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Better cognitive control of emotional information is associated with reduced pro-inflammatory cytokine reactivity to emotional stress

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Abstract

Stress is strongly associated with several mental and physical health problems that involve inflammation, including asthma, cardiovascular disease, certain types of cancer, and depression. It has been hypothesized that better cognitive control of emotional information may lead to reduced inflammatory reactivity to stress and thus better health, but to date no studies have examined whether differences in cognitive control predict pro-inflammatory cytokine responses to stress. To address this issue, we conducted a laboratory-based experimental study in which we randomly assigned healthy young-adult females to either an acute emotional stress (emotionally evocative video) or no-stress (control video) condition. Salivary levels of the key pro-inflammatory cytokines IL-1β, IL-6, and IL-8 were measured before and after the experimental manipulation, and following the last cytokine sample, we assessed participants' cognitive control of emotional information using an emotional Stroop task. We also assessed participants' cortisol levels before and after the manipulation to verify that documented effects were specific to cytokines and not simply due to increased nonwater salivary output. As hypothesized, the emotional stressor triggered significant increases in IL-1β, IL-6, and IL-8. Moreover, even in fully adjusted models, better cognitive control following the emotional (but not control) video predicted less pronounced cytokine responses to that stressor. In contrast, no effects were observed for cortisol. These data thus indicate that better cognitive control specifically following an emotional stressor is uniquely associated with less pronounced pro-inflammatory cytokine reactivity to such stress. These

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Declaration of interest

There are no conflicts of interest that could have inappropriately influenced the study or the reporting of the findings.

findings may therefore help explain why superior cognitive control portends better health over the lifespan.

Keywords

Life stress; cognition; emotion; Stroop; inflammation; cytokine; cortisol; risk; health; disease

Introduction

A large body of research has implicated psychological stress in the onset or progression of several disorders, including asthma, cardiovascular disease, certain cancers, and depression (Dienes et al., 2006; Slavich & Irwin, 2014). Because inflammation is involved in many different health outcomes, recent research has examined the role that pro-inflammatory cytokines play in linking stress with poor health (Cohen et al., 2012). Stress can trigger increased inflammatory activity at the molecular level (Slavich & Cole, 2013), and persistent elevations in inflammation can lead to a systemic inflammatory state that promotes disease (Cohen et al., 2012; Rohleder et al., 2010). Despite these associations, many people who experience stress do not develop inflammation-related health problems. Differences in how individuals biologically respond to stress might help explain health disparities following stress, but the factors that predict individual differences in cytokine reactivity to stress remain poorly understood.

One factor hypothesized to moderate biological reactivity to stress involves the extent to which individuals can cognitively control their thoughts and attention during stressful circumstances (Compton et al., 2013). Better cognitive control has been associated with less emotional reactivity to stress (Compton et al., 2011), and emotional responses to stress have in turn been found to predict individuals' pro-inflammatory cytokine reactivity to stress (Denson et al., 2009; Moons & Shields, 2015). One resulting possibility is that cognitive control, especially of emotional information, may influence cytokine responses to stress. To date, however, no studies have examined whether individuals' ability to cognitively control emotional information predicts their pro-inflammatory cytokine reactivity to emotional stress.

To address this issue, we randomly assigned healthy young-adult women to watch either an emotional stress-inducing or nonstress-inducing video, before and after which we assessed salivary levels of three cytokines – namely, interleukin (IL)-1β, IL-6 and IL-8. Salivary cytokine are ideal for examining stress-related inflammatory reactivity because they are clinically relevant and increase reliably on a much faster timescale than cytokines in blood (Slavish et al., 2015). In addition, we characterized participants' cognitive control abilities using an emotional Stroop task. Consistent with prior research (Slavich & Irwin, 2014), we hypothesized that participants in the emotional stress-induction condition would exhibit greater pro-inflammatory cytokine responses than participants in the control group. We further hypothesized that better cognitive control of emotional information would be associated with less pronounced cytokine reactivity to the emotional stress-inducing (but not

control) video, based on research showing that better cognitive control specifically within a stressful context predicts reduced reactivity to stress (Shields et al., 2015).

