INFLAMMATION PROMOTES INVESTMENT IN PRESENT VERSUS DELAYED OUTCOMES

by

JEFFREY W. GASSEN

Bachelor of Arts, 2012
University of Nebraska-Omaha
Omaha. Nebraska

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Jeffrey W. Gassen

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Major Professor

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Inflammation Promotes Investment in Present versus Delayed Outcomes

The relationship between inflammation and health has been studied for over 2,000 years (Egger & Dixon, 2014). First considered merely part of the healing process, the famed Roman surgeon and scientist, Cornelius Celsus, described the inflammatory response as redness, heat, and swelling that occurred in response to injury (Köckerling, Köckerling, & Lomas, 2013). With the advent of germ theory in the 19th century, the vital importance of inflammation to pathogen defense was also recognized, and inflammation became widely known as a targeted immune response to local infection or injury (Lederberg, 2000). Today, research has revealed that inflammation protects the body from a much broader range of noxious stimuli and conditions, including environmental irritants, psychosocial stressors, and other disruptors of physiological homeostasis that are common in the industrialized world (Dinarello, 2000; 2011; Gluckman et al., 2016). To defend against these threats to homeostasis, mediators of the inflammatory response – such as proinflammatory cytokines – coordinate cellular and molecular events that function to neutralize the threat and promote recovery (Medzhitov, 2008; Goshen & Yirmiya, 2009). Although such a response is critical to maintaining health, when chronic, inflammation is associated with a wide range of health problems, such as heart disease, obesity, allergies, and autoimmune disorders (see Hunter, 2012 for review). This is because the inflammatory response is metabolically costly, generates oxidative stress, and alters tissue function in a manner that is beneficial to immediate threat resolution, but contributes to disease when prolonged (Chovatiya & Medzhitov, 2014; Chung et al., 2009; Medzhitov, 2008). In other words, inflammation induces changes in the body that promote focus on overcoming an immediate threat, which can come at the expense of longevity when the inflammatory response remains unresolved.

Growing evidence suggests that inflammation also exerts a powerful influence on human cognition and behavior (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Haroon, Raison, & Miller, 2012; Raison, Capuron, & Miller, 2006). Following a pattern that resembles inflammation's impact on the body, acute inflammation appears to elicit psychological shifts that are beneficial in the context of threat defense (e.g., sickness behavior), while chronic inflammation is associated with various psychopathologies (Donzis & Tronson, 2014; Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017; Vogelzangs, Beekman, De Jonge, & Penninx, 2013). One possibility is that – similar to their effects at the cell and tissue levels – inflammatory mediators promote a general trade-off towards focusing on immediate versus delayed outcomes, which may assist current somatic defense and recovery efforts. Such a focus is often associated with the psychological construct of impulsivity (Bialaszek et al., 2015; Madden & Bickel, 2010; McKerchar & Renda, 2012). Impulsivity is related to many behaviors and tendencies that benefit defense and recovery from a threat – such escape behavior (Bjork, Dougherty, Huang, & Scurlock, 1998), preference for low-cost resources (Martin & Potts, 2004), and sensitivity to negative experience (Richardson, Freedlander, Katz, Dai, & Chen, 2014). However, like inflammation, impulsivity can also be problematic when chronically high (e.g., substance abuse, gambling, and obesity; for review see Arce & Santisteban, 2006). Here, I aim to test the hypothesis that inflammation promotes impulsivity by examining whether levels of active inflammation and cellular inflammatory tendency predict several psychological and behavioral traits that together comprise the construct of impulsivity (Bialaszek, Gaik, McGoun, & Zielonka, 2015; Madden & Bickel, 2010; McKerchar & Renda, 2012).

Inflammation and Somatic Defense

The inflammatory response is an adaptive defense mechanism against noxious stimuli and conditions in the body (Dinarello, 2000; 2011; Goshen & Yirmiya, 2009; Medzhitov, 2008). Inflammation is triggered by tissue resident and circulating sensory cells that utilize a variety of tools – such as pathogen- and damage-associated molecular pattern recognition – to detect infection, injury, and extreme deviation from physiological homeostasis (Medzhitov, 2008). In response to signals of pathogen presence or cellular distress, these sensory cells release mediators of the inflammatory response – including cytokines, chemokines, and many others – in order to facilitate elimination of the threat and restoration of normal functioning (Chovatiya & Medzhitov, 2014). In addition to recruiting specialized immune cells to deal with a threat, the inflammatory response involves alterations to tissue functional states, which allows for adaptation to the given instigator of the response (Medzhitov, 2008). Some of these tissue-level changes involve remodeling of local vascular networks (Costa, Incio, & Soares, 2007), increased vascular endothelial permeability (Rock, Latz, Ontiveros, & Kono, 2009), and modified sensitivity to certain hormones involved in energy regulation (Black, 2003).

Although inflammation is crucial to defending the body against insult and injury, the tissue-level changes at the center of the inflammatory response – coupled with their metabolic costs – can compromise health when protracted (Chovatiya & Medzhitov, 2014; Chung et al., 2009; Medzhitov, 2008). Take, for example, inflammation-induced insulin resistance. Inflammatory factors mediate the process of stress-related insulin insensitivity, which in the short-term increases energy availability for behavioral and immunological defenses (Black, 2003). However, when exposure to the stressor – and associated inflammatory response – is prolonged, the same process promotes or exacerbates metabolic disorders (e.g., obesity and

diabetes; Chen, Chen, Wang, & Liang, 2015). In sum, mediators of the inflammatory response facilitate a constellation of energetically costly changes to tissue functioning that combat noxious stimuli and conditions in the present, but damage health over time. Because many inducers of inflammation in our modern world are chronic, unresolved psychosocial stressors, it is of little surprise that chronic inflammation has emerged as a unifying risk factor for the numerous non-communicable diseases on the rise throughout industrialized nations (Dinarello, 2000; 2011; Gluckman et al., 2016, Hunter, 2012). As I present in the next section, research suggests that the complex relationship between inflammation and health is not restricted to internal conditions of the body. Instead, the pattern of inflammation inducing changes to physiology for the purpose of threat defense that can compromise health when prolonged extends to human psychology and behavior.

