

Immunological Effects of Induced Shame and Guilt

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Objective: To determine if inducing self-blame would lead to increases in shame and guilt as well as increases in proinflammatory cytokine activity and cortisol. Based on previous research and theory, it was hypothesized that induced shame would be specifically associated with elevations in proinflammatory cytokine activity. **Materials and Methods:** Healthy participants were randomly assigned to write about traumatic experiences in which they blamed themselves ($N = 31$) or neutral experiences ($N = 18$) during three 20-minute experimental laboratory sessions over 1 week. Tumor necrosis factor- α receptor levels (sTNF α RII), an indicator of proinflammatory cytokine activity, β 2-microglobulin, cortisol (all obtained from oral fluids), and emotion were assessed prewriting and postwriting. **Results:** Participants in the self-blame condition showed an increase in shame and guilt as well as an increase in sTNF α RII activity when compared with those in the control condition. Cortisol and β 2-microglobulin levels were unaffected by the procedures. Those individuals in the self-blame condition reporting the greatest increases in shame in response to the task showed the greatest elevations in proinflammatory cytokine activity, while levels of guilt and general negative emotion were unrelated to cytokine changes. **Conclusion:** These data suggest that inducing self-related emotions can cause changes in inflammatory products, and that shame may have specific immunological correlates. **Key words:** psychoneuroimmunology, emotion, shame, self-blame, cytokine, stress.

sTNF α RII = soluble receptor for tumor necrosis factor-alpha; TNF- α = tumor necrosis factor-alpha; HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome; IL-1 = interleukin-1; IL-6 = interleukin-6; β 2M = β 2-microglobulin; HPA = hypothalamic-pituitary-adrenal axis; BDI = Beck Depression Inventory; OMT = oral mucosal transudate; HLM = hierarchical linear modeling.

INTRODUCTION

Research linking affect and the endocrine and immune system has typically focused on mood disorders, such as depression, or general negative affect rather than examining the correlates of specific emotional states. However, certain emotions may be associated with specific patterns of autonomic and central nervous system activation (1, 2), suggesting possible distinct downstream hormonal and immunologic effects. We propose shame as a candidate for such effects based on our own and others' studies of immunologic correlates of the self-appraisals that can trigger this emotion.

Shame is a self-related emotion (like guilt and embarrassment) elicited by moral transgressions, personal shortcomings, or failures in which the self is judged as flawed, inferior, or inadequate (3, 4). Negative self-related cognitions, such as characterological self-blame, can induce this emotion; for example, shame can result from blaming an uncontrollable

aspect of the self for a negative event (ie, *I am bad*), whereas guilt can arise from blaming a more controllable aspect of one's behavior (ie, *I did something bad*) (5–7). Often, shame involves a sense of exposure in which a negative aspect of the self is revealed before a real or imagined audience (4). Shame is associated with the motivation to disengage or withdraw from the situation (eg, wanting to “shrink,” “disappear,” avoid interpersonal interaction) (4) and is often accompanied by nonverbal displays denoting submission or appeasement (eg, head down, gaze avoidance) (3, 8). While this phenomenological, motivational, and behavioral profile distinguishes shame from other related states, little is known about the specific physiological correlates of this emotion.

We have shown that the negative characterological self-appraisals associated with shame predict immune decline and, in some cases, accelerated progression of HIV infection. Negative characterological attributions (9) and self-reproach (10) predicted greater rates of CD4 helper T cell decline in separate samples of HIV-seropositive gay men. Sensitivity to the negative evaluations of others (ie, “rejection sensitivity”) predicted greater CD4 decline as well as a more rapid onset of AIDS and mortality in a 9-year study of HIV seropositive gay and bisexual men (11). Others have found associations between negative self-evaluation and immunologic parameters in healthy populations (12, 13).

The relationships between these specific self-appraisals and aspects of immune functioning and health in our studies remain significant when controlling for a variety of biobehavioral confounds (ie, health behaviors, medications), demographics, as well as general measures of depression or negative affect. However, because self-blame-related cognitions can induce shame, this more specific self-evaluative emotion could mediate the findings observed in previous studies. Congruent with the premise that shame may have direct immunologic effects, we found a relationship between persistent HIV-specific feelings of shame and guilt and CD4 decline over a 7-year follow-up period, with evidence that the relationship hinged on feelings of shame (unpublished data, with permission, O. Weitzman, ME Kemeny, JL Fahey).

However, even within longitudinal studies, the direction of causality is impossible to determine, particularly given recent

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evidence that immune products can influence the nervous system and mood (14). Several experimental studies have shown that inducing negative emotion in a laboratory setting can decline the proliferative response to mitogenic stimulation and increase NK cell activity (15, 16). While these studies provide evidence that negative affective states can cause short-term fluctuations in the immune system, no studies have elucidated the immunologic effects of inducing the self-related emotions.