Lastly, to examine the specificity of these effects, we assessed participants' cortisol reactivity to the stress-inducing or nonstress-inducing video. This permitted us to ensure that the emotional stressor triggered increases in pro-inflammatory cytokines but not cortisol, which would be expected given that this stressor did not involve characteristics – specifically, uncontrollability and social-evaluative threat – that prior research has shown are required for a cortisol response (Dickerson & Kemeny, 2004). Assessing cortisol also enabled us to verify that individual differences in cognitive control of emotional information were specifically related to differences in inflammatory responding and not nonwater salivary output more generally.

Methods

Participants and procedure

Participants were 37 healthy young-adult women from 18–22 years old (M_{age} = 19.19), sampled from a university community. Women taking hormone medication over the previous three months were excluded. Most participants (N = 21) were in the luteal phase of their menstrual cycle. Participants' average body mass index (BMI) was 23.07 (SD = 5.07). Oral health was controlled by ensuring participants' compliance with instructions on proper oral hygiene during the 48 h before the visit.

Participants arrived between 12 pm and 6 pm for a 1-h study visit and first completed brief screening measures.[1] They then provided baseline saliva samples for cytokine and cortisol measurement. Next, participants were randomly assigned to watch either a stress-inducing or nonstress-inducing video. A second saliva sample was collected approximately 10 min after the onset of the video, and participants then reported their state negative affect. Finally, participants completed the Stroop and were debriefed. The emotional stress manipulation was placed at the beginning of the study, prior to acclimation, to increase its stressfulness. The emotional stress-inducing video was not expected to influence performance on the cognitive task, given prior research showing that nonspecific negative mood inductions do not impair cognitive control (Baumeister et al., 1998). All procedures adhered to American Psychological Association ethical principles and received Institutional Review Board approval.

Emotional stress induction

Participants randomly assigned to the emotional stress-induction condition watched a 4-min video of a 2-day-old crying infant being circumcised. Stimuli of this nature reliably induce an immune response (Schaller et al., 2010). In contrast, participants in the control condition watched a length-matched, nonemotional video. As described below, we evaluated the success of this stress manipulation by assessing participants' negative affect post-video,

[1]Time of arrival did not influence the results.

using the Positive and Negative Affect Scale (Watson et al., 1988). Reliability for this measure was excellent ($\alpha = 0.91$).

Cytokine and cortisol assays

We assessed participants' cytokine and cortisol levels immediately before and approximately 10 minutes after the video. We focused on the cytokines IL-1β, IL-6, and IL-8 because they respond to emotional stressors and are implicated in the pathophysiology of several diseases (Slavich & Irwin, 2014). Saliva samples were obtained using a passive drool method. Samples were then immediately placed in a dry-ice-filled container and transported to a −80°C freezer. Cytokines were measured using high-sensitivity multiplex immunoassay kits manufactured by R&D Systems (Minneapolis, MN), which have a minimal detectable dose of 0.04 pg/mL for IL-8, 0.08 pg/mL for IL-1β, and 0.14 pg/mL for IL-6. The salivary cytokine levels that we obtained were similar to those observed in prior studies (Byrne et al., 2013). In addition, of note, cytokine levels derived from saliva tend to be higher than those derived from blood (Slavish et al., 2015). Cortisol, in turn, was measured using enzyme-linked immune sorbent assay (ELISA) kits manufactured by R&D Systems (Minneapolis, MN), which have a minimum detectable dose of 0.16 ng/mL.

Cognitive control

Cognitive control of emotional information was assessed using an emotional Stroop task. Participants viewed 108 Ekman male happy, sad, or angry expression faces with a superimposed happy, sad, or angry word (4 words per emotion). Thirty-six face/words plus an additional 12 control blurred faces were presented in each block (48 trials per block), with three blocks in total. Each trial began with the presentation of an emotional word overlaid on a face. Participants ignored the face and reported the emotion of the word. After participants responded, the face/word disappeared. The inter-trial interval varied from 1000–2000 ms.