Inflammation, Psychology, and Behavior

Research has shown that inflammatory mediators – particularly proinflammatory cytokines – have direct effects on human psychology and behavior (Dantzer, O'Connor, Freund, Johnson, & Kelley, 200; Dantzer & Kelley, 2007; Maier & Watkins, 1998). Cytokines are a class of small molecule immunological signaling proteins with pleotropic effects across the body (for review see Thomson & Lotze, 2003). A subset of these cytokines are considered classically proinflammatory, as they actively coordinate the inflammatory response (e.g., IL-6, IL-1β, and TNF-α). Cytokines also exert effects on the brain both in the periphery via action at afferent vagal fibers, and centrally by crossing the blood-brain barrier through active and passive transport systems or by being released from microglia (Goshen & Yirmiya, 2009; Thomson & Lotze, 2003). Through these pathways, inflammatory factors are able to influence behavior in humans and other animals (Dantzer & Kelley, 2007; Dinarello, 2000; Maier & Watkins, 1998).

Some research suggests that inflammation affects cognition and behavior in a way that complements the cellular and molecular events in the body targeted at removing, and recovering from, a somatic threat (e.g., Donzis & Tronson, 2014; Eisenberger et al., 2017). For example, the well-established phenomenon of "sickness behavior" involves a collection of behavioral and psychological symptoms – such as anhedonia, fatigue, and food neophobia – induced by an acute rise in proinflammatory cytokines. Sickness behavior is hypothesized to aid recovery from illness by promoting rest and conservation of energy for immunological defenses (Dantzer & Kelley, 2007; Goshen & Yirmiya, 2009). Much like the impact of inflammation at the tissue level, when inflammation is unresolved, negative psychological health consequences can result. Chronically elevated levels of inflammatory markers, for example, are associated with clinical depression, post-traumatic stress disorder (PTSD) and many other psychological and behavioral issues (Buckley, Blanchard & Hickling, 2002; Dantzer et al., 2008; Russell et al., 2007; Short, Adams, Garner, Sonuga-Barke, & Fairchild, 2016). These issues may arise because – similar to its effects on the body – the inflammatory process favors a general trade-off towards psychological tendencies that focus on immediate outcomes, otherwise known as impulsivity. As I describe in the next section, inflammation may promote impulsivity because focusing on the present is beneficial in the context of threat defense and somatic recovery (Bjork et al., 1998; Brumbach et al., 2009; Martin & Potts, 2004; Richardson et al., 2014). However, as a stable trait, high impulsivity also underlies various psychopathologies to which inflammation is related (e.g., depression and PTSD; Baker, Nievergelt, & O'Connor, 2012; Dantzer et al., 2008; Moustafa, Tindle, Frydecka, & Misiak, 2017; Weiss et al., 2012).

Impulsivity and Inflammation

Impulsivity is a complex psychological characteristic that has been described in scientific literature as the tendency to act without consideration of future consequences, present focus, and a preference for immediate rewards (Bialaszek et al., 2015; Madden & Bickel, 2010; McKerchar & Renda, 2012). Each of these definitions – together capturing the construct of impulsivity – has been critical to our understanding of the psychological processes that underlie many behavioral problems (for review see Arce & Santsteban, 2006). For example, trait impulsivity has been linked to substance abuse, gambling, criminal activity, driving accidents, and a host of other issues (Hilakivi et al., 1989; Lynam et al., 2000; Petry, 2001). In addition to these problematic behaviors, impulsivity is also a symptom of depression and PTSD, both of which are associated with chronic inflammation (Baker et al., 2012; Dantzer et al., 2008; Moustafa et al., 2017; Weiss et al., 2012).

Although pathologically high levels of impulsivity are undoubtedly maladaptive, in certain situations, acting impulsively may actually be helpful, especially in the context of threats to fitness (Brumbach et al., 2009; Frankenhuis, Panchanathan, & Nettle, 2016; Griskevicius, Tybur, Delton, & Robertson, 2011). For example, animal models have shown that impulsivity is related to a rapid acquisition of avoidance behavior (Moreno et al., 2010). Research in humans has revealed that impulsivity is associated with both a higher frequency of escape behavior (Bjork et al., 1998) and greater threat sensitivity (Richardson et al., 2014). Further, impulsivity in the appetitive domain, such as preference for immediate rewards, may promote maximizing access to available, low-cost rewards when the body is compromised or the future is uncertain (Martin & Potts, 2004; Kidd, Palmeri, & Aslin, 2013). Supporting this hypothesis, individuals who inhabit environments dense in extrinsic mortality threats (e.g., violent neighborhoods) –

particularly during the vulnerable period of childhood – tend to discount the future and exhibit a preference for immediate rewards (Brumbach et al., 2009; Frankenhuis et al., 2016; Griskevicius et al., 2011). Adversity early in life also leads to a proinflammatory phenotype, although it has yet to be determined if inflammation mediates the relationship between childhood stress and impulsivity (Chen et al., 2009). The psychosocial stress inherent in dangerous environments, however, represents only one of the many types of threats to physiological homeostasis known to elicit an inflammatory response (Medzhitov, 2008; Rohleder, 2014). If inflammatory mediators promote a present focus in order to behaviorally complement tissue level somatic defense and recovery efforts, higher levels of inflammation should be related to impulsivity regardless of the original instigator of the response (e.g., stress, illness, poor diet, or age; O'Connor et al., 2009).

The Current Research

Building on these insights, with the current research, I intended to test whether inflammation, a key bodily defense against threats to physiological homeostasis, promotes impulsivity. I employed structural equation modeling (SEM) to test my prediction that higher levels of inflammatory activity *in vivo* (i.e., plasma levels), and cellular inflammatory tendency (i.e, *in vitro* cytokine release by peripheral blood-derived mononuclear cells [PBMCs] in response to stimulation), would be associated with greater self-report and behavioral indices of impulsivity. Because I hypothesized that inflammation leads to problematic impulsive behavior when chronically elevated, a secondary prediction was that a proinflammatory tendency – representative of higher exposure to inflammation over time (Miller et al., 2009) – would be related to weekly alcohol consumption. Finally, I tested alternative models that allowed me to examine, 1) if the relationship between inflammation and impulsivity held when controlling for

other factors known to predict either construct, and 2) whether inflammation better represented an antecedent or consequence of impulsivity.

