Adaptive Human Behavior and Physiology
https://doi.org/10.1007/s40750-019-00110-7

ORIGINAL ARTICLE

Experimentally-Induced Inflammation Predicts Present Focus

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Received: 27 December 2018 / Revised: 25 January 2019 / Accepted: 3 February 2019
Published online: 19 February 2019

Abstract

Objective Here, we provide an experimental test of the relationship between levels of proinflammatory cytokines and present-focused decision-making.
Methods We examined whether increases in salivary levels of proinflammatory cytokines (interleukin-1β and interleukin-6) engendered by visually priming immunologically-relevant threats (pathogen threat, physical harm) and opportunities (mating) predicted temporal discounting, a key component of present-focused decision-making.
Results As hypothesized, results revealed that each experimental manipulation led to a significant rise in both salivary interleukin-1β and interleukin-6. Moreover, post-manipulation levels of each cytokine independently predicted temporal discounting across conditions. These results were not moderated by pre-manipulation levels of either cytokine, nor were they found using the difference between pre- and post-manipulation levels of cytokines as a predictor.
Conclusions Together, these results suggest that levels of proinflammatory cytokines may play a mechanistic role in the desire for immediately available rewards.

Keywords Inflammation · Life history theory · Temporal focus · Cytokines · Impulsivity

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40750-019-00110-7) contains supplementary material, which is available to authorized users.

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Making decisions in a rapidly changing world requires individuals to make trade-offs between taking advantage of opportunities or rewards that are currently available, or forgoing those opportunities in the hopes of achieving better opportunities down the road (Hey 1982; Hills et al. 2015; Radner and Rothschild 1975). For example, when foraging, organisms must decide whether it is better to exploit the resources available in their current food patch or forgo that opportunity to search for more bountiful resources elsewhere. This trade-off between investing in currently available opportunities versus those potentially available elsewhere or after a delay is a fundamental decision-making trade-off that operates across decision domains (Addicott et al. 2017; Cohen et al. 2007; Hey 1982; Hills et al. 2015) and is essential to understanding the behavior of a wide variety of species, ranging from humans to fungi (Addicott et al. 2017; Alba and Dorronsoro 2005; Cohen et al. 2007; Humphries et al. 2012; Lazer and Friedman 2007; Mason et al. 2008; Watkinson et al. 2005). Examining how organisms resolve this trade-off has thus been an important area of inquiry for disciplines as diverse as economics (March 1991; Sidhu et al. 2007), consumer research (Voss et al. 2008), neuroscience (Cohen et al. 2007), artificial intelligence (Korf 1985), psychology (Lazer and Friedman 2007; Mason et al. 2008), and even cell biology (Alba and Dorronsoro 2005).

In the evolutionary sciences, the trade-off between choosing immediate versus delayed rewards is often examined through the lens of risk-sensitive foraging theory, or RSFT (Caraco et al. 1980; McNamara and Houston 1992; Real and Caraco 1986). Although originally developed as a framework for understanding foraging behavior, specifically (Pyke et al. 1977), this framework has since been applied to examining the trade-off between present versus delayed rewards across a number of domains of decision-making (Fawcett et al. 2012; Kidd et al. 2013; Real 1990). For example, insights from RSFT have been utilized to understand mate preferences (Real 1990), human economic behavior (Winterhalder et al. 1999), and even how children choose snacks (Kidd et al. 2013).

According to RSFT, whether an organism should take advantage of current resource opportunities or wait for better alternatives will depend on (a) the risk that delayed rewards may become unavailable (i.e., the collection risk), and (b) the costs associated with not having immediate resource access, such as when energy invested in attempting to acquire resources could translate into greater fitness benefits if allocated toward accomplishing a different task (i.e., opportunity costs) (Fawcett et al. 2012; McNamara et al. 1991). Decades of research has found support for these predictions. For example, individuals living in unpredictable environments (a context with elevated collection risk) often exhibit a preference for smaller, sooner – rather than larger, later – rewards (Brumbach et al. 2009; Bulley et al. 2016; Frankenhuis and de Weerth 2013; Kidd et al. 2013; McGuire and Kable 2013). Others find that contexts in which the opportunity costs associated with resource acquisition are particularly high (e.g., when then benefits of investing effort in mating or somatic repair are paramount) also increase the preference for immediately available resources (Fawcett et al. 2012; McNamara et al. 1991). Although a reduced ability to delay gratification may appear to be 'irrational', 'bad', or 'maladaptive' on the surface, according to RSFT, it is the optimal course of decision-making for conditions in which the collection risk and opportunity costs associated with waiting for a delayed reward are elevated (Bulley et al. 2016; Frankenhuis and de Weerth 2013; McGuire and Kable 2013).