The current study had two primary goals: (1) to extend our longitudinal findings that self-blame-related cognitions and emotions have immunological correlates by examining the acute effects of these states under controlled laboratory conditions and (2) to specifically examine the associations between shame and immunological changes.

We chose to focus on one aspect of the immune system, the inflammatory response, for several reasons. First, recent evidence suggests an association between negative affect and increased levels of inflammatory products, such as proinflammatory cytokines (eg, interleukin [IL] 1 and 6, tumor necrosis factor- α [TNF- α]) and other markers of immune activation. Individuals with major depression show elevations in markers of immune activation relative to matched controls (eg, IL-1 and 6, soluble receptor for IL-6, activated T cells) (17). Preliminary findings indicate that immune activation could also be associated with negative affect within subclinical ranges. Psychological stressors (ie, examinations, public speaking) can increase proinflammatory cytokine activity (18, 19), suggesting that inflammatory processes could be sensitive to the emotions experienced in these circumstances.

Second, withdrawal is a key component of shame (ie, wanting to "hide," "disappear," avoid social interaction, displaying behaviors denoting withdrawal/submission), suggesting that it is among the emotions associated with disengagement. Certain proinflammatory cytokines can exert central effects that result in behavioral disengagement in animals and humans (eg, reduced exploratory behavior, social disinterest) (20, 21). We posit that shame and other disengagement-related affective states are part of an integrated psychobiological response that includes elevations in proinflammatory cytokines, and these molecules could help maintain the disengagement associated with this emotion.

We selected two markers of immune activation for inclusion in this study. TNF- α is a proinflammatory cytokine primarily released by activated macrophages that plays an important role in initiating inflammatory processes. The soluble receptor for TNF- α (sTNF α RII) reflects TNF- α activity (22, 23); we chose to assess sTNF α RII because it is more stable and reliably measured than TNF- α (24). We assessed β_2 -microglobulin (β 2M), a general marker of immune activation. Elevated β 2M levels can reflect heightened activity of lymphocytes and monocytes (25). We also assessed cortisol because cytokines can stimulate the hypothalamic-pituitary-adrenal axis (HPA) (14), and cortisol levels have been shown to increase in affective disorders (eg, depression) and in response to certain threatening situations (26, 27). Additionally,

these particular markers were chosen because they can be reliably assessed in oral fluids (27, 28), providing a less reactive and invasive way to measure neuroendocrine and immune activity. This was particularly important because this study examined the physiological correlates of distinctive emotions, and detection of these differences may require less emotionally provocative means of assessment than blood draws.

Based on previous experimental studies (1, 16, 29), emotion was induced by asking participants to recall past traumatic, emotional experiences in the laboratory on three separate days. Participants were instructed to focus on an experience in which they blamed themselves. We predicted that this procedure, designed to induce self-blame, would lead to increases in shame and guilt, as well as increases in sTNF- α RII, β 2M, and cortisol. Further, we predicted that those individuals who experienced more shame in response to the procedures would show the greatest increases in these biological parameters. We used this repeated-measures design (with three separate laboratory sessions) to increase the reliability that any observed physiological changes were caused by the emotion induction procedures and not due to other potential sources of variability in these parameters.

MATERIALS AND METHODS

Participants

Fifty-one undergraduate students were recruited to participate in a study on the "psychological and physiological effects of writing about personal events." Students were excluded if they reported health behaviors (eg, smoking), the use of prescription medication (eg, corticosteroids), psychiatric disorders (eg, depression), or chronic or acute health problems (eg, arthritis, flu) that could affect the neuroendocrine or immune system. Two participants were excluded from the analyses because of missing data for one or more of the biological variables. The final sample included 32 female and 17 male participants (mean age = 19.9, SD = 2.0); 35% were white, 22% were Asian, 25% were of Middle Eastern decent, and 18% were of other ethnicities.

Procedure

Participants were scheduled for three sessions during a week that they did not have an examination, paper, or presentation in any of their classes (to reduce the likelihood that academic stressors could confound relationships). All sessions took place between 4:00 and 7:00 PM to control for diurnal variations in neuroendocrine parameters and because afternoon sessions have been associated with greater cortisol responses (26). Participants were asked to not exercise or use nonprescription medication the day of a scheduled appointment and to not consume caffeine, dairy products, or chips (which can cause bleeding of the gums) 1 hour before their sessions.

After arriving for the initial session, participants gave their informed consent and were seated in individual cubicles. After resting for 10 minutes to adapt to the experimental setting, participants provided saliva and oral mucosal transudate (OMT) samples for hormonal and immunologic assessment. Participants then completed questionnaires to assess baseline mood, health behaviors, and other individual differences. After completing these measures, participants were randomly assigned to the experimental ($N = 31$) or control ($N = 18$) conditions. Participants were blocked by gender because of sex differences in cortisol responses (27).

