INFLAMMATION, EARLY LIFE STRESS, AND COOPERATION: FROM INDIVIDUALS TO SOCIETIES

by

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Inflammation, Early Life Stress, and Cooperation: From Individuals to Societies

Despite large-scale cooperation being a defining characteristic of human societies, research finds that certain individuals and groups are consistently more willing to cooperate for the public good than are others (O'Gorman, Heinrich, & Van Vugt, 2008; Sasaki, Okada, & Unemi, 2007). Research into the factors that encourage or curtail cooperative behavior is critically important, as facilitating cooperation is key to solving many of the major problems that humanity faces today. For example, coordinating both local and international cooperation is essential to mitigating the environmental, economic, and health consequences of climate change (Barrett, 2014; Bestill, 2001; Karl & Trenberth, 2003).

Why do some people cooperate more than others? Research in the field of experimental economics has provided useful insights into the factors that impact cooperation. For example, studies find that those with a more present focus tend to cooperate less in laboratory games than those who are more future-focused (Balliet, Parks, & Joireman, 2009; Yi et al., 2007). Others find that cultural norms – such as a culture's emphasis on civic duty – also regulate the extent to which those in a given population cooperate with each other (Gächter, Herrmann, & Thöni, 2010). More recently, research into the neurobiology underlying cooperation has revealed that individual differences in levels of certain hormones (e.g, testosterone; Reimers & Diekhof, 2015; Ryder et al., 2020; Van Honk et al., 2012) and neural sensitivity to social rewards (Fett et al., 2012; Izuma et al., 2008; Rilling et al., 2002) also influence cooperative behavior.

Here, I build on this previous work by combining insights from the evolutionary sciences, experimental economics, and psychoneuroimmunology to examine the role that the immune system plays in regulating cooperation. When combined, this research predicts that bodily inflammatory activity – which represents an internal context associated with physiological and

behavioral shifts that prioritize investment in immediate rather than distal rewards (Dantzer, 2001; Dantzer & Kelley, 2007; Gassen et al., 2019a,b; Kelley et al., 2003) – would predict relatively lower levels of cooperation relative to what is observed in its absence. These patterns are favored in the context of heightened inflammation because (a) an individual has a reduced probability of survival and is thus less likely to realize future rewards from building social capital (see e.g., Gassen et al., 2019a,b; Gassen & Hill, 2019) and (b) one has an increased need for immediate energetic resources due to the immunometabolic shifts that occur during an inflammatory response (Lacourt et al., 2018; O'Neill, Kishton, & Rathmell, 2016; Treadway et al., 2019). Moreover, this research predicts that these patterns should be moderated in important ways by one's early life environments. In particular, it predicts that developmental exposure to stress during childhood – which is found to increase one's sensitivity to the psychological and behavioral sequelae of inflammation later in life (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012) – will be associated with an increased tendency to act less cooperatively in the context of high inflammation relative to what is observed among those who developed in less stressful environments.

I tested these hypotheses in a series of three studies that examined relationships between inflammatory activity and cooperation at multiple levels of social organization: the level of the individual, the level of the group, and the level of the population. In the first two studies, I tested whether higher levels of inflammation were associated with lower levels of cooperative behavior in economic games at the level of the individual (Studies 1-2) and the level of the group (Study 2). Additionally, I tested whether the relationship between inflammation and cooperation were moderated by exposure to early life stress (i.e., low childhood socioeconomic status [SES]). I predicted that higher levels of inflammation would predict reduced cooperation, particularly for

individuals who grew up in stressful childhood environments (i.e., relative to those from less stressful environments). In Study 3, I examined whether these patterns manifest themselves at the international level. In particular, I examined whether countries with a higher infectious disease prevalence – which is an ecological context that promotes heightened inflammatory activity (Ferrucci & Fabbri, 2018; Gattone et al., 2001; Nazmi et al., 2010; Thompson et al., 2014) – would invest less in public goods. Further, consistent with the predicted results for Studies 1-2, I predicted that the tendency to decrease investment in public goods in the context of high infectious disease prevalence would be greater for poorer countries than wealthier countries.