Among the variables that impact the collection risk and opportunity costs associated with waiting for delayed rewards are factors that bear on the body's internal, physical condition (Higginson et al. 2018; Liesenjohann et al. 2015; Metcalfe et al. 1998; Nonacs 2001; Olsson et al. 2002). When the body is in good condition and its physiological needs have been met, the individual is in less need of immediate resources to help maintain basic physiological functioning or manage metabolically costly repair, and the probability of surviving long enough to realize delayed rewards is relatively high (Katz and Naug 2015; McNamara and Houston 1992; Wang and Dvorak 2010). Conversely, when the body is in poor condition or its physiological needs have not been met, more immediate rewards should be favored over those available after a delay, as current energy demands are higher, and the future is relatively less certain. Consistent with this hypothesis, research finds that fasted honeybees – compared to those who are satiated – exhibit a preference for exploiting currently available resources when foraging (Katz and Naug 2015). Others find similar results in humans, revealing that individuals whose blood glucose levels are low – indicating high energy need – show a greater preference for immediate rewards than those whose blood glucose levels have been experimentally elevated (Wang and Dvorak 2010).

The Activities of the Immune System as a Predictor of Present Focus

One of the key ways in which the body monitors its internal physical condition occurs via the activities of the immune system. The immune system identifies disease-causing, non-self organisms or molecules within the body, and responds with a set of biochemical and cellular defenses designed to eliminate them (Chovatiya and Medzhitov 2014; Matzinger 2002). Although activation of the immune system is remarkably efficient at managing numerous types of internal (e.g., tumorigenesis) and external (e.g., pathogens) survival threats, its deployment is physiologically costly and imperfect. For example, acute immunological activity can increase bodily energy expenditure up to 57% in humans (Clark et al. 1996; Lochmiller and Deerenberg 2000), and even low-grade inflammation – occurring in the absence of an acute immunological response – comes at a substantial metabolic and physiological cost to the body (Berk et al. 2013; Dantzer et al. 2008; Dantzer 2009). Accordingly, immunological activity represents a context that is associated with increased resource needs and a relatively lower probability of survival to collect later-available rewards.

Considering immunological activity (a) increases the body's need for immediately available resources (Clark et al. 1996; Lochmiller and Deerenberg 2000) and (b) may indicate a relatively diminished probability of survival to reap later-available rewards (Chovatiya and Medzhitov 2014; Matzinger 2002), Gassen et al. (under review, see references for pre-print access) recently proposed that signaling by the immune system may play an important role in the value that individuals place on immediately available rewards (Gassen et al., under review; Hill et al. 2016). Specifically, they hypothesized that signaling by the immune system should predict decision-making characterized by impulsivity, present focus, and an inability to delay gratification.

When immune cells are stimulated, they secrete a complex array of signaling proteins, such as cytokines, which promote inflammation, clear/prevent infections, and heal injuries (Chovatiya and Medzhitov 2014; Matzinger 2002; Thomson and

Lotze 2003). In addition to coordinating the activities of the immune cells themselves (e.g., white blood cells), cytokines also have the ability to directly influence the activities of the nervous system and, in turn, behavior (Banks 2005; Benveniste 1992; Hopkins and Rothwell 1995). For example, cytokines orchestrate sickness behavior, the constellation of physical, psychological, and behavioral changes – such as anhedonia, diminished foraging, and social avoidance – that regularly occur in the context of an acute immune response (Dantzer 2001; Dantzer and Kelley 2007). Although originally believed to be a maladaptive byproduct of pathogen presence, sickness behavior is now understood to reflect an adaptive response by the host organism that functions to mitigate bodily damage from infection and conserve energy for use in immunological defense (Aubert et al. 1995; Dantzer 2001; Medzhitov et al. 2012).

Given that cytokines are released in the context of immunological events in the body and also impact the activities of the nervous system in a variety of ways, it was hypothesized that higher levels of inflammation would predict a more present (as opposed to future) focus and a greater preference for smaller, immediate over larger, delayed rewards. Although support for this model was found using cross-sectional data (Gassen et al., under review), to date, this hypothesis has not been tested experimentally.