Method

Participants

Participants were 159 individuals who were either undergraduates at Texas Christian University or residents of the surrounding community (80 men, 79 women; M_{age} = 20.17 years, *SD* = 2.75). Eligibility requirements included 1) being without history of chronic medical disorders, 2) being non-obese (body mass index [BMI] below 30), 3) being a non-smoker, 4) not taking hormonal contraceptives (females), 5) being free from acute illness for at least two weeks, 6) abstaining from steroidal and non-steroidal anti-inflammatory medications, exercise, and alcohol for at least two days prior to the session, and 7) fasting the morning of the session. All women participated 4-7 days after the first day of their last menstrual period. Participants completed all relevant measures as a part of a larger study investigating the influence of the immune system on psychological characteristics. Community participants received a $50 gift card for participation, while undergraduate students were given the choice between participating for the gift card or in exchange for partial course credit.

Materials and Procedure

All testing sessions began at 7:30 AM after each participant fasted for a minimum of eight hours. Upon receiving informed consent and ensuring that participants had followed the requirements of the study (e.g., abstaining from anti-inflammatory drugs, etc.), participants entered the lab in groups of 2-6 and sat at partitioned computer terminals. Participants completed all questionnaires using Qualtrics online experimental survey software (Qualtrics, 2015). After completing all survey measures, participants were ushered one at a time into an adjoining,

private room where 85 mL of blood was drawn via venipuncture into heparinized (or EDTA-containing) Vacutainer® tubes (Becton-Dickinson, Franklin Lakes, NJ). After completion of the blood draw, participants were thanked, debriefed, and compensated.

Measures of impulsivity. Because impulsivity is a multifactoral construct consisting of several different characteristics, such as acting without consideration of future consequences, behavioral disinhibition, present focus, and delay discounting (Bialaszek, Gaik, McGoun, & Zielonka, 2015; Madden & Bickel, 2010; McKerchar & Renda, 2012), four separate indicators of impulsivity were measured in order to capture each of these traits and tendencies.

First, participants responded to the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), which consisted of asking participants to indicate how much each of 30 statements described the way they think and act. These statements measured psychological and behavioral traits across three domains of impulsivity: Attentional (8-items, e.g.; "I don't pay attention"), Motor (11 items; e.g., "I do things without thinking"), and Nonplanning (11 items; e.g., "I say things without thinking"). Each item was answered on a 4-point scale (1: *Rarely/never*, 4: *Almost always/always*). Together, the scale yielded acceptable reliability ($\alpha = .85$) and was formed into a mean composite with a higher score indicating greater tendency towards acting without consideration of future consequences.

Next, present focus was measured by presenting participants with a slider scale with which they indicated how "far away" certain periods of time felt (Zauberman et al., 2009). The slider ranged from *very short* to *very long* with 100 points of reference from the first endpoint to the last. Participants were asked, "How long from now does __ feel?" for one day, one month, three months, and six months. A mean composite of perceived distance from each time period was computed ($\alpha = .85$), with a longer perceived distance indicating a more present focus.

Participants also filled out the short-form Delaying Gratification Inventory (DGI; Hoerger, Quirk, & Weed, 2011) to measure preference for immediate over delayed outcomes. The short-form DGI is comprised of 10 statements regarding one's ability to delay gratification for which the participant rated how much each item described him or her. Sample items included "I try to spend my money wisely" and "I have given up physical pleasure or comfort to reach my goals". Participant agreement with each item was indicated on a 9-point scale (1: *Strongly disagree*, 9: *Strongly agree*). The scale yielded good reliability ($\alpha = .70$) and was formed into a mean composite variable with a higher score representing a greater ability to delay gratification.

Participants next completed a monetary task in order to assess delay discounting (Griskevicius et al., 2012; Wilson & Daly, 2004). Participants made 20 choices between two hypothetical rewards. Each of these dichotomous choices were presented in random order with the following statement: "Do you want to get $__ tomorrow OR get $__ 33 days from now?" The 'tomorrow' values were always smaller than the later values and the differences between the two values across the choices varied from $1 to $70. The total number of times a participant chose the immediate, smaller value was summed into a composite with a higher score indicating greater temporal discounting.

Finally, in order to assess problematic impulsive behavior, we asked participants to report their typical weekly alcohol consumption. Participants answered the question, "On average, how many alcoholic drinks do you have in a given week?" by typing in a whole number. All impulsivity measures can be found in Appendix A.

Immunological measures. First, systemic *in vivo* inflammatory activity was quantified via plasma levels of the classically proinflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) using commercially available

high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems; Minneapolis, MN). Samples were plated in duplicate per manufacturer instruction, with all intra- and inter-assay variance coefficients falling below 10%. After the samples were collected, but prior to quantification, the manufacturer changed the capture antibody used in the IL-1β assay, which resulted in assay failure for this particular cytokine. For this reason, analyses involving *in vivo* inflammation include only IL-6 and TNF-α. The final measure of *in vivo* inflammatory activity was total white blood cell count, which has been used in previous research as an inflammatory marker (Farhangi et al., 2013). White blood cell count was quantified using flow cytometry.

Second, the inflammatory tendencies of peripheral blood-derived mononuclear cells (PBMCs) were assessed using mitogen stimulation. PBMCs were isolated from whole blood using density gradient centrifugation in Ficoll® Paque Plus (Sigma-Aldrich, St. Louis, MO-Histopaque (GE Healthcare Life Sciences), washed several times in Hank's balanced salt solution (Caisson Labs, Logan, UT), counted, and plated into Falcon^{TM} 96-well tissue culture plates (Corning, Tewksbury, MA) in RPMI-1640 cell culture medium supplemented with 10% heat-inactivated fetal bovine serum, 2mM L-glutamine, 1mM sodium pyruvate, 100 U of penicillin/mL, 100µg of streptomycin/mL, and 0.25µg of amphotericin B/mL (Caisson Labs, Logan, UT) at a density of 2.5 x 10^5 cells/well, in a 200µL volume. PBMCs were incubated for up to 3 days at 37°C, 5% CO2, and 100% humidity. In order to measure the capacity of participants' PBMCs to respond to mitogen stimulation, PBMCs were plated in media only and with 1µg/mL of the B and T cell mitogen and gram-negative bacterial cell wall component, lipopolysaccharide (LPS), obtained from *Escherichia coli* (serotype 026:B6, Sigma-Aldrich, St. Louis, MO), in triplicates. Cell culture supernatants were collected at 2, 24, 48, and 72 hours, then stored at -80°C until assayed for levels of IL-6, IL-1β, and TNF-α.

