at 1200*g*. Plasma was divided into aliquots and stored at −30 °C until further analysis. Interleukin-6 concentrations were quantified in duplicates using commercial high-sensitivity ELISA kits (Quantikine HS human IL-6; R&D Systems; Minneapolis, MN, USA) with a minimum detectable concentration of 0.039 pg/ml. Inter- and intra-assay variability were below 10%. C-reactive protein was measured by in Clinical Chemistry Laboratory of St. Paul's Hospital (Vancouver, Canada), using a high-sensitivity chemiluminescence technique on an Immulite 2000 instrument (Diagnostic Products Corporation, Los Angeles, USA). This assay has an intra-assay variability of 2.2% and a detection threshold of 0.20 mg/l.

2.4. Statistical analyses

The distributions of all variables were evaluated prior to analyses. Because CES-D scores, IL-6, and CRP levels were skewed, they were subjected to log-10 transformations. We then used the weekly CES-D ratings to calculate indices reflecting trait and state components of depression. To capture each subject's general tendencies for depressive symptoms—i.e., their trait level—we computed a series of average within-person CES-D scores over 20 weeks. State levels of depression were defined as the CES-D score the week before the final blood draw (the "absolute" model), or as the score that week after trait levels had been subtracted out (the "relative" model.) For exploratory purposes, we also identified the peak CES-D score over 20 weeks for each participant, and computed a within-person standard deviation to estimate the degree of variation. To test specific hypotheses, we first calculated Pearson correlations to test bivariate associations of each of the indices of depressive mood with the biological outcomes at the end of the observation period. Second, hierarchical linear regression equations were used to determine whether indices of depressed mood predicted variability of IL-6 and CRP over the study, controlling for potential confounders (age, BMI, and baseline IL-6 or CRP, resp.). Since no missing data occurred in the last week before measurement of inflammatory mediators, all analyses were performed on the full sample of $n = 65$ subjects.

3. Results

3.1. Preliminary analyses

Fig. 1 shows results of web-based assessment of depressive symptoms using CES-D in the 20 weeks between the two blood draws. The average trait CES-D score over the 20-week period was 8.71 (SD = 4.22; range = 0.25–17); suggesting that women in our study were experiencing mild to moderate symptoms. Using a cut-off score of 10 as suggested by Andresen et al. (1994), 52 of 65 participants (80%) were found to have depressive symptoms in a clinically relevant range at least once during the 20 weeks of observation. With regard to state levels, the average CES-D score on the visit before the final blood draw was 7.5 (SD = 5.51; range = 0–23). When trait levels of symptoms were subtracted from this value to get a "relative" index of state depression, the sample average was −0.71 (SD = 3.29; range = −7.71 to 6.67), suggesting that participants tended to be happier than usual during this week of the monitoring period. The average maximum 14.72 (SD = 5.82; range = 2–27) and the average standard deviation over 20 weeks was 3.30 (SD = 1.57; range = 0.62–7.85). Average IL-6 concentrations at the beginning of the observation period were 0.59 pg/ml (SEM = 0.05; range = 0.22–2.84) and 0.57 at the end of the observation period (SEM = 0.04; range = 0.24–2.36). Average CRP concentrations were 0.32 mg/l (SEM = 0.07; range = 0.19–2.6) at the beginning and 0.56 mg/l (SEM = 0.09; range = 0.19–2.8) at the end of the observation period. IL-6 concentrations after the observation period were associated with baseline IL-6 ($r = 0.25$; $p = 0.04$), but not with BMI ($r = 0.14$; $p = 0.28$) or with age ($r = 0.16$; $p = 0.25$). CRP concentrations after the observation period were associated with baseline CRP ($r = 0.64$; $p < 0.01$) and BMI ($r = 0.30$; $p = 0.02$) but not with age ($r = 0.07$; $p = 0.61$).