The Evolution of Cooperation

Cooperation is defined as any behavior that involves one individual or group providing a benefit to another (Melis & Semmann, 2010; West, Griffin, & Gardner, 2007). Cooperative systems are ubiquitous in nature, occurring in various forms both within and between numerous species of plants and animals (Cheney, 2011; Clutton-Brock, 2009; Dudley, 2015; Kiers et al., 2011), as well as bacteria (Xavier & Foster, 2007), viruses (Turner & Chao, 1999), and amoebae (Jiang, Levine, & Glazier, 1998). Cooperation even takes place at lower levels of biological organization. For example, cells cooperate within a single multicellular organism and genes cooperate within a single genome (Nowak, 2006).

For some time, cooperation presented a puzzle for the gene-centric view of evolution, as it was believed that selection should exclusively favor selfish strategies that increase one's own genetic representation in the next generation at the expense of competitors' (Darwin, 1871; Dugatkin, 1997). However, decades of theory and research have since situated cooperation within the gene-centric view, demonstrating that genes, cells, and individuals can often increase their own fitness by providing fitness benefits to others (Axelrod & Hamilton, 1981; Boyd &

Richerson, 2009; Nowak, 2006; Riolo, Cohen, & Axelrod, 2001). For example, one condition that favors the evolution of cooperation is relatedness, an effect that is articulated in the logic of kin selection theory (Foster, Wenseelers, & Ratnieks, 2006; Grafen, 1984; Hamilton, 1964; Nowak, 2006; Smith, 1964). Kin selection theory predicts that individuals will tend to invest benefits in genetic relatives (i.e., inclusive fitness) when the costs of that altruistic act to the actor (c) are less than the benefits provided to the recipient (b) multiplied by the genetic relatedness (r) between the two parties (i.e., $r \times b > c$). This same basic equation can also be applied to understanding the evolution of cooperation between non-kin (Clutton-Brock, 2009; Santos, Pacheco, & Santos, 2016; Taborsky, Frommen, & Riehl, 2016). Cooperation between non-relatives is similarly favored when the reciprocal benefits that an actor can expect from cooperating – either in the form of resources or reputation – outweigh the costs (i.e., $b > c$). These mathematical insights, simplified here for brevity, have been instrumental to the understanding of how cooperation evolves (Axelrod & Hamilton, 1981; Boyd & Richerson, 2009; Clutton-Brock, 2009; Nowak, 2006; Riolo et al., 2001).

Heterogeneity in Human Cooperation

Although cooperation is not a uniquely human phenomenon, humans do surpass most other species in the scale and complexity of our cooperative structures, particularly among non-kin. For example, human societies are characterized by division of labor, trade, and a redistribution of group resources toward solving collective problems (Boyd & Richerson, 2009; Melis & Semmann, 2010; Rand & Nowak, 2013). Despite cooperation being a common thread in human social systems, people do differ in the extent to which they cooperate with others. This is evidenced both by the myriad violent conflicts that have occurred across human history (e.g., Clauset, 2018; Schleussner et al., 2016; Stewart et al., 2002), as well as decades of empirical

research demonstrating that some individuals consistently choose to cooperate for the public good, while others consistently behave more selfishly (Andreoni, 1988; Fehr & Gächter, 2000; O'Gorman et al., 2008; Sasaki et al., 2007).

Research in experimental economics often involves using cooperative games to examine the factors that influence cooperation (for a review see Kagel & Roth, 2016). For example, in the commonly used public goods game (Fehr & Gächter, 2000; Fischbacher, Gächter, & Fehr, 2001; Ledyard, 1994), participants are endowed with a sum of money that they can either bank into a private account or contribute to a group account. If the money is invested in the private account, participants keep the entire sum. If the money is invested in the group account, however, participants receive only a marginal return on their investment. Research finds that individual strategies in public goods games differ considerably: some individuals categorically cooperate, others always keep the entire sum in their personal account (free-ride), and still others adopt a mixed strategy, cooperating on some trials and free-riding on others (Fehr & Gächter, 2000; Fischbacher et al., 2001; Ledyard, 1994; O'Gorman et al., 2008).