The Current Research

The current research was designed to test whether experimentally manipulated levels of proinflammatory cytokines would predict post-manipulation levels of delay discounting. Specifically, we predicted that manipulations of immunologically-relevant threats (physical harm, pathogen threat) and opportunities (mating) would promote increased present focus (i.e., temporal discounting) through their impact on proinflammatory cytokine release. Moreover, because present-focused decision-making is hypothesized to be an outcome associated with immune activation, per se, we predicted that higher levels of inflammation would predict greater present-focused decision-making regardless of the context that elicited the inflammatory response (e.g., illness, stress, diet, sexual activity, etc.) (Chovatiya and Medzhitov 2014; Matzinger 2002; Thomson and Lotze 2003).

We tested our hypothesis by randomly assigning participants to one of three priming conditions: physical harm, pathogen threat, or sexual arousal; each of these conditions was predicted to elicit an increase in proinflammatory cytokines. Participants' levels of proinflammatory cytokines were measured both prior to (Time 1) and approximately 20 min after (Time 2) exposure to the priming procedure. We predicted that higher Time 2 levels of proinflammatory cytokines (i.e., post-manipulation levels) would predict greater temporal discounting. Further, consistent with the idea that the impact of cytokines on decision-making is mechanistic and therefore path independent (i.e., not dependent on the cues eliciting release), we predicted that temporal focus would vary as a function of Time 2 cytokine levels, per se, regardless of (a) a participant's Time 1 levels of inflammation, (b) the degree to which cytokine levels changed in response to the manipulation (i.e., from Time 1 to Time 2), and (c) the nature of the manipulation used to elicit the inflammatory response.

Method

Participants

See Table 1 for characteristics of the sample. The sample included a total of 161 undergraduates (54 in pathogen threat condition [36 women]; 53 in physical harm condition [46 women]; 54 in mating condition [39 women]; M_{age} = 19.17 years, SD_{age} = 1.21). Sample size was determined a priori based on the recommendation by Cohen (1988) that researchers have 30 participants within each testing condition to achieve 80% power in cases in which the expected effect size is medium to large. We increased this target to a minimum *N* of 50 participants per condition, given the expected difficulty in quantifying levels of salivary interleukin-6 (IL-6). Participants were instructed not to eat or drink (except water) for two hours before their lab session, and not to exercise, engage in sexual activity (e.g., making out, sexual intercourse), or smoking on the day of their lab session. Students received partial course credit in exchange for participation.

Materials and Procedure

The protocol used in the current research was approved by the Florida State University Institutional Review Board (IRB). Participants first provided informed consent, filled out personality questionnaires, and provided a saliva sample (Time 1) via passive drool. Next, participants viewed slideshows of photographs presented via Inquisit software (Millisecond Software, Seattle, WA), which served as the priming procedure. After the slideshow, participants completed a short questionnaire, followed by three behavioral tasks (all presented sequentially). The first two behavioral tasks were conducted as part

Table 1 Characteristics of the sample (N = 161)

Sex: Men = 37; Women = 121; Did not respond = 3
Age: *M* = 19.17 years, *SD* = 1.21
Race
White/Caucasian: 80.7% (*n* = 130)
Black/African American: 8.7% (*n* = 14)
Asian: 3.1% (*n* = 5)
Multiracial: 1.2% (*n* = 2)
Other: 6.2% (*n* = 10)
Moderate Exercise (avg. days per week): *M* = 5.15, *SD* = 2.07
Sleep (avg. hours per night): *M* = 7.18, *SD* = 4.27
Body mass index: *M* = 23.27 kg/m^2, *SD* = 3.49
Childhood SES (1–7): *M* = 4.74, *SD* = 1.28
Current SES (1–7): *M* = 4.49, *SD* = 1.48
Perceived Stress (1–5): *M* = 2.84, *SD* = .70

Participants were instructed not to eat or drink (except water) for two hours before their lab session and not to exercise, engage in sexual activity (e.g., making out, sexual intercourse), or smoke on the day of their lab session

of an unrelated line of research on interpersonal perception (an approach / avoid task using social targets and a brief minimal personality group categorization task).

The final task, a temporal discounting task, was included for the purposes of the current study. The second saliva sample took place 20 min after the end of the priming slideshow – a period of time in which changes in salivary cytokine levels are detectable post-manipulation (for review, see Slavish et al. 2015) and close in time to the administration of our dependent measure. Participants then completed additional questionnaires and tasks unrelated to the current study, were thanked, debriefed, and awarded credit for their participation.