3.2. Association of trait depressive symptoms with inflammation

To test the hypothesis that trait depressive mood would be associated with peripheral inflammatory activity, we first computed Pearson correlations between the average

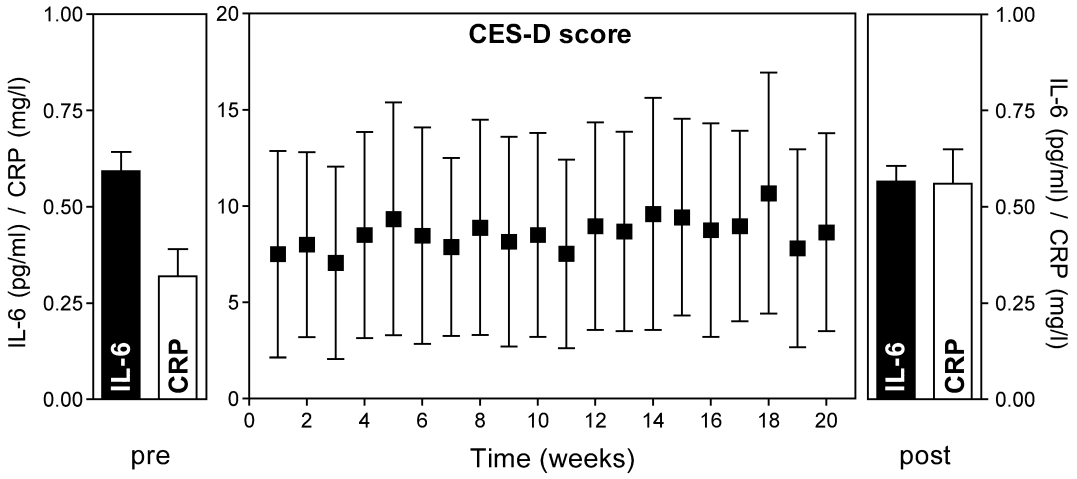

Fig. 1. CES-D scores (±SD) over a time period of 20 weeks, and plasma interleukin-6 (IL-6) and C-reactive protein (CRP) concentrations (means ± SEM) at the beginning and the end of the 20-week observation period.

web-based CES-D ratings of 20 weeks with subsequent IL-6 and CRP levels in plasma. These analyses indicated that average CES-D was not associated with inflammatory activity (IL-6: $r = 0.09$; $p = 0.46$; CRP: $r = 0.14$; $p = 0.27$). These results were confirmed by hierarchical regression controlling for baseline IL-6 or CRP, as well as age and BMI (IL-6: $\beta = 0.09$; $p = 0.49$; $R^2 = 0.1$; $\Delta R^2 = 0.01$; CRP: $\beta = 0.01$; $p = 0.90$; $R^2 = 0.44$; $\Delta R^2 = 0$).

3.3. Association of state depressive symptoms with inflammation

To test the hypothesis that absolute levels of recent depressive symptoms are associated with peripheral inflammatory activity, we computed Pearson correlations between the last week's CES-D score and subsequent plasma IL-6 and CRP levels in plasma. Results showed a positive association of IL-6 with last week's CES-D ($r = 0.28$; $p = 0.04$), indicating that higher symptoms related to more IL-6. However, in a hierarchical linear regression controlling for baseline IL-6, age, and BMI, the association was attenuated to marginal significance ($\beta = 0.27$; $p = 0.09$; $R^2 = 0.40$; $\Delta R^2 = 0.07$). Absolute recent depressed mood was not associated with CRP concentrations in plasma ($r = 0.09$; $p = 0.58$; $\beta = -0.01$; $p = 0.97$; $R^2 = 0.49$; $\Delta R^2 = 0$).

To test whether relative levels of recent depressive symptoms are associated with peripheral inflammatory activity, we first computed a Pearson correlation between the "relative" state depression index and subsequently measured inflammatory mediators. Results showed a positive association of "relative" depressed mood with IL-6 ($r = 0.35$; $p = 0.03$). This result was confirmed by hierarchical regression controlling for baseline IL-6, as well as age and BMI ($\beta = 0.36$; $p = 0.03$; $R^2 = 0.20$; $\Delta R^2 = 0.12$). These findings indicate that to the extent that participants were more dysphoric than usual the week before the blood draw, they showed greater increases in circulating concentrations of IL-6 over the follow-up period. Relative recent depressed mood was not associated with CRP concentrations in plasma ($r = 0.06$; $p = 0.71$; $\beta = 0.03$; $p = 0.80$; $R^2 = 0.50$; $\Delta R^2 = 0$) (Fig. 2).