A MILLIPLEX® MAP Human Cytokine Panel magnetic bead kit (EMD Millipore Corporation, Billerica, MA) and a Luminex MAGPIX® fluorescent detection system (ThermoFisher Scientific, Waltham, MA) were used with all intra- and inter-assay variance coefficients falling below 10%. Inflammatory tendencies were calculated as difference scores computed by subtracting levels of each cytokine in the media condition at each time point (i.e., in the absence of stimulation) from levels of that cytokine at each time point when plated with LPS point. Thus, a higher value represented a greater inflammatory tendency in response to stimulation at each time point.

Alternative explanations. In order to rule out alternative explanations for the relationship between inflammation and impulsivity, several other variables known to covary with impulsivity, inflammation, or both, were assessed. Because previous research has found that early life stress is a risk factor for trait impulsivity (Brumbach et al., 2009), I first collected an index of childhood socioeconomic status (SES), an often used proxy measure of exposure to various childhood stressors (e.g., Evans, Gonnella, Marcynyszyn, Gentile, & Salpekar, 2005). Childhood SES was measured with a research-validated scale (Griskevicius et al., 2011), consisting of three items to which participants indicated agreement or disagreement on a 7-point scale (1: *Strongly disagree,* 7: *Strongly agree*). These items were: (a) “My family usually had enough money for things when I was growing up”; (b) “I grew up in a relatively wealthy neighborhood”; (c) “I felt relatively wealthy compared to the other kids in my school.” Together, the scale yielded acceptable reliability ($\alpha = .80$) and was formed into a mean composite with a higher score indicating a higher childhood SES. Additional demographic and biobehavioral measures related to inflammatory processes were collected (O’Connor et al., 2009): age, gender, ethnicity, physical activity, sleep, and current stress levels. To measure physical activity,

participants were asked, “How would you describe your regular level of activity or exercise?”, sleep was measured by asking participants to report on the number of hours of sleep they had gotten the night before the testing session, and current stress levels were reported using the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). The PSS consisted of 10 questions about symptoms of stress experienced within the last month. Participants answered each question using a 5-point scale (0: *Never*, 4: *Very often*). Reliability for the scale was acceptable ($\alpha = .80$), and a mean composite was computed with a higher score representing a higher perception of current stress. See Appendix B for all covariate measures.

Analytic Plan

I first examined the data to determine if all assumptions for accurate estimation using structural equation modeling (SEM) were met (Kline, 2016; MPlus 7.4 statistical software; Muthén & Muthén, 2015). First, plasma levels of both IL-6 and TNF- α, as well as white blood cell count were positively skewed, these values were log-transformed, which corrected the distribution to approximate normality. All *in vitro* cytokine release scores were also positively skewed. These values were square root transformed, as log-transformations over-corrected the distributions so that they became negatively skewed. Data for all other variables approximated normal distributions. Because the *in vitro* cytokine release scores contained a hierarchical structure with four time points nested within each participant, a complex analysis able to compute standard errors and model fit statistics while accounting for non-independence was required. I applied the TYPE = COMPLEX data command which allows for specifying each individual participant as a cluster. All missing data were at random, meeting the requirement for estimation using the robust maximum likelihood (MLR) estimator that is the default when applying the TYPE = COMPLEX command. I 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). Adequate model fit was indicated by a non-significant χ^2 value ($p > .05$), a CFI value > .95, an RMSEA value < .05 with the upper bound of the confidence interval less than .10, and an SRMR statistic < .05. Modification indices were consulted for suggestions to improve model fit and applied only when theoretically grounded (Schreiber, Nora, Stage, Barlow, & King, 2006). Before I estimated the full hypothesized model (see Figure 1 for hypothesized model), I conducted a confirmatory factor analysis (CFA) to first test the validity of the proposed underlying factor structure of the model. This initial step included loading indicators on the latent factors of active inflammation (plasma IL-6, plasma TNF-α, and white blood cell count), inflammatory tendency (*in vitro* release of IL-1β, IL-6, and TNF-α), and impulsivity (BIS-11, temporal focus, DGI, and delay discounting). Upon reaching acceptable fit with the CFA, I then tested the hypothesized structural path model. The hypothesized model involved specifying inflammatory tendency as a predictor of impulsivity, mediated through active inflammation. This allowed me to test for direct effects of both inflammatory tendency and active inflammation on impulsivity, as well as an indirect effect of inflammatory tendency on impulsivity through active inflammation.