A cognitive control score was calculated for each participant by subtracting latencies to correctly label words on a control blurred/indistinguishable face from latencies to correctly label words on an angry face. We selected angry faces because anger produces the biggest emotion-related interference on such tasks (Gotlib et al., 2004). However, using happy or sad faces as the interfering faces did not alter the findings. Higher scores on this task indicate worse cognitive control of emotional information.

Analytic strategy

Variables with significant skew (IL-1β, IL-6, IL-8, cortisol, and negative affect) were log-transformed for analyses. To test the hypothesis that the emotional stress-inducing video would increase pro-inflammatory cytokine activity and that differences in cognitive control would predict these responses, we conducted an Emotional Stroop × 2 (Condition: Stress vs. Control) × 3 (Cytokine Type: IL-1β, IL-6, IL-8) mixed-model analysis of variance (ANOVA) using Condition as a between-subjects factor, Cytokine Type as a within-subjects factor, Emotional Stroop as a continuous variable, and post-video cytokines as the outcome. These analyses controlled for participants' age, BMI, hormonal cycle, and baseline cytokine levels. The covariates were chosen to avoid confounding the relation of biological reactivity and

cognitive control with extraneous variables, but importantly, the results did not differ when these covariates were excluded. Analyses of cortisol were conducted using an ANOVA with the same covariates and factors, except that cortisol replaced the cytokine variables. Degrees of freedom in mixed-models were estimated using the Satterwaite approximation, which relaxes assumptions of homogeneity but entails that the degrees of freedom often contain noninteger numbers. All reported means and standard errors are least-squares means and their respective standard errors.

Results

Preliminary analyses

Participants in the emotional stress induction and control groups did not differ on measures of age, BMI, menstrual cycle phase, or baseline levels of IL-1β, IL-6, IL-8, or cortisol (ps > 0.17). Importantly, however, participants in the emotional stress condition reported more post-video negative affect (M = 2.82, SE = 0.07) than those in the control condition (M = 2.51, SE = 0.08), $t(34) = 2.866$, $p = 0.007$, indicating that the experimental manipulation was successful. Finally, consistent with research showing no effects of acute negative mood inductions on Stroop performance, participants' cognitive control scores did not differ between conditions, $t(34) = 0.115$, $p = 0.909$, which is critical for ensuring independence between the factors under study.

Primary analyses

The mixed-model ANOVA used to test the main hypotheses revealed a significant main effect of Condition on cytokine reactivity, $F(1,25.7) = 4.75$, $p = 0.039$, $\eta^2_{partial} = 0.156$, and a nonsignificant Condition × Cytokine Type interaction, $p = 0.816$ (Table 1). These results indicate that cytokine reactivity differed significantly for participants in the two conditions and that this effect was similar for all three cytokines (Table 2). Indeed, as hypothesized, participants in the emotional stress condition had greater cytokine reactivity (M = 3.74, SE = 0.09) than participants in the control group (M = 3.35, SE = 0.12), $t(27.6) = 2.585$, p = 0.015. Therefore, the emotional stress induction was successful in triggering increased inflammatory activity relative to the control task.

Next, we examined the joint influence of Condition and participants' emotional Stroop scores in predicting their pro-inflammatory cytokine levels. These analyses revealed a significant Condition × Emotional Stroop interaction effect, $F(1,25.7) = 8.00$, $p = 0.009$, $\eta^2_{partial} = 0.237$, indicating that participants' cytokine reactivity depended on both their experimental condition and their ability to exert cognitive control over emotional information. In addition, we found that the three-way Condition × Emotional Stroop × Cytokine Type interaction was nonsignificant, $p = 0.334$, indicating that these effects did not differ for the three cytokines assessed (Figure 1).