Finally, we tested the hypothesis that an interaction of trait and state components of depressive mood is what predicts inflammation. Therefore an interaction term was calculated by multiplying the average CES-D ratings of 20 weeks with the last week's CES-D rating and entered into the last step of a hierarchical linear regression together with the last week's and the 20 weeks' score, controlling for baseline inflammatory activity, age, and BMI. Results showed that interaction of state and trait depressed mood was not a significant predictor of peripheral inflammation (IL-6: $\beta = -0.28$; $p = 0.71$; $R^2 = 0.21$; $\Delta R^2 = 0.01$; CRP:

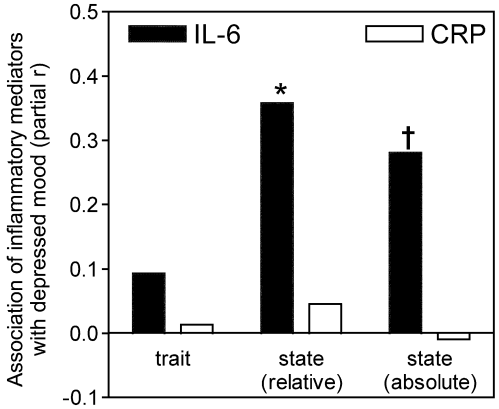

Fig. 2. Association of trait vs. state depressive symptoms with subsequently measured peripheral inflammation. Shown are partial correlations for prediction of plasma interleukin-6 (IL-6) and C-reactive protein (CRP) by average depression over 20 weeks ("trait"), by levels or depressive symptoms in the last week relative to average depressive symptoms ("state (relative)"), or by absolute level of depressive symptoms in the week before measurement of inflammation ("state (absolute)"). The analyses control for age, body mass index (BMI), and baseline IL-6 or CRP concentrations. ($^{*}p < 0.05$; $^{\dagger}p < 0.10$).

$\beta = -0.31$; $p = 0.64$; $R^2 = 0.50$; $\Delta R^2 = 0$). This analysis was repeated using the "relative" state depressed mood index. Results showed that interaction of relative state and trait depressed mood was not a predictor of peripheral inflammation (IL-6: $\beta = -0.13$; $p = 0.82$; $R^2 = 0.21$; $\Delta R^2 = 0$; CRP: $\beta = -0.02$; $p = 0.97$; $R^2 = 0.50$; $\Delta R^2 = 0$).

3.4. Additional analyses

Several additional hypotheses might be tested. To exclude the possibility that the association of recent depressive symptoms was found because the participants experienced a peak in depressive mood during the last weeks before assessment of inflammation, we calculated an index containing the maximal depression score of all 20 weeks before IL-6 or CRP measurement. If peak depression instead of recency underlies the findings, the peak index should be a predictor of inflammation. However, Pearson correlation revealed that maximum CES-D scores were not associated with subsequent plasma IL-6 ($r = 0.09$; $p = 0.50$) or CRP ($r = 0.13$; $p = 0.28$). These results were confirmed by hierarchical regressions controlling for baseline IL-6 or CRP, as well as age and BMI (IL-6: $\beta = 0.07$; $p = 0.59$; $R^2 = 0.09$; $\Delta R^2 = 0$; CRP: $\beta = 0.02$; $p = 0.88$; $R^2 = 0.44$; $\Delta R^2 = 0$).

Another possibility might be that those participants with the least stable mood, i.e. those with the highest variability of depressive symptoms, have the highest peripheral inflammation. We therefore calculated an additional index summarizing the standard deviation of each participant's CES-D ratings and correlated it with subsequent inflammation. Pearson correlation revealed no association of mood variability with peripheral IL-6 ($r = -0.07$; $p = 0.56$) or CRP ($r = -0.14$; $p = 0.28$). These results were confirmed by hierarchical regressions controlling for baseline IL-6 or CRP, as well as age and BMI (IL-6: $\beta = -0.10$; $p = 0.43$; $R^2 = 0.10$; $\Delta R^2 = 0.01$; CRP: $\beta = -0.04$: $p = 0.67$; $R^2 = 0.44$; $\Delta R^2 = 0$).