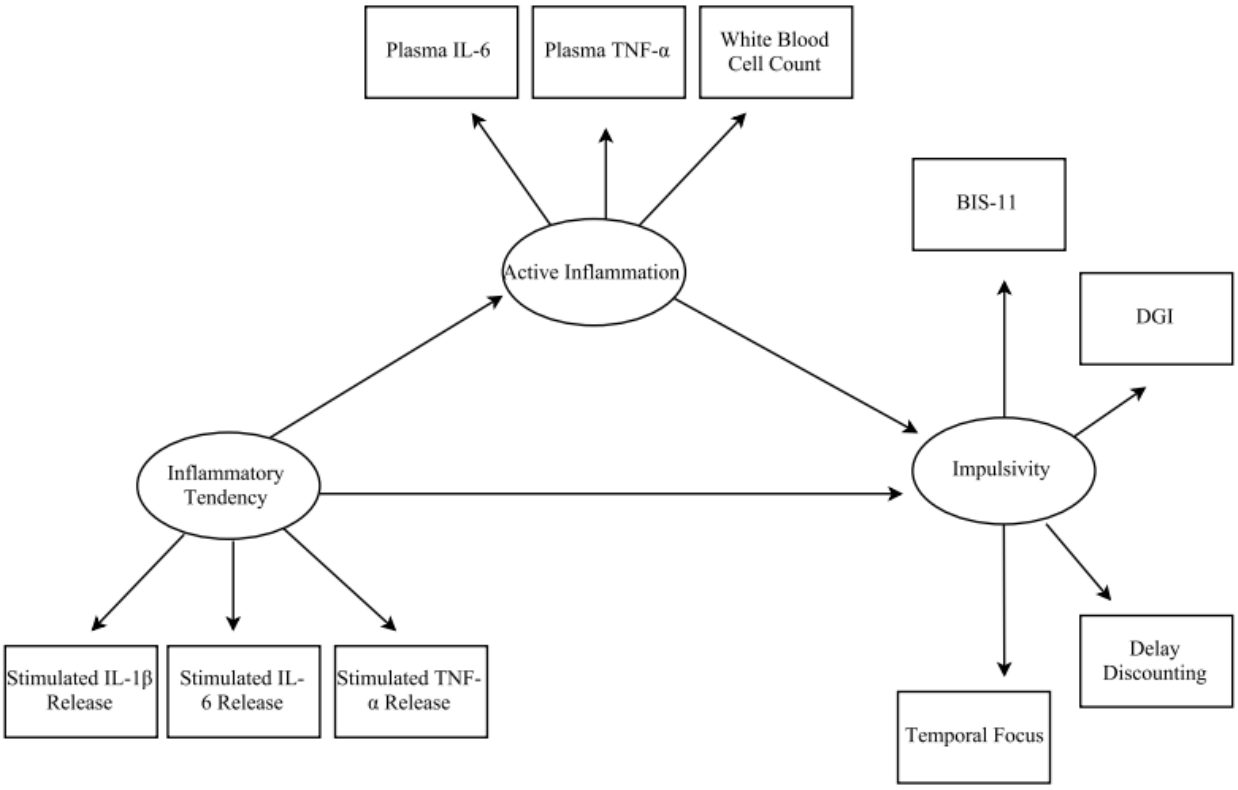

Figure 1. Hypothesized final model accounting for underlying factor structure determined by the confirmatory factor analysis.

Finally, I conducted a secondary analysis of the final model to assess if either active inflammation or inflammatory tendency predicted greater alcohol consumption by regressing reported drinking behavior on both exogenous predictors. Two additional models were tested to rule out alternative explanations: 1) the final model was tested a second time with significant covariates included to examine if the relationship between inflammation and impulsivity remained when controlling for these factors, and 2) active inflammation and inflammatory tendency were regressed on drinking behavior to statistically assess if inflammation better represented an antecedent or consequence of impulsivity.

Table 1

Descriptive Statistics for Observed Variables

Variable	*M* (*SD*)
BIS-11	2.12 (.35)
DGI	6.61 (.87)
Temporal Focus	64.17 (20.41)
Delay Discounting	6.60 (3.77)
Plasma IL-6	1.62 (1.43)
Plasma TNF-α	.96 (.31)
White Blood Cell Count	6.22 (1.85)
Stimulated IL-1β Release	1484.32 (1483.37)
Stimulated IL-6 Release	5492.94 (3763.23)
Stimulated TNF-α Release	1639.80 (1242.48)
Alcohol Consumption	3.63 (5.39)

Note. BIS-11 = Barratt Impulsiveness Scale; DGI = Delaying Gratification Inventory. All cytokine measures were transformed prior to analyses; shown here are the raw values prior to transformation in pg/mL. White blood cell count was also transformed; shown here raw as number $\times 10^9$/L. Stimulated release values shown here collapsing across the four time points: 2, 24, 48, and 72 hours. Alcohol consumption measured by reported number of alcohol drinks consumed in an average week. Alcohol consumption was square root transformed prior to analysis; shown here in its raw form.

Results

Confirmatory Factor Analysis

Descriptive statistics for the indicator variables and covariates are shown in Table 1. The results of the confirmatory factor analysis revealed that all factors loaded significantly onto their respective latent constructs (see Table 2 for factor loadings). Factor loadings were moderate to high for all indicators, with the exception of delay discounting and temporal focus (βs < .22). All model fit indices indicated adequate fit, with the exception of the SRMR value of .057 (see Table 3 for all fit statistics). No modification indices were theoretically grounded, and were thus not applied. Taking into consideration the weak factor loadings of delay discounting and temporal focus, as well as the SRMR statistic, a second CFA model was tested with these two indicators

removed. Results of the scaling corrected-χ^2 difference test revealed that the second CFA model was not a better fit to the data, $\chi^2(15) = 3.52$, $p > .05$. Therefore, I proceeded to test the hypothesized path model using the factor structure of the first CFA model.

Table 2

Estimates for Confirmatory Factor Analysis

	Standardized	Unstandardized	*SE*	*p*	R^2
Impulsivity					
BIS-11	.69	scaled	.10	<.001	.48
DGI	-.78	-2.79	.09	<.001	.61
Temporal Focus	.22	18.35	.09	.019	.05
Delay Discounting	.24	3.73	.09	.007	.06
Active Inflammation					
Plasma IL-6	.86	scaled	.15	<.001	.75
Plasma TNF-α	.38	.20	.09	<.001	.82
White Blood Cell Count	.42	.18	.13	.002	.17
Inflammatory Tendency					
Stimulated IL-1β Release	.82	scaled	.06	<.001	.67
Stimulated IL-6 Release	.75	1.80	.07	<.001	.56
Stimulated TNF-α Release	.91	.93	.05	<.001	.82

Note. Estimates listed for final CFA model. Standard errors, *p*-values, and R^2 shown for standardized estimates. BIS-11 = Barratt Impulsiveness Scale; DGI = Delaying Gratification Inventory.

Structural Path Analysis

Results of hypothesized model. Standardized parameter estimates of regression paths for the final model are shown in Figure 2. Fit statistics for the hypothesized path model revealed adequate fit (see Table 3). The direct effect of inflammatory tendency on active inflammation was significant, such that a higher tendency to release proinflammatory cytokines in response to LPS stimulation predicted greater plasma levels of inflammation (*a* path), $b = .01$, $t = 2.20$, $p =$

.03. The direct effect of active inflammation on impulsivity was also significant (*b* path), $b = .33$, $t = 2.40$, $p = .02$, with higher levels of active inflammation predicting greater impulsivity. Although the total and direct effects from inflammatory tendency to impulsivity were not significant (*c* and *c'* paths), *p*s < .60, the significant *a* and *b* paths are sufficient to declare partial statistical mediation (Hayes, 2009; 2013). Examination of R^2 revealed that 13.5% of the variance in the latent construct of impulsivity was explained by its relationships with inflammation and inflammatory tendency.