Participants assigned to the experimental group were given the following written instructions (modified from [29] to focus on an experience of self-blame): "During each of the three writing days, I want you to write about one of the most traumatic and upsetting experiences of your life; please focus on an experience that made you feel bad about yourself or that you blame yourself for. It could be an experience such as a difficult romantic relation-

ship, a time when you did not live up to your own or someone else's expectations, or a traumatic experience that you feel responsible for. You can write about different traumatic experiences that made you feel bad about yourself each day or about the same experience for all 3 days. The important thing is that you write about your deepest thoughts and feelings. Ideally, whatever you write about should deal with an event or experience that you have not talked with others about in detail."

Those assigned to the control group received the following instructions (modified from [29]): "During each of the three writing days, I want you to write about what you did during the past 24 hours. You should describe your activities and schedule in detail, discussing the facts and circumstances as objectively as possible. You might describe what you had for dinner last night, what time you got up this morning, and so forth. The important thing is you discuss the facts and try to remain objective about your activities."

Both groups were given 20 minutes to write about their assigned topics. After the writing period, participants sat quietly for 10 minutes, then provided the second set of saliva and OMT samples and completed a momentary mood measure. This rest period was used to capture cortisol activity during the emotion induction, because it takes approximately 30 minutes after the onset of a stressor to produce maximal elevations in cortisol levels (26).

This procedure was repeated on days 2 and 3 (except assignment to condition, which only occurred on day 1 and remained constant across the three sessions). At the end of the third experimental session, participants received course credit and/or \$10.

Questionnaire Measures

The Affects Balance Scale questionnaire instructs participants to rate the degree to which they currently are feeling 40 different emotions on a scale from 1 to 5 (30). This scale generates total scores of negative and positive affect, as well as four positive emotion subscales (joy, contentment, affection, and vigor) and four negative emotion subscales (anger, depression, anxiety, and guilt). This measure has demonstrated high reliability and construct validity. The guilt dimension contains items reflecting both shame and guilt. For the purposes of this study, the guilt subscale was used as a measure of shame and guilt and also was subdivided into separate shame and guilt subscales based on the theoretical distinction between these emotions (4). The shame subscale included "ashamed" and "blameworthy" emotion descriptors ($\alpha = 0.74$). The guilt subscale included "regretful," "remorseful," and "guilty" descriptors ($\alpha = 0.72$).

The Daily Health Behavior Questionnaire was used to assess health behaviors on the day of the study such as caffeine and alcohol consumption, number of cigarettes smoked, amount of exercise activity, drug use, and sleeping and eating patterns.

Essay Evaluation Measure assessed participants' perceptions of the essays completed during the writing session (29) and served as a manipulation check. Using a 7-point scale ranging from not at all (1) to a great deal (7), participants rated their essays on several dimensions, including the extent to which their writing was personal, emotional, and meaningful. Additionally, those in the experimental condition were asked how much they blamed themselves for the experience at the time it occurred. This measure was completed after each writing session, and the average rating across the 3 days was used in analyses.

The Beck Depression Inventory (BDI) is a 21-item questionnaire that assesses the cognitive, affective, and vegetative symptoms of depression rated on a 4-point scale from 0 to 3 (31). The BDI is a well validated and widely used measure of depression.

Neuroendocrine and Immune Measures

The biological parameters in this study were obtained from oral fluids, because they provide an established method for assessing cortisol (27) and have been validated for assessing certain inflammatory products (28). In a validation study (28), levels of $\beta 2M$ and sTNF α RII in oral fluids were significantly and highly correlated with those obtained from plasma. Therefore, using oral fluids is a less reactive and invasive way to reliably measure neuroendocrine and immune activity.

An OraSure collection device (Epitope, Beaverton, OR) was placed between the lower cheek and gum; this placement collects samples containing

mainly OMT (32). An Omni-Sal collection device (Saliva Diagnostic Systems, Vancouver, WA) was placed under the tongue for saliva collection. OMT and saliva are both oral fluids; OMT is a filtrate of blood plasma while saliva contains enzymes and other particles from the parotid and salivary glands. OMT was collected for sTNF α RII and $\beta 2M$ assessment rather than saliva because OMT values are more highly correlated with blood plasma values (28).