Another potential explanation for the association of recent depression with inflammation is that in some participants IL-6 levels rose prior to the last week's CES-D rating, and thereby induced depressive mood through central nervous system signaling as occurs in sickness behavior. Although we cannot directly test this hypothesis because no IL-6 measures were collected during the observation period, the general ability of inflammation to induce depressive mood can be estimated by testing whether IL-6 at the beginning of the observation period is associated with subsequent absolute CES-D ratings. Pearson correlation showed a moderate association ($r = 0.21$; $p = 0.09$), however, in a hierarchical regression analyses controlling for age and BMI, plasma IL-6 was not a significant predictor of the subsequent CES-D score ($\beta = 0.15$; $p = 0.35$; $R^2 = 0.06$; $\Delta R^2 = 0.02$). We also tested whether IL-6 predicted the deviation from each individual's trait depression. Pearson correlation ($r = 0.13$; $p = 0.19$) as well as hierarchical regression ($\beta = 0.11$; $p = 0.53$; $R^2 = 0.03$; $\Delta R^2 = 0.01$) revealed that IL-6 was not a predictor of relative depressive mood. This hypothesis was not tested for CRP, because CRP has not been reported to directly signal into the central nervous system.

4. Discussion

We set out in the present study to determine whether long-term or trait-like depressive symptoms versus short-term or state-like depressive symptoms over 5–6 months are associated with variability of systemic inflammation in healthy young women. Results showed that the average level of depressive symptoms, as assessed weekly for half a year, is not associated with variability in circulating IL-6 or CRP over the same period. However, we found a marginally significant association of the depression rating during the last week of the assessment period with subsequently measured IL-6 concentrations, and we found that the deviation of an individual's depression rating from the individual's average depression level was a significant predictor of over-time changes in systemic IL-6. No associations were found between state or trait depressive symptoms and CRP concentrations, and peripheral inflammation was not predicted by an interaction of state and trait depressive symptoms. We further found that neither the peak level of depressive symptoms nor the variability over 20 weeks was a predictor of inflammation, and that IL-6 levels did not predict subsequent depression.

Taken together the present findings not only point to a recency effect, i.e. that only the most recent mood ratings predict inflammatory activity, but they also reveal that it seems to be the deviation of an individuals usual mood, and not so much the absolute level of depressive mood, that is associated with increasing IL-6. In other words, if an individual is in a more depressed mood than usual, her plasma concentration of IL-6 is higher, while it is lower if her current level of depressed mood is lower than usual.

This is the first study to explicitly compare long-term vs. short-term effects of depressive symptoms on systemic inflammation by obtaining weekly depression ratings. However, its findings are in line with and extend the results of previous studies reporting an association of depressive characteristics with inflammatory mediators for IL-6, but not for CRP. Our results share some similarity with those by Danner et al. (2003), who found that the percentage of men with increased concentrations of CRP was significantly higher only among those who recently had a major depressive episode (in the previous 6 months), but not if the episode occurred earlier than 6 months before the study. In contrast to our results, they did not find such a pattern in women (Danner et al., 2003). This contradiction might be explained by the differences between the two studies, with Danner et al. looking at major depressive episodes and percentages of increased CRP concentrations, and ours looking at weekly assessments of depressive symptoms and continuous indicators of inflammation. Kling et al. (2007) have investigated women with remitted major depression

and found increased concentrations of the inflammatory mediators CRP and serum amyloid A (sAA) as compared to healthy controls (Kling et al., 2007). One could argue that this contradicts our results, because a possible interpretation would be that the effects of depression on inflammation are strong enough to persist even into remission. On the other hand, since patients were assessed only once, results by Kling et al. do not allow any conclusions about what came first, depression or inflammation. Furthermore, the discrepant findings might just be explained by differences in study design and sample: Women in the study by Kling et al. (2007) are about twice as old as our participants, and Kling et al. find differences in CRP and SAA, while in the present study, only IL-6 but not CRP could be predicted by depressive symptoms. It could be speculated that CRP as a more stable molecule is more likely to be associated with trait depression, while IL-6 might be more likely to be associated with state depression.