Experimental Manipulation We used previously published slideshows to prime states that should elicit an anticipatory immune response: a pathogen threat (photographs of others who were visibly ill; Schaller et al. 2010), a non-pathogen physical harm threat (photographs of others pointing a gun at the camera; Schaller et al. 2010), or mating activity (photographs of heterosexual couples in intimate positions without visible nudity; Ainsworth and Maner 2014). Participants were randomly assigned to view one of these primes. In each slideshow, nine photographs were presented for 10 s each, in random order with repetition, for a total of five minutes.

Temporal Discounting Participants completed a well-validated measure of temporal discounting (Griskevicius et al. 2011, 2013). Participants were presented with 20 dichotomous choices (in random order) between two hypothetical monetary rewards: one immediate reward and one delayed by 33 days (e.g., "Do you want to get $__ tomorrow OR get $__ 33 days from now?"). Immediate rewards were smaller than delayed rewards; the differences between the rewards varied from $1 to $70. The number of times the participant chose the smaller, immediate reward was our dependent measure; a higher score indicated greater temporal discounting.

Cytokine Assays Saliva was collected into scintillation vials via passive drool. After collection, all samples were immediately stored at −80 °C until assayed for levels of interleukin-1 beta (IL-1β) and interleukin-6 (IL-6). These cytokines were chosen because of their well-documented proinflammatory properties (Kiecolt-Glaser et al. 2003; Medzhitov 2008; Thomson and Lotze 2003). IL-1β, in particular, plays an especially key role in coordinating both local and systemic inflammatory processes (Dinarello 1991, 1996). It must be noted that in certain contexts, IL-6 is not exclusively proinflammatory, and this cytokine can even have anti-inflammatory properties (e.g., during and after exercise) (Del Giudice and Gangestad 2018). This should be considered when interpreting the results of the current research.

We measured salivary IL-1β and IL-6 levels at each time-point utilizing commercially-available enzyme-linked immunosorbent assay (ELISA) kits (Salimetrics, Carlsbad, CA), with sensitivities of .37 pg/mL (IL-β) and .07 pg/mL (IL-6). These assays were conducted in-house; all samples were assayed in duplicate per manufacturer instructions. The inter-assay coefficients of variation (CVs) were 5.25% (IL-1β) and 14.07% (IL-6). The intra-assay CVs were 2.18% (IL-1β) and 5.38% (IL-6).

IL-6 is often difficult to detect in saliva, as it is a relatively large molecule that does not pass easily into this medium, and levels are typically very low in healthy participants. Accordingly, numerous samples of IL-6 ($N = 99$) were lost for both time-points due to values falling below the standard curve. Because this was an issue of assay sensitivity, rather than user error (see Salimetrics 2019), we did not re-run these samples as they were unlikely to reach values high enough to fall within the standard range of the assay.

Potential Covariates We measured a number of variables previously found to influence inflammation or present focus: age, gender, race, physical activity, sleep, body mass index (BMI), stress, recent illness, and socioeconomic status (Griskevicius et al. 2011; Slavish et al. 2015). We included these as covariates to examine the robustness of our primary model. Physical activity was measured by asking participants, "How many days per week do you do moderate physical activity for …? ", sleep was measured by asking, "Over the past week, how much sleep did you get each night, on average?", stress was measured using the Perceived Stress Scale ($\alpha = .86$; PSS; Cohen et al. 1983), recent illness was measured with the question, "When was the last time you felt sick?", and socioeconomic status (SES) was measured using established three-item scales for both childhood ($\alpha = .79$) and adult ($\alpha = .81$) SES (Griskevicius et al. 2011).

Data Analysis Plan

According to our theoretical model (Gassen et al., under review), (a) *state* levels of inflammatory activity – here, quantified by levels of inflammation at Time 2 – were expected to predict increased present focus (also measured at Time 2), and (b) any relationship between baseline, trait levels of proinflammatory activity – quantified by basal levels of inflammation taken at Time 1 – would operate indirectly through its impact on state levels of inflammation measured at Time 2.