After obtaining the saliva and OMT samples, the vials were immediately refrigerated for no longer than 16 hours and then stored at -80°C . Cortisol was measured using high sensitivity salivary cortisol immunoassay kit (Salimetrics, State College, PA). $\beta 2M$ was measured using the IMx automated microparticle enzyme immunoassay system (Abbott, Abbott Park, IL). The interassay and intraassay coefficients of variation were less than 8% and 5%, respectively. sTNF α RII was measured by using Quantikine Human sTNF-RII enzyme immunoassay kit manufactured by R&D Systems (Minneapolis, MN). The interassay and intraassay coefficients of variation were less than or equal to 5%. Protein in oral fluids was quantified by the Bradford method (33) using the Bio-Rad protein assay kit with bovine plasma albumin as the standard. To normalize the data for an analyte, the ratio of the experimental value for the analyte to the protein concentration in the same test sample was used. Because the analyte-to-protein ratio controls for differences in salivary flow rate, which could be altered by the experimental procedures or vary between individuals, the ratio values are more reliable than the analyte values alone (28). All sTNF α RII and $\beta 2M$ results are reported using these ratios because of this advantage.

Statistical Analyses

Hypotheses were tested using hierarchical linear modeling (HLM) (34). The study was a three-level nested design. Time (level 1; before vs. after writing) was nested within days (level 2; days 1, 2, and 3), which was nested within condition (level 3; experimental vs. control). The day was dummy-coded into two contrast variables (day 1 vs. day 2 and 3; day 2 vs. day 3). To determine the effects of the writing manipulation on emotion and biological outcomes, we tested whether the condition, time, day, and interaction effects predicted the emotion and biological measures (which included prewriting and postwriting measures). When an interaction effect was significant, regression analyses within the subsamples were performed to determine the pattern of the effect (ie, simple effects analyses). Additionally, we tested whether each emotion measure predicted each biological measure for the participants in the experimental condition. HLM estimated regression coefficients for each predictor using least-squares estimates and robust standard errors to adjust for nonnormality of the data.

RESULTS

Manipulation Check and Baseline Information

The essay evaluations completed by participants (after each writing session) demonstrated compliance with experimental instructions. Those in the experimental condition wrote about events in which they had experienced high levels of self-blame ($M = 5.3$, $SD = 1.3$), and they rated their essays as more personal [$F(1, 47) = 44.25$, $p < 0.01$], more meaningful [$F(1, 47) = 111.70$, $p < 0.01$], and more emotional [$F(1, 47) = 47.30$, $p < 0.01$], than participants in the control condition. A review of the writing samples also verified that participants wrote essays consistent with their assigned topic. While control group participants recounted the mundane details of their daily schedule, those in the experimental condition wrote poignant essays dealing with a variety of experiences of self-blame, including academic difficulties, acts of violence, serious accidents, and relationship problems among family, friends, or dating partners.

A series of t tests were computed to test for differences between the experimental and control groups at baseline (day

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1 prewriting assessment, before random assignment). There were no significant differences between groups on the baseline biological, health behavior, depressed mood, or demographic variables ($p > 0.15$). However, participants in the experimental group reported higher levels of negative emotion [$t(47) = 2.63, p < 0.05$] and higher levels of shame [$t(47) = 2.01, p = 0.05$] than those in the control group at the baseline assessment point. All analyses controlled for baseline negative emotion or shame because of this group difference. The reported analyses control for baseline negative emotion because it includes the shame subscale; analyses were identical when controlling for baseline levels of shame.

Self-Reported Emotion

Consistent with hypotheses that shame and guilt would increase when writing about an experience of self-blame, the time by condition interaction significantly predicted the combined shame and guilt subscale value ($B = 0.14 [0.033], p < 0.001$, as shown in Figure 1). Follow-up analyses revealed that this was caused by an increase in shame and guilt from prewriting to postwriting in the experimental group ($B = 0.27 [0.065], p < 0.001$), and a small but significant decline in the control group ($B = -0.019 [0.0081], p < 0.05$). The time by condition interactions for the other negative emotion subscales were also significant (anger, depression, and anxiety; $p < 0.01$). However, within the experimental group, the time effect was significantly stronger for shame and guilt ($B = 0.27$) than the other negative emotion subscales [anger, $B = 0.18, t(30) = 2.07$; depression, $B = 0.14, t(30) = 3.04$; anxiety, $B = 0.05, t(30) = 5.29; p < 0.05$], indicating that shame and guilt were induced to a greater degree than the other negative emotions.