The association of recent depressive symptoms with circulating IL-6 concentrations points to short-term effects of depressed mood on IL-6, but not CRP in younger individuals. This has some implications for the potential mechanisms involved in mediating this association. Rather than long-term dysregulations in the balance of stress systems, as formulated in the concept of allostatic load (McEwen and Stellar, 1993), the link between depression and circulating IL-6 is likely to be of short-term or acute nature in our sample of healthy young women. In fact, an acute impact on inflammation as measured by plasma IL-6 has been documented for psychosocial stress. Several recent studies have shown that short-term, acute laboratory stress has the potential to significantly increase circulating levels of inflammatory mediators. In agreement with our study, IL-6 appears to be a more stress-responsive inflammatory mediator as CRP (Miller et al., 2005b; Edwards et al., 2006; Pace et al., 2006; von Kanel et al., 2006, for a review see Steptoe et al., 2007). Although it is not known what sources contribute to the rise in circulating IL-6, increases might be mediated by a fast reacting stress hormone, such as norepinephrine, epinephrine, or adrenocorticotropic hormone (ACTH), which either activates immune cells or other sources of IL-6, such as adipose tissue (Yudkin et al., 2000). In immune cells, acute psychological stress has been shown to activate the inflammatory transcription factor NF-κB via norepinephrine signaling (Bierhaus et al., 2003). It is of course unclear whether short-term increases in depressive mood exert similar effects as psychosocial stress on norepinephrine or other fast reacting stress mediators. It has been shown, however, that patients with major depression show heightened activation of NF-κB in response to psychosocial stress (Pace et al., 2006).

Another mechanism might be that cells producing inflammatory mediators become glucocorticoid resistant in depressed individuals. We have previously shown that glucocorticoid sensitivity of inflammatory cytokines is subject to dynamic regulation, and responds to acute psychosocial stress (Rohleder et al., 2001, 2003). In a sample of women with clinical depression we were further able to show that while glucocorticoid sensitivity increased in the healthy control subjects, those participants with clinical depression developed a relative glucocorticoid resistance (Miller et al., 2005b). These findings suggest the possibility that acute changes in mood bring about systemic inflammation by diminishing the potency of glucocorticoids, which are a central pathway involved in regulating production of inflammatory mediators. These effects may be especially pronounced in depressed individuals.

The results of the present study need to be interpreted in the light of some limitations. First and most importantly, the participants of our study were physically healthy young women with a higher than average vulnerability for depressive mood. This limits the generalizability of our findings to the population at large. Further more, allostatic load is a process that needs several years or decades to develop and exert its negative effects. Our findings that recency of depressive symptoms is more important than long-term or trait components might therefore also be limited to this younger age group, whereas in older individuals a different picture might emerge because allostatic processes related to depression would have more time to play out. Our finding that peripheral inflammation does not predict subsequent depressive symptoms is limited to a single, one-time assessment of IL-6. To definitely exclude a mechanism such as sickness behavior, we would have needed repeated IL-6 measurements at the beginning of the observation period. Finally, IL-6 levels were relatively low in the present sample, probably because it was comprised of healthy young women. Some might be argue that IL-6 concentrations in this range are unimportant, because they are unlikely to exert any immediate negative health consequences. While this is probably true, one might also argue that if depressive mood can induce increases of circulating IL-6 that are detectable even at such a low level, these increases might very well sum up to a significant inflammatory burden over the life-span.

In summary, the findings of the present study lead us to conclude that in a younger age group, changes in circulating IL-6 concentrations are mediated by recent deviations from an individual's average mood, and not by long-term depressive mood, while CRP is not associated with depressed mood at all in this age group. In other words, it appears to be the state, and not the trait, component of depressive mood that stimulates peripheral inflammation, and that this only shows in IL-6 as a fast-reacting inflammatory mediator, but not in the more stable CRP. These findings imply that mechanisms might be comparable to those acting in acute psychosocial stress, and that in young age, negative health consequences of depressive mood might be prevented if treated adequately.

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