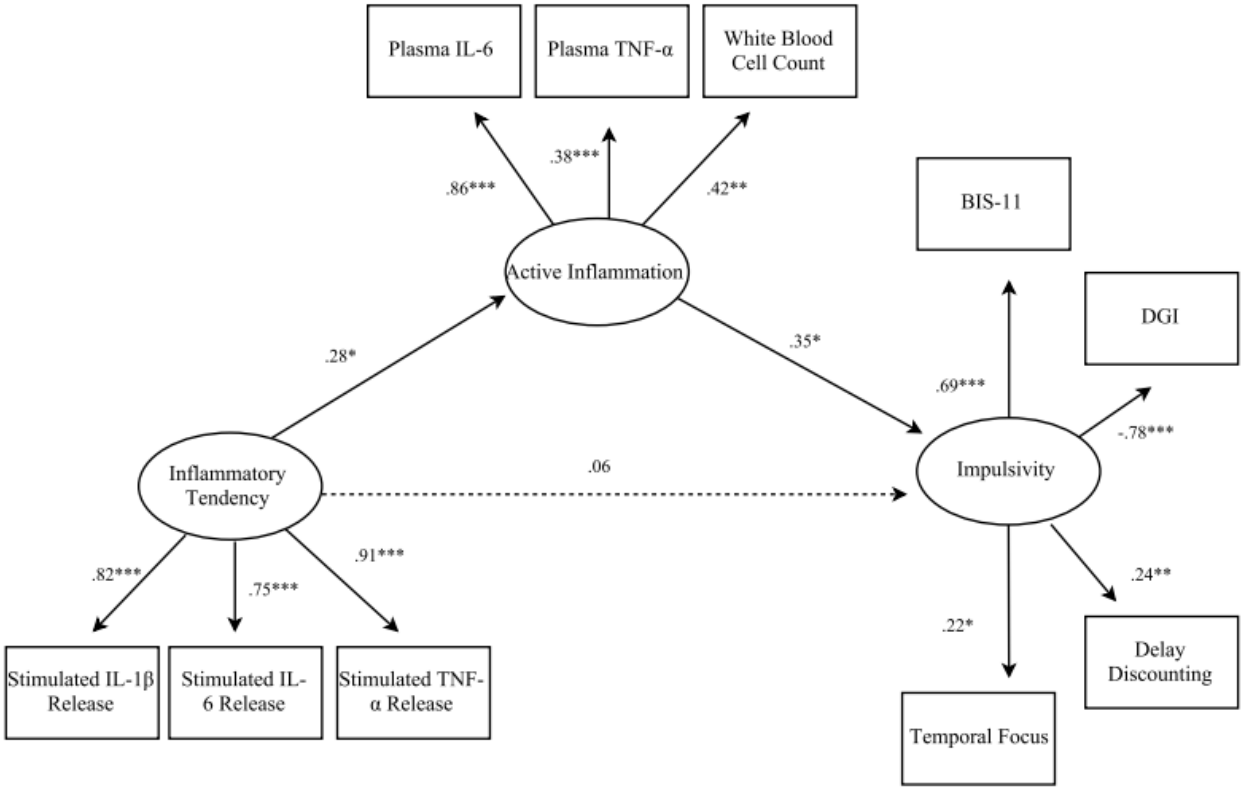

Figure 2. Final model shown with standardized estimates. Dotted lines denote non-significant paths.
***$p < .001$; **$p < .01$; *$p < .05$.

Results of exploratory model. Next, alcohol consumption was added to the model by regressing this variable on both measures of inflammation. Model fit indices were inconsistent (see 'Exploratory Model' in Table 3), so results should be interpreted with caution. No modification suggestions to improve model fit were theoretically grounded. Results revealed a significant relationship between inflammatory tendency and alcohol consumption, $b = .21$, $t = 2.05$, $p = .04$, with a higher inflammatory tendency predicting a greater number of reported alcoholic drinks consumed in an average week. The direct effect of active inflammation on alcohol consumption was not significant, and was actually negative ($p = .26$). Alcohol consumption was positively correlated with the latent construct of impulsivity ($p < .001$). Although this result does not rule out that active inflammation leads to more drinking by way of mediation through general impulsivity, the negative direct effect of active inflammation on alcohol consumption suggests that this is unlikely to be the case.

Results of alternative models. The first alternative model involved testing the final model with significant covariates of inflammation and impulsivity included. First, the three latent constructs were regressed on childhood stress, current stress, age, gender, ethnicity, physical activity, and sleep. Results revealed that weekly exercise was negatively related to impulsivity, $b = -.01$, $t = -2.32$, $p = .03$, while current stress was positively related to impulsivity, $b = .11$, $t = 3.15$, $p = .002$. No other covariates were significantly related to any latent construct (ps > .14). Next, the final model was again estimated with these significant covariates included. Model fit was acceptable (see 'Alternative Model 1' in Table 3). Importantly, the direct effect of inflammatory tendency on active inflammation remained significant, $b = .27$, $t = 2.09$, $p = .04$, as did the effect of active inflammation on impulsivity, $b = .30$, $t = 2.33$, $p = .02$. The final alternative model involved testing the causal path from impulsive behaviors that may increase

inflammatory signaling (i.e., drinking; O'Connor et al., 2009), to both latent inflammation constructs. Model fit indices revealed poor model fit (see 'Alternative Model 2' in Table). Further interpretation of the regression paths revealed that neither active inflammation, nor inflammatory tendency, were significantly predicted by alcohol consumption (*p*s >. 11).