Biological Outcomes

We predicted that writing about a traumatic experience that involves self-blame would lead to increases in sTNF α RII, β 2M, and cortisol for the experimental group compared with the control group. As shown in Figure 2, sTNF α RII was significantly predicted by the time by condition interaction ($B = 1.02 [0.50], p < 0.05$). Follow-up analyses revealed this was because of increases in sTNF α RII from prewriting to postwriting in the experimental group ($B = 1.87 [0.74], p < 0.05$) and no changes within the control group ($B = -0.15 [0.69], p > 0.10$). Contrary to hypotheses, β 2M was not predicted by the condition by time interaction ($B = 0.0004 [0.0034], p > 0.10$). However, there was a significant time by day interaction contrast (day 1 vs. day 2 & 3) ($B = -0.0067 [0.0028], p < 0.05$); β 2M levels decreased from prewriting to postwriting on day 1 ($B = -0.011 [0.0054], p < 0.05$) and did not change on days 2 and 3 in both conditions ($B = 0.0077 [0.0051], p > 0.10$). Cortisol was also not significantly predicted by the condition by time interaction ($B = 0.046 [0.053], p > 0.10$). There was a significant time by day interaction contrast (day 1 vs. day 2 & 3) ($B = -0.078 [0.035], p < 0.05$); cortisol decreased from prewriting to postwriting on day 1 ($B = -0.26 [0.091], p < 0.01$) but did not change on days 2 and 3 in both conditions ($B = -0.038 [0.052], p > 0.10$). All analyses were also performed controlling for health behaviors, but these covariates did not change the results of any analyses.

Relationship Between Emotion and Biological Variables

Hypotheses predicted that those in the experimental condition who reported greater increases in shame in response to

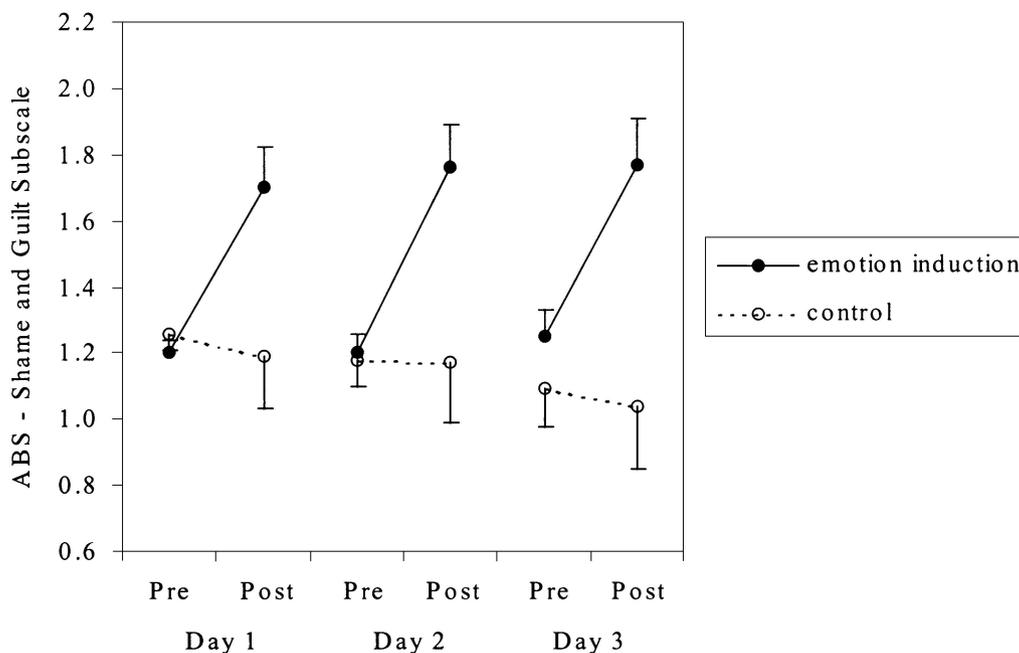


Figure 1. Change in shame and guilt from prewriting to postwriting for the experimental and control groups for the three laboratory sessions, expressed as mean \pm standard error of the mean. All values control for baseline (time 1, day 1) levels of negative emotion. ABS = Affects Balance Scale.