To understand this interaction between Condition and Emotional Stroop, we conducted analyses of least-squares means. As hypothesized, among participants demonstrating better cognitive control (i.e. interference costs 1 SD below the mean), those in the emotional stress condition did not exhibit a greater cytokine response (M = 3.62, SE = 0.13) than those in the

control condition (M = 3.72, SE = 0.17), $t(27.6) = -0.485$, $p = 0.631$. Conversely, among participants demonstrating average (i.e. interference costs at the mean) or worse cognitive control (i.e. interference costs 1SD above the mean), those in the emotional stress condition exhibited a significantly greater cytokine response than those in the control condition, $ps \leq 0.01$. In sum, therefore, individuals exhibiting better cognitive control of emotional information had no or only a negligible cytokine response to the emotional stressor, whereas those exhibiting average or poor cognitive control had a typical cytokine response to the stressor.

To verify that these results represented a specific link between cognitive control and cytokine reactivity and that they were not due to a general increase in secretory output from salivary glands, we focused next on cortisol reactivity. Cortisol reactivity was not expected to differ by condition given that the emotional stressor did not include characteristics that have been shown to be required for a cortisol response – namely, uncontrollability and social-evaluative threat. As hypothesized, participants in the emotional stress condition did not exhibit greater cortisol reactivity than participants in the control condition, $F(1,30) = 0.76$, $p = 0.390$ (Table 2). We also examined whether individual differences in cognitive control were associated with differences in cortisol responding or whether there was a Condition × Emotional Stroop interaction effect in the prediction of cortisol responding, but there were not, $Fs < 1.14$, $ps > 0.295$. Therefore, differences in cognitive control of emotional information appear to be specifically related to differences in cytokine reactivity to emotional stress and not salivary output or salivary stress hormone reactivity more generally.

Discussion

Psychological stress is a well-known trigger of pro-inflammatory cytokine activity, but few studies have examined factors that predict individual differences in these reactions. We addressed this issue by showing that individuals' ability to exert cognitive control over emotional information was strongly associated with their salivary cytokine reactivity to a brief emotional stressor. These effects were specific to participants in the emotional stress condition and were robust when adjusting for participants' baseline cytokine levels, age, BMI, and menstrual cycle phase. Moreover, the emotional stressor did not trigger increases in cortisol, and there were no associations between participants' cognitive control characteristics and their cortisol dynamics. As such, we conclude that better cognitive control of emotional information specifically predicts reduced inflammatory reactivity to stress in young-adult women. These effects may thus help explain why superior cognitive control is associated with better lifespan health.

Although no studies have examined associations between cognitive control and inflammatory reactivity to stress, one study has investigated links between cognitive control and cortisol reactivity. Specifically, Compton et al. (2013) found that better cognitive control during a cognitive stressor predicted less cortisol reactivity. We did not observe such associations here, but we also did not expect these effects given that the emotional stressor we employed did not involve uncontrollability or social-evaluative threat, which are required for cortisol reactivity (Dickerson & Kemeny, 2004).

What mechanism might underlie salivary cytokine increases in the timeframe assessed here? We can only speculate, but the observed increases may represent a stress-induced redistribution of immune system resources. Saliva contains high concentrations of cytokines that are part of a complex network of immune system mediators that are involved in innate and adaptive immunity (Fábián et al., 2012). During stress, cytokines are redistributed closer to sites of potential injury or infection (e.g. the mouth) to protect the host against possible viruses or bacteria (Dhabhar & McEwen, 1996). This redistribution is partially mediated by sympathetic activity, which is extremely rapid and could thus cause increases in cytokine levels within the timeframe assessed here (Bosch et al., 2005). Notably, this is not the first study to document increases in salivary cytokines approximately 10 minutes after onset of a stressor (Minetto et al., 2005).

Several limitations of this study should be noted. First, the sample was relatively small, homogenous, and female. Additional research is thus needed to examine the generalizability of these effects. Second, research has demonstrated the validity of oral measures of cytokine activity (Slavish et al., 2015), but confirmatory results using other sampling procedures would be beneficial. Third, we examined only one type of stress – namely, emotional stress. Because other stressors (e.g. uncontrollable, socially evaluative stressors) elicit different biological responses and may be preferentially associated with mental health outcomes such as learned helplessness (Grahn et al., 1999), future research should study relations between cognitive control, cytokines, and other types of stress. Finally, although the stress manipulation was experimental, all of the associations with cognitive control were correlational. Future studies should thus examine whether cytokine reactivity differs after manipulating cognitive control.