To assess this hypothesis, we first conducted two preliminary statistical models to test for (a) a direct effect of the experimental priming condition on temporal discounting and (b) a direct effect of the experimental priming condition on Time 2 levels of proinflammatory cytokines. We predicted (a) no main effect of experimental priming condition on levels of proinflammatory cytokines or temporal discounting and (b) a main effect of Time (across types of manipulation) on levels of proinflammatory cytokines (i.e., Time 2 levels were predicted to be significantly higher than Time 1 levels).

Our primary statistical model (see Fig. 1 of main text) was estimated using structural equation modeling (SEM; MPlus 7.4 statistical software, Muthén & Muthén, Los Angeles, CA). We assessed model fit using four fit indices: χ^2 test of model fit, the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). In this model, Time 1 cytokine levels (resting levels of IL-1β and IL-6) were predicted to be associated with Time 2 cytokine levels (post-manipulation levels of IL-1β and IL-6), which were themselves hypothesized to predict temporal discounting (greater present focus).

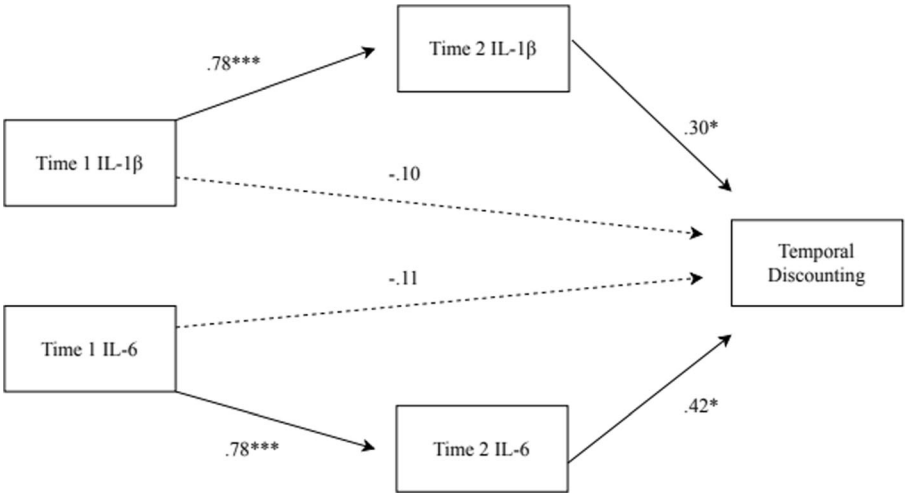

Fig. 1 Structural equation model for relationship between proinflammatory cytokines and temporal discounting shown here with standardized estimates. Dotted lines denote non-significant paths. Priming condition controlled for at each path. IL-1β = interleukin-1β; IL-6 = interleukin-6. ***$p < .001$, **$p < .01$; *$p < .05$

Results

Values for IL-1β and IL-6 were positively skewed and were log-transformed prior to analysis. Complete IL-1β data were missing for 27 participants (i.e., missing at T1 or T2; pathogen threat condition: 9, non-pathogen threat condition: 10, mating activity condition: 8), due to issues with sample collection or cytokine levels falling outside of assay range. Additionally, because levels of IL-6 are difficult to capture in saliva (see "Method" section for more information), numerous samples of IL-6 were lost for both time-points due to values falling below the standard curve (pathogen threat condition: 38, non-pathogen threat condition: 27, mating activity condition: 34). For our primary statistical model, missing data were handled, per convention, using full information maximum likelihood estimation at the time of the analysis (Dong and Peng 2013). Bivariate correlations between all variables analyzed in the current research are displayed in Table 2.

Preliminary Model 1: Experimental Manipulation on Temporal Discounting

We conducted a preliminary one-way, three-level analysis of variance (ANOVA) to test for a main effect of the between-subjects factor of priming condition (pathogen threat, non-pathogen threat, or mating activity) on our dependent measure, temporal discounting. Results revealed that rates of temporal discounting did not differ between the three conditions, $F(2, 158) = .002$, $p = .998$.