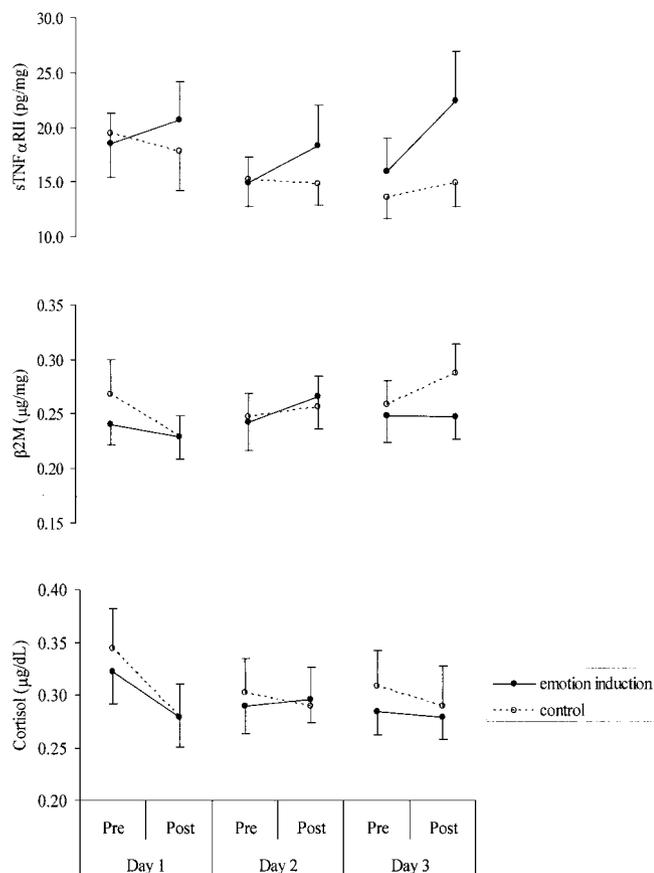


Figure 2. Change in sTNF α RII (top), β 2M (middle), and cortisol (bottom) from prewriting to postwriting for the experimental and control groups for the three laboratory sessions, expressed as mean \pm standard error of the mean. sTNF α RII = soluble receptor for tumor necrosis factor- α ; β 2M = β 2-microglobulin.

the procedures would also show greater increases in sTNF- α RII, β 2M, and cortisol. To test this, hierarchical linear models were performed predicting the biological variables from the emotion variables among participants in the experimental condition. As hypothesized, within the experimental group, increases in shame were associated with increases in sTNF- α RII [$B = 1.24 (0.64), p = 0.053$], which is a relatively small effect ($r = 0.14$). However, sTNF α RII was not significantly predicted by guilt or negative emotion ($p > 0.10$). β 2M and cortisol were not significantly predicted by shame, guilt, or negative emotion ($p > 0.10$).

Potential Moderators

Despite random assignment, participants in the experimental condition reported higher levels of negative emotion and shame at baseline (prewriting assessment on day 1, before random assignment). While all analyses controlled for baseline levels of negative emotion or shame, we also ran ancillary analyses to determine if those who reported higher levels of negative emotion or shame at baseline had different psychological or biological responses to the manipulation. There was no evidence that the baseline levels of negative emotion or

shame moderated the condition by time interaction for shame, negative emotion, or sTNF α RII ($p > 0.15$).

Because shame is a core component of depression (3), it is possible that the observed effects are simply a function of depressive symptomatology; those with higher levels of depressive symptoms may have responded to the manipulation with greater levels of shame and also showed greater changes in proinflammatory cytokine activity. However, BDI depression scores did not moderate any of the emotional or biological responses to the manipulation ($p > 0.15$), and controlling for depressed mood did not alter the results, indicating that this factor cannot account for the experimental findings. Additionally, gender did not moderate the emotional or biological responses to the experimental procedures ($p > 0.15$).

DISCUSSION

This study was designed to elucidate the biological effects of experiencing self-related emotions, particularly shame. A diary-writing procedure (experienced for 20 minutes on three separate days) was used to induce self-blame. Participants in this condition showed increases in shame and guilt as well as increases in proinflammatory cytokine activity when compared with participants in a control condition. Consistent with our predictions, those individuals who reported the greatest changes in shame during the procedure showed the greatest changes in cytokine activity. Guilt and other negative emotions were unrelated to this physiological parameter. Cortisol and β 2M were unaffected by the procedures. These data suggest that experiencing shame may have immunological correlates. They also are consistent with previous findings that cognitive states involving self-blame have physiological effects, possibly resulting from their ability to induce shame.

Instructing individuals to write about a traumatic experience for which they blamed themselves increased shame, guilt, sadness, and other negative emotions. However, consistent with the literature specifically tying shame and guilt to self-blame (5, 6), the self-related emotions were differentially activated by the procedures. To our knowledge, this is the first experimental paradigm that has been shown to successfully induce shame and guilt to a greater extent than other negative emotions. Approximately equal levels of shame and guilt were reported. This may be because instructions did not specify that individuals pick an experience in which they blamed their behavior (associated with guilt) or an experience in which they blamed more stable, characterological aspects of themselves (associated with shame) (6, 7). A review of the diaries indicates that both types of attributions were present.

We found that TNF- α receptor-to-protein ratios in oral fluids increased in response to the self-blame induction procedures, demonstrating that inducing negative self-related states can cause alterations in this parameter. These changes were robust, with sTNF α RII activity increasing on average 25% above baseline values. The effect was internally replicated; a consistent pattern of results was obtained across the three experimental sessions on separate days. The strength and

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reliability of these results are particularly striking, given the rapidity of the changes within a 30-minute timeframe.

We predicted that those who experienced greater changes in the specific, self-evaluative emotion of shame would also show greater changes in the biological parameters. Consistent with hypotheses, we found that increases in shame, but not guilt, in response to the self-blame induction procedure were correlated with increases in TNF- α activity. These data add to the growing theoretical and empirical evidence suggesting that shame and guilt are distinct emotions. Shame and guilt differ in their phenomenology, antecedents, conceptualizations of the self, implications for interpersonal behavior, and along the dimension of disengagement (4, 8). This study suggests the possibility that the acute experience of the two emotions could be differentiated physiologically as well.