Several strengths are also noteworthy. First, all of the results held across the three cytokines that were measured, providing a within-study replication of the effects. Second, we employed the emotional Stroop task, which is a gold-standard measure of cognitive control. Third, the effect sizes obtained in this study indicated that cognitive control accounted for a large amount of variance (i.e. 23.7%) in stress-induced changes in cytokines, even after controlling for covariates. Finally, as a result, the data may elucidate a biological mechanism underlying previously observed associations between cognitive control and health (Shields et al., 2015).

In conclusion, we found that individuals who demonstrate better cognitive control over emotional information exhibit less pronounced salivary cytokine responses to an emotional stressor. Although stress increases risk for several inflammation-related disease conditions that represent the leading causes of death in the United States today (Slavich, 2015), many individuals who experience major stressors do not get ill. The present data are important in this context as they highlight a novel mechanism – specifically, cognitive control – that could potentially be modified to reduce inflammatory reactivity and improve health. Additional research should examine the generalizability of these findings and elucidate neurocognitive and biological mechanisms that link cognitive control with cytokine reactivity and health.

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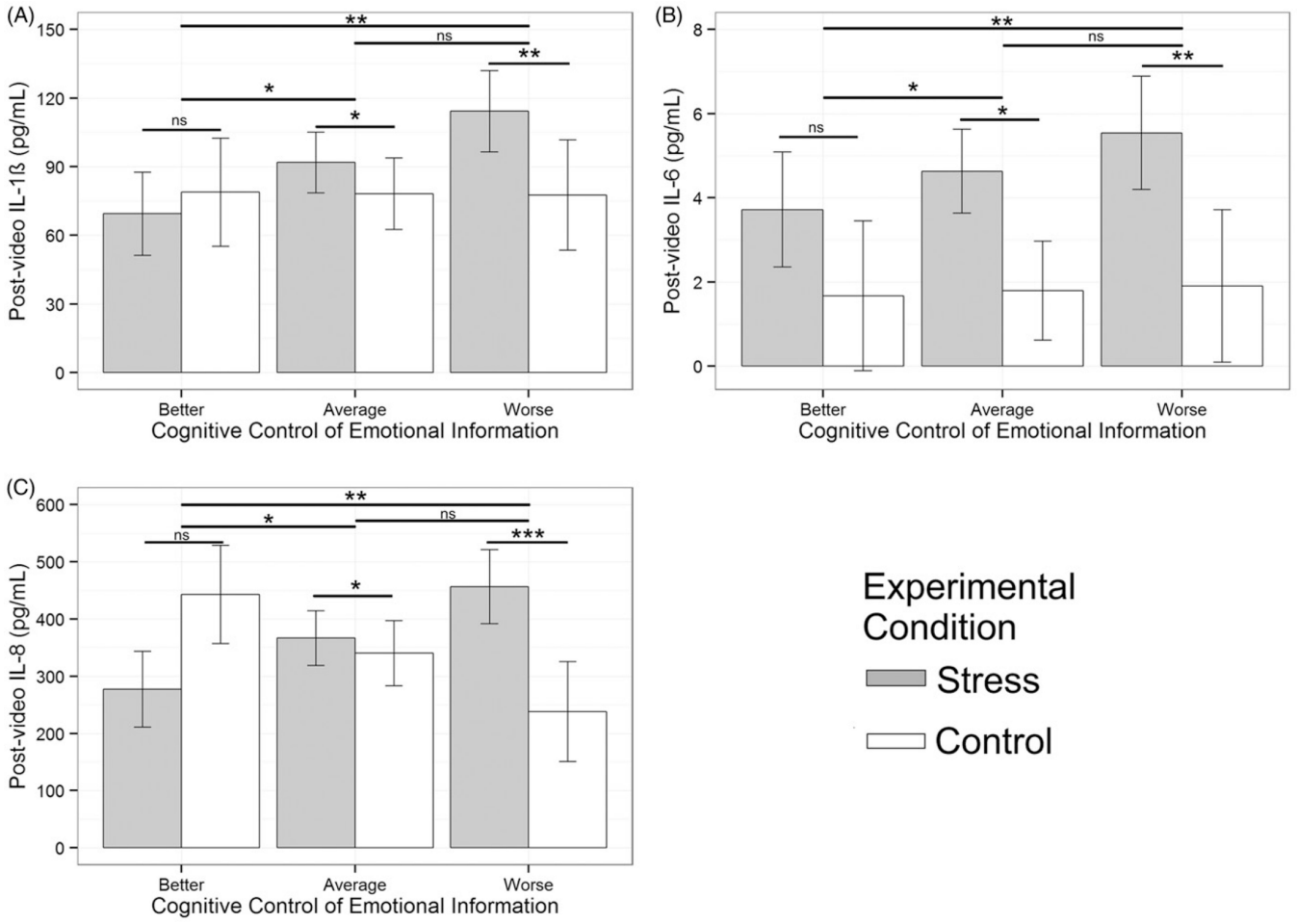