Preliminary Model 2: Experimental Manipulation of Salivary Cytokines

Next, we tested two separate 3 (priming condition; between-subjects) × 2 (time point; within-subjects) mixed-model ANOVAs (one for IL-1β and one for IL-6). These

Table 2 Bivariate correlations between all variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Time 1 IL-6	–													
2. Time 2 IL-6	.73***	–												
3. Time 1 IL-1β	.28*	.14	–											
4. Time 2 IL-1β	.18	.21†	.73***	–										
5. Temporal Discounting	.22†	.42***	.11	.27***	–									
6. Age	.06	.30**	−.19*	−.06	−.01	–								
7. Race	−.18	−.09	−.06	−.04	−.05	.04	–							
8. Body Mass Index	.14	.10	.07	−.04	.08	−.05	−.23**	–						
9. Sex	−.19	.04	−.11	−.12	−.14	−.02	.28***	−.14	–					
10. Last Time Sick	.002	.16	.06	.16	−.06	−.05	−.24**	.20*	.03	–				
11. Perceived Stress	.02	.10	−.05	.02	−.02	.04	−.03	−.09	.05	.07	–			
12. Sleep Last Week	−.18	−.20	−.05	−.05	−.12	−.07	−.07	.15	.06	.20†	−.01	–		
13. Exercise Per Week	−.01	−.02	−.02	−.11	−.09	−.10	.06	.23**	.03	.12	−.05	−.03	–	
14. Childhood SES	.02	.10	−.10	.003	.06	.10	.02	−.11	.09	.04	.02	−.22*	.03	–
15. Adult SES	−.06	−.04	−.01	.04	.02	.07	.06	.02	.06	.07	−.06	−.03	−.06	.53***

Cytokine values were log-transformed prior to analysis. IL-6 = interleukin-6; IL-1β = interleukin -1beta; SES = socioeconomic status. † indicates marginal significance at $p \leq .07$, * indicates significance at *$p \leq .05$, **$p \leq .01$, and ***$p \leq .001$

models were conducted to examine whether the priming procedure led to a change in salivary cytokine levels, and whether this change was moderated by condition.

See Table 3 for descriptive statistics. Our results revealed a significant increase in levels of both IL-1β, $F(1, 131) = 13.58$, $p < .001$, $d = .24$, and IL-6, $F(1, 60) = 7.22$, $p = .009$, $d = .28$, from Time 1 to Time 2. As predicted, no main effect of priming condition or interactions between priming condition and time were found for either cytokine ($Fs < .95$, $ps > .38$). These results indicated that the experimental manipulation led to a statistically significant increase in levels of each cytokine, but this effect was not moderated by condition.

Primary Model: Salivary Cytokine Levels on Temporal Discounting

Next, to assess whether post-manipulation salivary cytokine levels predicted temporal discounting scores, we tested a structural regression model. We specified Time 1 and Time 2 salivary cytokine levels as predictors of temporal discounting, while controlling for the effects of priming condition on each path within the model (see Fig. 1). We regressed each Time 2 cytokine value on its respective Time 1 value, and simultaneously regressed temporal discounting on all Time 1 and Time 2 cytokine values (i.e., for both IL-1β and IL-6).

Standardized parameter estimates are displayed in Fig. 1. Fit statistics for the model indicated good fit: $\chi^2(5) = 6.42$, $p = .27$, RMSEA = .04, CFI = .99, SRMR = .03. Results revealed that higher cytokine levels at Time 1 significantly predicted higher levels at Time 2 for both IL-1β, $\beta = .78$, $SE = .04$, $t = 22.00$, $p < .001$, and IL-6, $\beta = .78$, $SE = .05$, $t = 14.80$, $p < .001$. As predicted, participants' pre-manipulation (basal) levels of proinflammatory cytokines did not significantly predict temporal discounting when

Table 3 Descriptive statistics for cytokines and temporal discounting scores by condition

Measures	Time 1 M (SD)	Time 2 M (SD)
Disease Condition		
IL-1β	2.07 (.56)	2.20 (.40)
IL-6	.63 (.77)	.84 (.46)
Temporal Discounting Sum	–	7.46 (3.32)
Physical Harm Condition		
IL-1β	2.22 (.57)	2.29 (.48)
IL-6	.81 (.57)	1.01 (.32)
Temporal Discounting Sum	–	7.43 (4.11)
Mating Condition		
IL-1β	2.07 (.53)	2.22 (.38)
IL-6	.87 (.67)	.92 (.64)
Temporal Discounting Sum	–	7.43 (3.62)

Cytokine levels shown here natural log-transformed. Transformed cytokine variables were used in all analyses. Temporal discounting sum is number of times participant chose immediate over delayed reward across 20 binary choices. IL-1β = interleukin-1β; IL-6 = interleukin-6

controlling for post-manipulation cytokine levels ($ps > .46$). Instead, temporal discounting was independently predicted both by Time 2 levels of IL-1β, $\beta = .30$, $SE = .14$, $t = 2.17$, $p = .03$, and by Time 2 levels of IL-6, $\beta = .42$, $SE = .20$, $t = 2.08$, $p = .04$. Indirect effects of Time 1 cytokine levels on temporal discounting mediated through Time 2 levels were significant for both IL-1β, $\beta = .23$, $SE = .11$, $t = 2.15$, $p = .03$, and IL-6, $\beta = .33$, $SE = .16$, $t = 2.07$, $p = .04$. Overall, the primary model accounted for 18.5% of the variance in temporal discounting across the sample.