What factors influence whether or not individuals cooperate in cooperative games? Some studies have shown that the composition of a group plays a role in determining the extent to which members of that group cooperate (Bonacich, Shure, Kahan, & Meeker, 1976; Capraro & Barcelo, 2015; Isaac & Walker, 1988). For example, one study found that small (i.e., N = 3-10) and large (i.e., N = 30-100) groups tend to cooperate less than intermediate-sized groups (i.e., N = 15-30) (Capraro & Barcelo, 2015). In addition to group composition, others find that intergroup competition also impacts cooperative behavior. Specifically, competition between groups facilitates greater cooperation within groups (Cárdenas & Mantilla, 2015). Finally, culture also appears to play a role in group cooperation, with groups from cultures with strong

(compared to weak) attitudes toward civic duty behaving more unselfishly and contributing more to public accounts (Gächter, Herrmann, & Thöni, 2010; Heinrich et al., 2001; Oosterbeek, Sloof, & Van De Kuilen, 2004).

In addition to these group-level factors, individual differences in personality traits also affect cooperative behavior. For example, one study found that individuals high in agreeableness (compared to those scoring low on this personality dimension) were more likely to cooperate in one-shot public goods games and endorse prosocial values (Schroeder, Nettle, & McElreath, 2015; Volk, Thöni, & Ruigrok, 2011). Others find that those with higher trait levels of honesty-humility contribute a greater amount of money to the group account in public goods games compared to those with lower levels (Hilbig, Zettler, & Heydasch, 2012). Additionally, individuals' general tendency to discount the future also appears to influence cooperation. Specifically, those who are more present-focused tend to cooperate less than those with a more future focus (Harris & Madden, 2002; Stevens & Hauser, 2004).

More recently, researchers have also identified several key brain regions that are involved in coordinating cooperative behavior. For example, functional magnetic resonance imaging (fMRI) studies find that activity in prefrontal cortical regions (i.e., dorsolateral prefrontal cortex; orbitofrontal cortex; Bacloni et al., 2018; Decety et al., 2004; Rilling et al., 2002; Willis et al., 2018), as well as in the parietal cortex and anterior insula (Decety et al., 2004), increases while individuals are engaged in cooperative games. This suggests that both neural networks involved in executive functioning (Nowrangi et al., 2014), and those involved in attention and arousal (Brooks et al., 2012; Posner, 1993), play a role in regulating cooperation. Separate research finds that higher reported enjoyment of charitable giving is linked to increased activity in the ventral

striatum (Speans et al., 2019), a brain region crucial in processing both social and non-social rewards (Bhanji & Delgado, 2014; Delgado, 2007; Izuma et al., 2008).

In addition to these insights into the neural architecture of cooperative behavior, research have also begun to uncover how different bodily messenger systems – such as the endocrine system and networks of neuropeptides – impact cooperation (e.g., Bacloni et al., 2018; Decety et al., 2004; Reimers & Diekhof, 2015; Ryder et al., 2020; Van Honk et al., 2012). For example, studies find that individuals with higher levels of testosterone (compared to lower levels) are more cooperative in certain contexts, and less cooperative in others (Reimers & Diekhof, 2015; Ryder et al., 2020; Van Honk et al., 2012). Specifically, individuals with higher testosterone levels tend to be more generous toward in-group members (Reimers & Diekhof, 2015), but more hostile toward out-group members (Reimers & Diekhof, 2015) than those with lower testosterone levels. Others have found that exogenous administration of oxytocin – a neuropeptide that regulates social bonding (Carter et al., 1992; De Dreu et al., 2011; Kosfeld et al., 2005) – promotes parochial altruism, or the tendency to favor cooperation with in-group members (De Dreu et al., 2012). Still others have reported that higher levels of the stress hormone cortisol predict a reduced tendency to punish defectors in cooperative games, suggesting that the hypothalamic-pituitary-adrenal axis plays a role in coordinating cooperation (Pfattheicher & Keller, 2014). Together, this research indicates that individual differences in neurobiology underlie individual differences in the tendency to cooperate.

For a long time, many researchers assumed that hormones and neurotransmitters were the primary signaling molecules involved in regulating behavior. However, more recently, research has shown that immune signaling proteins – such as cytokines – also play an important role in this context (e.g., Chen et al., 2017; Danzter, 2001; Gassen & Hill, 2019; Jewett & Krueger,

2012; Miller et al., 2009). For example, research finds that, even outside the context of acute illness, cytokines are involved in coordinating the activities of the nervous system, which has implications for sensory function (Chen et al., 2017; Miller et al., 2009, sleep (Jewett & Krueger, 2012), learning (Gonzalez et al. 2009), the stress response (Goshen & Yirmiya, 2009), and even social behavior (Hennessey et al., 2014; Gassen & Hill, 2019; Lisboa et al., 2018; Moon et al., 2015). I turn to this research now.