Table 3

Summary of Model Fit Indices

Model	$\chi^2(df)$	CFI	RMSEA	SRMR
CFA Model 1 (Final)	40.38(32)	.97	.02 [.00, .04]	.057
CFA Model 2	32.07(17)	.94	.03 [.02, .06]	.051
Final Model	40.38(32)	.97	.02 [.00, .04]	.057
Exploratory Model	60.89(39)	.92	.03 [.01, .04]	.06
Alternative Model 1	57.99(50)	.97	.02 [.00, .03]	.058
Alternative Model 2	43.19(12)	.87	.07[.05, .09]	.053

Note. CFA = confirmatory factor analysis; CFI = comparative fit index; RMSEA = root mean square error of approximation; SRMR = standardized root mean square residual.
*$p < .05$

Discussion

The inflammatory response leads to events in the body that are beneficial in the context of an immediate somatic threat, but lead to health consequences when inflammation is chronically elevated. Taking into consideration previous research finding that inflammation can also direct cognition and behavior, I studied whether inflammation affects psychology in a manner that similarly facilitates focus on an immediate threat, but compromises health over time. Specifically, I tested the relationship between inflammatory activity and the psychological characteristic of impulsivity. Results indicated that higher active inflammation – as quantified by

plasma levels of IL-6, TNF-α, and white blood cell count – predicted more impulsivity. Further, greater cytokine release by PBMCs in response to LPS stimulation (i.e., inflammatory tendency), indirectly predicted more impulsivity, as partially mediated through levels of active inflammation. The relationships remained significant when controlling for factors known to covary with both inflammation and impulsivity. These results suggest that active inflammation at the time of participation is particularly influential on impulsivity across our laboratory measures, which is consistent with previous research into the impact of inflammation on psychology (Dantzer & Kelley, 2007; Donzis & Tronson, 2014; Eisenberger et al., 2017).

One pathway through which active inflammation is elevated involves a higher cellular tendency to release proinflammatory cytokines in response to a challenge (Miller & Chen, 2013). Because participant PBMCs were washed of extracellular signaling factors and any other debris that may influence reactivity, this inflammatory tendency likely represents a relatively stable trait that leads to greater overall exposure to inflammation over time (Miller et al., 2009). I hypothesized that inflammation would lead to potentially beneficial impulsive tendencies in the short-term that only result in problematic behavior when the inflammatory response is chronically active. As predicted, inflammatory tendency only – and not active inflammation – was associated with greater weekly alcohol consumption.

Because this research was cross-sectional, I was only able to statistically assess the causal direction of the relationship between inflammation and impulsivity. It could be, for example, that impulsive tendencies lead to behaviors that elicit an inflammatory response (e.g., unprotected sex, poor diet, or substance abuse). Another possibility is that there exists a bi-directional relationship between inflammation and impulsive behaviors, such that inflammation increases impulsivity, which in turn compounds inflammatory load. Although model fit indices suggested

that inflammation better represented an antecedent – rather than a consequence – of impulsivity, only experimental or longitudinal data would be able to accurately assess this causal chain. Such research is currently underway in our lab.

Future studies are needed to delineate the factors that predict higher levels of active inflammation and a proinflammatory cellular tendency. Although not replicated in my sample, previous research has found that early childhood stress can lead to a proinflammatory phenotype into adulthood (Miller et al., 2009). Genes also appear to play an important role, with certain genotypes at loci corresponding to cytokine receptor functioning even modifying biological sensitivity to environmental stress (Dinarello, 2000; Goshen & Yirmiya, 2009). Another possibility is that chronic inflammation is the result of an accumulation of stressors from multiple sources, or what is referred to as "allostatic load" (McEwen, 1998). Thus, clear relationships between inflammation and any single instigator of the inflammatory response may be elusive.

Finally, although previous research has demonstrated that general impulsivity can benefit threat detection and avoidance, additional work should examine the contexts in which inflammation-induced impulsivity is beneficial and harmful. For example, although the construct of impulsivity is related to that of risk-taking, we might find that inflammation increases only the former, but not the latter. Current research in our lab is exploring this possibility. Better understanding of the outcomes associated with impulsivity of inflammatory origins may yield low-cost interventions that can ameliorate behavioral problems notoriously resistant to current treatment strategies. For example, anti-inflammatory medications may be helpful as adjunct treatments for behavioral disorders related to impulsivity, such as substance abuse or certain mental illnesses.

Overall, the results of the present research provide evidence that inflammation regulates impulsivity, which has implications for future research in a diverse range of fields, including health and social psychology, psychoneuroimmunology, and behavioral neuroscience.

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Appendix A

Barratt Impulsiveness Scale (BIS-11)

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

1	2	3	4
Rarely/Never	Occasionally	Often	Always/Almost Always

1. I plan tasks carefully
2. I do things without thinking.
3. I make-up my mind quickly.
4. I am happy-go-lucky (reverse-scored).
5. I don't "pay attention."
6. I have "racing" thoughts.
7. I plan trips well ahead of time (reverse-scored).
8. I am self-controlled (reverse-scored).
9. I concentrate easily (reverse-scored).
10. I save regularly (reverse-scored).
11. I "squirm" at plays or lectures.
12. I am a careful thinking (reverse-scored).
13. I plan for job security (reverse-scored).
14. I say things without thinking.
15. I like to think about complex problems (reverse-scored).
16. I change jobs.
17. I act "on impulse."
18. I get easily bored when solving thought problems.
19. I am a steady thinker (reverse-scored).
20. I act on the spur of the moment.
21. I change residences.
22. I buy things on impulse.
23. I can only think about one thing at a time.
24. I change hobbies.
25. I spend or charge more than I earn.
26. I often have extraneous thoughts when thinking.
27. I am more interested in the present than the future.
28. I am restless at the theater or lectures.
29. I like puzzles (reverse-scored).

30. I am future oriented (reverse-scored).

Short-Form Delaying Gratification Inventory (DGI)

Please indicate your agreement or disagreements with the following statements using the scale provided.

1	2	3	4	5	6	7	8	9
Strongly Disagree				Neither Agree nor Disagree				Strongly Agree

1. I would have a hard time sticking with a special, healthy diet (reverse-scored).
2. I do not consider how my behavior affects other people (reverse-scored).
3. I would be willing to give up physical pleasure or comfort to reach my goals.
4. When I am faced with a physically demanding chore, I would put off doing it (reverse-scored).
5. I cannot be trusted with money (reverse-scored).
6. I try to eat healthy because it pays off in the long run.
7. I cannot motivate myself to accomplish long-term goals (reverse-scored).
8. I try to spend my money wisely
9. I try to consider how my actions will affect other people in the long-term.
10. I feel like my hard work will pay off in the end.