Follow-Up Model 1: Primary Statistical Model Controlling for Covariates

We repeated the primary statistical model controlling for age, sex, race, physical activity, sleep, BMI, stress, recent illness, and socioeconomic status. Results again revealed that Time 1 cytokine levels significantly predicted Time 2 levels for both IL-1β, $\beta = .77$, $SE = .04$, $t = 17.90$, $p < .001$, and IL-6, $\beta = .73$, $SE = .07$, $t = 10.84$, $p < .001$. Further, neither Time 1 levels of IL-1β, $\beta = -.23$, $SE = .14$, $t = -1.65$, $p = .10$, nor Time 1 levels of IL-6, $\beta = -.28$, $SE = .20$, $t = -1.41$, $p = .16$, directly predicted temporal discounting. Instead, temporal discounting was significantly predicted by Time 2 levels of both IL-1β, $\beta = .48$, $SE = .14$, $t = 3.50$, $p < .001$, and IL-6, $\beta = .66$, $SE = .20$, $t = 3.38$, $p = .001$.

Follow-Up Model 2: Model for Magnitude of Cytokine Level Change as Predictor of Temporal Discounting

Next, in two separate models, we regressed temporal discounting on the absolute change in levels of each cytokine (in pg/mL) from Time 1 to Time 2 (first model) and the percent change in levels of each cytokine from Time 1 to Time 2 (second model). Temporal discounting was not predicted by absolute changes in either IL-1β, $\beta = -.09$ $SE = .11$, $t = -.78$, $p = .44$, or IL-6, $\beta = .16$, $SE = .16$, $t = .95$, $p = .34$, nor was this outcome predicted by the percent change in levels of either IL-1β, $\beta = .07$ $SE = .09$, $t = .74$, $p = .46$, or IL-6, $\beta = -.08$, $SE = .15$, $t = -.53$, $p = .60$. This indicates that post-manipulation levels of proinflammatory cytokines – regardless of whether they were high or low prior to the manipulation and regardless of the magnitude of the change – predict post-manipulation levels of temporal discounting.

Follow-Up Model 3: Separate Models for each Cytokine

Given the large amount of missing data for salivary IL-6 levels, we also tested relationships between each cytokine and temporal discounting in two separate regression models (i.e., one for each cytokine). These results confirmed those of the combined model. For IL-6, results revealed that higher levels of this cytokine at Time 1 significantly predicted higher levels at Time 2, $\beta = .75$, $SE = .06$, $t = 12.98$, $p < .001$. Higher Time 2 levels of IL-6, in turn, predicted greater temporal discounting, $\beta = .43$, $SE = .18$, $t = 2.38$, $p = .02$. The direct effect of Time 1 IL-6 levels on temporal discounting was not significant ($p = .55$). However, the indirect effect of Time 1 IL-6 levels on temporal discounting mediated through Time 2 levels was significant, $\beta = .32$, $SE = .14$, $t = 2.33$, $p = .02$. Similar results were found for IL-1β. Higher Time 1 IL-1β levels significantly predicted higher Time 2 levels, $\beta = .76$, $SE = .04$, $t = 20.24$, $p < .001$,

which, in turn, predicted greater temporal discounting, $\beta = .30$, $SE = .13$, $t = 2.39$, $p = .02$. The direct effect of Time 1 IL-1β levels on temporal discounting was not significant ($p = .37$). However, the indirect effect of Time 1 IL-1β levels on temporal discounting mediated though Time 2 levels was significant, $\beta = .23$, $SE = .10$, $t = 2.35$, $p = .02$.