Figure 1.

Moderation of pro-inflammatory cytokine responses to acute stress by cognitive control of emotional information for participants randomly assigned to an acute emotional stress (emotionally evocative video) versus no-stress (control video) condition. Across the three cytokines measured (i.e. IL-1β, IL-6, and IL-8), better cognitive control of emotional information was associated with less pronounced cytokine reactivity for participants randomly assigned to the emotional stress (but not control) condition, even after adjusting for several covariates – specifically, participants' baseline cytokine levels, age, body mass index, and menstrual cycle phase. The bar graphs present raw data (pg/mL) for illustrative purposes, while analyses, as well as the indicators of significance on the bar graphs, controlled for covariates and used the natural log transformation of each cytokine to correct for skew.

Table 1

Type III SSs mixed-model ANOVA table from primary analysis.

Variables	MSE	df_1	df_2	F	p
Baseline Cytokines	378.23	1	84.9	359.21	**<0.001**
Condition	0.21	1	25.7	4.75	**0.039**
Emotional Stroop	0.00	1	25.8	2.05	0.164
Cytokine Type	0.42	2	69.3	7.06	**0.002**
Body mass index	0.00	1	25.7	1.11	0.303
Age	0.12	1	26.0	1.85	0.186
Phase of the menstrual cycle	0.00	1	26.2	0.13	0.726
Condition × Emotional Stroop	0.44	1	25.7	8.00	**0.009**
Condition × Cytokine Type	0.01	2	59.7	0.20	0.816
Emotional Stroop × Cytokine Type	0.04	2	59.1	0.80	0.455
Condition × Emotional Stroop × Cytokine Type	0.06	2	59.4	1.12	0.334

Significant effects are presented in boldface.

Table 2

Descriptive statistics of natural log-transformed cytokine and cortisol levels by experimental condition.

Variables	Pre-video Mean (*SE*)	Post-video Mean (*SE*)	Correlation pre- to post-video
Control condition			
Interleukin-1β (ln)	4.30 (0.27)	4.06 (0.23)	0.92
Interleukin-6 (ln)	0.93 (0.19)	0.80 (0.17)	0.86
Interleukin-8 (ln)	5.69 (0.21)	5.61 (0.18)	0.82
Cortisol (ln)	1.19 (0.20)	1.04 (0.21)	0.94
Emotional stressor condition			
Interleukin-1β (ln)	4.14 (0.24)	4.24 (0.20)	0.88
Interleukin-6 (ln)	1.29 (0.16)	1.43 (0.15)	0.61
Interleukin-8 (ln)	5.52 (0.19)	5.70 (0.16)	0.80
Cortisol (ln)	1.14 (0.18)	0.92 (0.18)	0.87

All cytokine and cortisol values were natural log transformed to correct for skew.