Delay Discounting Task

For the following task, we are interested in your snap judgments as they relate to money. You will be presented with a series of monetary choices. Please indicate your preference for which option **you** would pick.

Please answer each question as QUICKLY as possible.

1. Do you want to get **$64 tomorrow** OR get **$65 33 days from now?**
2. Do you want to get **$69 tomorrow** OR get **$71 33 days from now?**
3. Do you want to get **$86 tomorrow** OR get **$92 33 days from now?**
4. Do you want to get **$45 tomorrow** OR get **$49 33 days from now?**
5. Do you want to get **$42 tomorrow** OR get **$47 33 days from now?**
6. Do you want to get **$49 tomorrow** OR get **$57 33 days from now?**
7. Do you want to get **$72 tomorrow** OR get **$86 33 days from now?**
8. Do you want to get **$41 tomorrow** OR get **$51 33 days from now?**
9. Do you want to get **$58 tomorrow** OR get **$76 33 days from now?**
10. Do you want to get **$37 tomorrow** OR get **$54 33 days from now?**
11. Do you want to get **$53 tomorrow** OR get **$87 33 days from now?**?
12. Do you want to get **$56 tomorrow** OR get **$99 33 days from now?**
13. Do you want to get **$35 tomorrow** OR get **$67 33 days from now?**
14. Do you want to get **$39 tomorrow** OR get **$81 33 days from now?**
15. Do you want to get **$28 tomorrow** OR get **$62 33 days from now?**
16. Do you want to get **$31 tomorrow** OR get **$78 33 days from now?**
17. Do you want to get **$35 tomorrow** OR get **$98 33 days from now?**
18. Do you want to get **$16 tomorrow** OR get **$55 33 days from now?**

19. Do you want to get **$24 tomorrow** OR get **$94 33 days from now?**
20. Do you want to get **$9 tomorrow** OR get **$60 33 days from now?**

Time Perception Task

For the next set of questions, we are interested in your perceptions. Please provide your perceptions by using the slider scales and labels provided. When you are ready to begin, please click the next arrow.

1----------100

Very Short Very Long

1. How long from now does 1 day feel?
2. How long from now does 1 month feel?
3. How long from now does 3 months feel?
4. How long from now does 6 months feel?

Alcohol Consumption

For the following question, please enter a whole number.

"On average, how many alcoholic drinks do you have in a given week?"

Appendix B

Childhood Socioeconomic Status (SES)

Please rate your agreement or disagreement with how each statement applies to and your family during **your early childhood (ages 0-12).**

1	2	3	4	5	6	7
Strongly Disagree			Neither Agree nor Disagree			Strongly Agree

1. I grew up in a relatively wealthy neighborhood.
2. My family usually had enough money for things when I was growing up.
3. I felt relatively wealthy compared to the other kids in my school.

Age

What is your current age (whole number)?

Physical Activity

How would you describe your regular level of activity or exercise?

1	2	3	4	5	6	7
Light			Moderate			Strenuous

Sleep

How many hours of sleep did you get last night (whole number)?

Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983)

The questions in this scale ask you about your feelings and thoughts during **the last month.** Please answer how often the following cases have applied to you over the course of **the last month.**

0	1	2	3	4
Never	Almost Never	Sometimes	Fairly Often	Very Often

1. How often have you been upset because of something that happened unexpectedly?
2. How often have you felt that you were unable to control the important things in your life?
3. How often have you felt nervous and stressed?
4. How often have you felt confident about your ability to handle your personal problems?
5. How often have you felt that things were going your way?
6. How often have you found that you could not cope with all of the things that you had to do?
7. How often have you been able to control irritations (e.g. irritating things or people) in your life?
8. How often have you felt that you were on top of things?
9. How often have you felt that difficulties were piling up so high that you could not overcome them?
10. How often have you felt that things were going your way?

VITA

Jeffrey William Gassen was born May 4, 1989, in Bakersfield, California. He is the third child and only son of Nancy and Kelly Gassen. In 2012, he received a Bachelor of Arts degree from the University of Nebraska at Omaha, where he studied psychology. In 2015, he began graduate study at Texas Christian University, where he is currently pursuing a Doctor of Philosophy degree in Experimental Psychology under the mentorship of Dr. Sarah E. Hill.

VITA

Personal Background	Jeffrey William Gassen Born May 4, 1989 in Bakersfield, California Daughter of Kelly and Nancy Gassen
Education	GED, Northeast Community College, Norfolk, Nebraska, 2007 Bachelor of Arts, Psychology, University of Nebraska-Omaha, Omaha, Nebraska, 2012
Experience	Teaching Assistant, Department of Psychology, Texas Christian University, Fort Worth, Texas, 2015-Present
Professional Memberships	Society for Personality and Social Psychology Human Behavior and Evolution Society International Society for Evolution, Medicine, and Public Health Southwestern Psychological Association Psi Chi National Honor Society in Psychology Society for Neuroscience

ABSTRACT

INFLAMMATION PROMOTES INVESTMENT IN PRESENT VERSUS DELAYED OUTCOMES

by Jeffrey Gassen

Thesis Advisor: Sarah E. Hill, Associate Professor of Psychology

The inflammatory response involves a coordinated set of molecular and cellular events that promote defense against and recovery from current somatic threats. While a controlled inflammatory response is critical to survival, chronic, unresolved inflammation is associated with numerous long-term health problems. Growing evidence suggests that the effects of inflammation on human psychology follow a similar pattern. Here, I build on these insights by examining if inflammatory activity predicts impulsivity, a psychological characteristic that may complement tissue level defense and recovery efforts, but that contributes to problematic behavior over time. I found that higher levels of active inflammation predicted greater impulsivity. Further, results revealed an indirect effect of cellular inflammatory tendency (i.e., cytokine release in response to mitogen stimulation) on impulsivity, partially mediated through levels of active inflammation. In sum, inflammation appears to regulate impulsive tendencies, which may be adaptive in the context of somatic defense and recovery.