Our findings also support the premise that acute changes in proinflammatory cytokine activity may be related to specific emotions, like shame, rather than more global affective states. Acute changes in general negative affect in response to the self-blame manipulation were unrelated to changes in the TNF- α system. Depression did not moderate the effects, indicating that inducing negative self-related states increased TNF- α activity even among nondepressed individuals.

While sTNF α RII ratios increased in response to writing about an experience of self-blame, β 2M levels were not affected. It is possible this is because the procedures differentially activated certain classes of immune cells. Elevations in sTNF α RII ratios reflect activation of the TNF system; TNF- α and sTNF α RII levels are correlated (22, 23) and increased production of TNF- α can increase sTNF α RII concentrations (35). Because TNF- α is released by activated macrophages, an immune cell that plays a central role in orchestrating the inflammatory response, increases in sTNF α RII levels indicate an underlying state of macrophage activation (24). Thus, it appears that this emotion induction procedure may have activated macrophages, resulting in an increase in TNF- α activity. In contrast, lymphocytes, another major class of immune cells, were probably not strongly activated by these procedures because β 2M levels did not change and this immune product is released by both lymphocytes and macrophages. The majority of studies of stress, psychological factors, and the immune system have focused on lymphocytes; these data support a growing animal and human literature suggesting that psychological states may activate macrophages and the proinflammatory cytokines they produce (14).

The mechanisms explaining increases in the TNF- α system in response to psychological states has not been elucidated. These changes do not appear to be idiosyncratic to oral fluid assessment. Other studies have found increases in TNF- α production in stimulated plasma mononuclear cells within similar timeframes (19). The sTNF α RII-to-protein ratio obtained from oral fluids (OMT) is independent of salivary flow rate and correlates with plasma levels of the receptor (28), indicating that TNF- α activity likely increased in other compartments as well. Both sympathetic and HPA products can influence macrophage activity as well as cytokine expression

and production (36), and these systems have been proposed as possible mediators of the stressor/psychological state–cytokine relationship. Because the present study found no effect of the procedure on salivary cortisol levels, it is unclear whether cortisol plays a role in mediating the effects on cytokine activity observed in this study. Further research testing sympathetic activity and other neurobiological systems as potential mediators is clearly warranted.

We found that cortisol levels decreased in both conditions during the first experimental session and did not change during the second and third sessions. This observed decline during the first session could have been caused by elevated baseline cortisol values because of participants' uncertainties and experienced uncontrollability regarding the upcoming experimental protocol (37). Hypotheses predicted that cortisol levels would increase in response to writing about an experience of self-blame; however, no differences were detected between experimental and control conditions. While it is possible that methodological factors precluded detecting increases in cortisol levels, the study was conducted in the late afternoon and cortisol was assessed 30 minutes from stress onset to maximize the chances of capturing a cortisol response (26). The failure to observe cortisol elevations is consistent with a recent meta-analysis that we conducted, which found that emotion induction paradigms do not reliably elicit cortisol changes. Instead, cortisol increases were most likely to occur when two conditions were present: a task that is likely to elicit negative appraisals of the self (eg, making a speech) and an evaluative audience (26). The task used for the current study did induce negative appraisals of the self but took place in an anonymous confidential setting. Extrapolating from these findings, it is possible that cortisol elevations might have been obtained if the experimental procedure required revealing the shame-inducing experience in a social–evaluative context.

In a series of studies, we have demonstrated that negative self-appraisals, centered on self-blame, predict immune decline and accelerated HIV-related disease progression. Negative characterological attributions, self-reproach, and rejection sensitivity predicted a greater decline in CD4 cells as well as a decline in time to AIDS onset and/or death in HIV seropositive men (9–11). Overall, depression or general negative affect did not mediate the relationships observed in these studies. We proposed that these effects could be because self-blaming attributions trigger persistent feelings of shame that, in turn, have neurobiological and immunological correlates. In a first test of this hypothesis, we found that persistent feelings of HIV-related shame predicted CD4 decline over a 7-year follow-up period when guilt, depression, anxiety, and other affective states did not (unpublished data, with permission, O. Weitzman, M.E. Kemeny, J.L. Fahey).

The present study supports the premise that shame may have immunological effects by demonstrating that a procedure designed to elicit self-blame increased levels of shame and guilt as well as cytokine activity, and that the strongest immunological effects occurred in those reporting the greatest changes in shame. It is possible that persistent, repeated ex-

posure to shame-inducing situations could translate into sustained activation of the TNF cytokine system, which could have long-term health effects in the context of inflammatory disease (eg, rheumatoid arthritis, cardiovascular disease). However, this would be dependent on a myriad of factors, including the magnitude and chronicity of the circumstances, the individual's vulnerability (ie, health status, personality), and the nature of the emotional experiences themselves. For example, when emotional expression is coupled with cognitive processing of the experience, it can lead to positive immunological effects (29). Therefore, acute laboratory-induced effects cannot be extrapolated to infer long-term health consequences; it is unclear what the clinical significance of such changes would be. However, most studies of psychological predictors of the immune system and health focus on stress and depression; these data suggest that self-appraisals, such as self-blame, and basic emotions, such as shame, deserve additional attention (38).