Discussion

In the current research, we used insights from RSFT to predict that the activities of the immune system would have an impact on the preference for immediate versus delayed rewards. Specifically, we predicted that inflammation – given its link with increased energy need and diminished survival probability – would increase the desire for smaller, sooner – rather than larger, later – rewards. The results of the current research found support for this hypothesis, demonstrating that levels of proinflammatory cytokines measured after visually priming immunologically-relevant threats and opportunities predicted levels of temporal discounting. This relationship was not influenced by (a) the specific nature of the experimental manipulation, (b) pre-manipulation cytokine levels, or (c) an interaction between the two. This is consistent with the hypothesis that proinflammatory cytokines play a mechanistic role in regulating temporal focus, with higher levels of cytokines predicting greater temporal discounting.

These results are consistent with cross-sectional research by Gassen et al. (under review) which found that inflammation (measured in peripheral blood) mediates a link between proinflammatory cellular tendencies (assessed in vitro using lipopolysaccharide-stimulated peripheral blood mononuclear cells) and several measures of present focus. Together, these results lend convergent support for the hypothesis that proinflammatory cytokines may play a mechanistic role in present-focused decision-making. In addition to providing evidence of a novel role for cytokines in directing the activities of the nervous system, the current results also lend support for a novel application of RSFT. Specifically, these results suggest that the internal condition of the body may play an important role in calibrating decisions about risk and reward across a wide-range of decision domains (Hill et al. 2016; Rickard et al. 2014; Waynforth 2012).

Our research has important limitations. First, it is possible that salivary cytokine measures merely capture a localized, oral immunological response (e.g., Teles et al. 2009). Indeed, some evidence suggests that plasma and salivary levels of cytokines are not strongly correlated (e.g., Williamson et al. 2012). Although the limitation of our use of salivary cytokine measures must be considered, the present results are consistent with previous work that used multiple inflammatory markers in peripheral blood (Gassen et al., under review). Further, recent experimental work has found consistency between salivary and plasma cytokine levels in the context of experimental manipulations that elicit an increase in inflammation (La Fratta et al. 2018; Slavish et al. 2015). Finally, that we found a change in salivary cytokine levels from Time 1 (pre-manipulation) to Time 2 (post-manipulation) itself indicates that we are capturing a facet of a systemic immune response, not merely oral inflammation.

In addition to these limitations, it should be noted that our sample was predominately female. Further, we did not achieve equal allocation of sex in each condition. However, as previously noted, controlling for sex, as well as other covariates (see Potential Covariates), changed neither the pattern nor the significance of the results. Lastly, the current study did not utilize a neutral comparison group whose cytokine levels were expected to remain unchanged in response to the manipulation. This important limitation should be considered when interpreting the results of the current research. Because of this limitation, we cannot conclude that the manipulation, per se, caused the predicted changes in cytokine levels; however, this does not detract from our ability to conclude that post-manipulation levels of proinflammatory cytokines predict temporal discounting (something that is not predicted by Time 1 levels or the magnitude of the change from Time 1 to Time 2).

Future research may help to address these concerns and expand the results of the current study. For example, future experiments examining relationships between inflammation and present focus might benefit from utilizing a well-validated manipulation to increase levels of proinflammatory cytokines (e.g., Trier Social Stress Task; Steptoe et al. 2007), as well as including a neutral control group. This research may also test the relationship between proinflammatory cytokines and a greater number of outcomes related to present-focused decision-making. This would help determine whether the link between inflammation and present-focused decision-making is specific to the preference for immediate versus delayed rewards, or whether increases in inflammation also influence other components of this construct, such as motor impulsivity and an inability to delay gratification (Evenden 1999). Other future studies, work likely requiring non-human animals, will be necessary to help elucidate and experimentally manipulate the relevant neural mechanisms linking proinflammatory cytokines to these cognitive alterations. Finally, additional research is needed to determine the precise nature of the relationship between plasma /serum and salivary levels of proinflammatory cytokines, both basal and in the context of experimental manipulations. Such research will help determine the validity of salivary cytokine measures, which are often less invasive and more economical than blood-based measures.

Conclusions

Although the current research has important limitations, our research provides support for the hypothesis that levels of proinflammatory cytokines may play a key role in temporal focus. Our findings suggest that the numerous factors that promote inflammation may also contribute to impulsive tendencies that negatively impact health and well-being. Further, these results suggest the possibility for novel pharmacological and behavioral strategies for reducing the personal, social, and economic costs of impulsive behaviors.

Funding This project was supported by two National Science Foundation awards: BCS #1551201 awarded to S. E. Hill and BCS #1227089 awarded to J. K. Maner and L. A. Eckel.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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