Appraisal and emotional processes are thought to play a key role in determining biological responses to stressful conditions (39). Our findings suggest that situations that evoke negative self-related appraisals and emotions may be particularly likely to activate processes relevant to inflammation. Consistent with this premise, social-evaluative speech stressors, which provide a context in which a negative aspect of the self could be revealed to others, have been associated with increased production of proinflammatory cytokines (19). In healthy students undergoing examination stress, those who reported greater increases in feelings of uncontrollability (as measured by the Perceived Stress Scale) showed the largest increases in TNF- α activity (18), and attributions of uncontrollability have been associated with shame (5). While tentative, it is possible that the elevations in inflammatory products reported in these studies could be caused in part by the experience of self-related appraisals and emotions. Assessing these negative self-related states may account for a portion of the interindividual variability in observed immunological changes.

What might be the significance of the particular immunological change observed in this study? It is possible that these changes are nonfunctional side effects of the neurophysiological correlates of the emotions experienced. Alternatively, these changes could have an adaptive value in the context of a shame-inducing experience. Stressful life events can induce at least two distinctive psychobiological responses. The first, well-studied response is the fight-flight reaction, in which emotions such as fear and anger are thought to organize the mobilization of physiological resources to actively deal with the stressor (40). A second response involves goal disengagement, which may be adaptive after exposure to uncontrollable situations or those in which the solution require skills or characteristics that the individual does not possess (41–43). Less is known about the emotions that coordinate the behavioral and physiological responses that serve disengagement goals. We argue that shame is in this category (38), based on evidence that it is elicited in situations experienced as uncon-

trollable and reflecting shortcomings within the self (4, 5), and its experiential and behavioral components are consistent with disengagement and/or withdrawal (eg, wanting to hide, disappear, avoid interpersonal interaction; displays of submission/appeasement) (3, 4, 8).

We propose that shame, and other disengagement-related emotions, are part of an integrated psychobiological response that may be adaptive in uncontrollable situations when disengagement is the most functional response. The physiological component of this response may include activation of macrophages and the subsequent production of proinflammatory cytokines since animal research has shown that injections of these substances can have central effects and induce a profound form of behavioral disengagement (reductions in social and exploratory behavior, sexual behavior, grooming) (20). Similar changes have been found in humans (21). These cytokines play an adaptive role in the context of an infection because behavioral disengagement reduces overall energy expenditure possibly in the service of mobilizing fever and other functional physiological responses to contain the infection (14). We posit that these responses are also elicited in other contexts where behavioral disengagement would be adaptive, ie, uncontrollable contexts.

While we found evidence that shame, and not guilt or negative emotion, was linked to proinflammatory cytokine activity, our ability to make conclusive causal statements about the shame-proinflammatory cytokine association is limited by several factors in this study. First, the effect size for the relationship between shame and TNF- α activity was small (and significant at the $p = 0.053$ level), suggesting there are other factors that contribute to the changes in the TNF- α system in this context. The magnitude of the effect may have been reduced by measurement issues; one study that assessed stimulated TNF- α production found the greatest changes 1 hour from the onset of stress (19). Additionally, the effect size may have been reduced because the experimental manipulation lacked the power to induce robust changes in shame, or because it lacked specificity, as participants experienced shame, guilt and complex of other negative emotions. Future studies could clarify the specificity of these findings by recruiting participants adept at differentiating discrete emotional states (eg, actors) (1, 15), using a more directed writing task that continually focuses participants on the shame-inducing component of the experience, or comparing the immunologic responses to several induced negative emotional states that vary along the dimension of disengagement (eg, anger, fear and shame). The relatively small number of participants in the emotion induction group may have limited the power in the gender analyses; future research could clarify whether gender moderates these effects.

In the current study, we verify that inducing self-blame can result in elevated levels of shame and guilt. We also show that these self-blame inducing conditions result in alterations in the immune system, particularly activation of proinflammatory cytokine activity. Finally, we show that these cytokine changes are particularly tied to the experience of shame. To

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our knowledge, there are no other published studies that evaluate the acute effects of shame on immunological parameters. We also propose a model that provides an adaptive link between the experience of shame and the induction of proinflammatory cytokine activity. This model is based on a growing literature indicating that cytokines can affect mood, cognition and motivation and may play an adaptive role in the body's response not only to pathogens but to other threats as well.

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