Inflammation, Immunometabolism, and Effort

The immune system is the primary mechanism through which the body monitors its internal condition and protects itself from illness and injury (Blalock, 1984; Janeway, Travers, Walport, & Shlomchik, 2005; Matzinger, 2012). When the cells of the immune system detect infectious agents or cellular damage, they secrete an array of small signaling proteins called cytokines. Cytokines, in turn, play an important role in directing the host's immune response. For example, a subset of these proteins – proinflammatory cytokines – initiate inflammatory cascades, help clear infection and damaged cells, and promote tissue repair (Janeway et al., 2005; Medzhitov, 2008; Thomson & Lotze, 2003).

In addition to coordinating the activities of the immune system, proinflammatory cytokines also influence neurotransmission and behavior (Banks, 2005; Benveniste, 1992; Hopkins & Rothwell, 1995). Cytokines access the brain directly by passively crossing the blood-brain barrier via circumventricular organs and actively via saturable transport systems (Banks, 2005; Banks & Broadwell, 1995). Within the brain, cytokine receptors are expressed in neurons and glial cells in a variety of brain regions including, but not limited to, the hippocampus (Friedman, 2001), the pituitary gland (Arzt et al., 1999), and several cortical structures (Lee, Nagai, & Kim, 2002; Utsuyama & Hirokawa, 2002; Zalcman et al., 2012). Cytokines also

indirectly influence central nervous system activity via activation of peripheral nerves (e.g., vagal afferents) that modify neurotransmission and trigger *de novo* cytokine synthesis by resident microglia (Banks, 2005; Beneveniste, 1992; Rothwell & Hopkins, 1995).

Over two decades of research demonstrate that proinflammatory cytokines have profound effects on behavior (e.g., Chen et al., 2017; Danzter, 2001; Fang et al., 1998; Gassen & Hill, 2019; Jewett & Krueger, 2012; Miller et al., 2009). For example, research in both human and non-human animals finds that in the context of acute illness, proinflammatory cytokines induce a constellation of psychological and behavioral symptoms – such as fatigue, anhedonia, reduced foraging, and diminished mating motivation – collectively referred to as "sickness behavior" (Aubert, Vega, Dantzer, & Goodall, 1995; Dantzer, 2001; Dantzer & Kelley, 2007). Sickness behavior was first believed to be a maladaptive byproduct of infection, but it is now understood to represent an adaptive strategy by the host organism to prioritize behaviors that protect the body from damage and conserve energy for immunological defenses and recovery (Dantzer, 2001; Dantzer & Kelley, 2007; Medzhitov, Schneider, & Soares, 2012).

Conserving immediately available energetic resource is paramount in the event of an inflammatory response because inflammation induces immunometabolic shifts that both (a) increase energy expenditure (Muehlenbein et al., 2010) and (b) reduce cellular energy availability (Lacourt et al., 2018; O'Neill, Kishton, & Rathmell, 2016; Treadway et al., 2019). Specifically, research finds that during infection or experimental exposure to immune-stimulating agents (e.g., vaccine) – contexts where inflammation is elevated – individuals' resting metabolic rates increase by an average of 8% (Muehlenbein et al., 2010). Moreover, when activated by the detection of infection or cellular damage, participating proinflammatory immune cells switch on metabolic pathways that allow for quick utilization of energetic

resources and that produce metabolic intermediates necessary for cellular proliferation and key effector functions (O'Neill et al., 2016). Specifically, research into the metabolic profiles of immune cells involved in the inflammatory response has revealed that activated macrophages, dendritic cells, and certain T cell subsets rely heavily on glycolysis for energy production (e.g., Gubser et al., 2013; Krawczyk et al., 2010; Michalek et al., 2011; O'Neill et al., 2016). Although less efficient than other glucose-dependent metabolic pathways (e.g., oxidative phosphorylation), glycolysis is an especially fast way to generate adenosine triphosphate (ATP; major source of cellular energy) and produce pro-growth biosynthetic intermediates, such as ribose, amino acids, and fatty acids (e.g., pyruvate) needed to make new cells (Metallo et al., 2013; O'Neill et al., 2016; Wang et al., 2019). However, because glycolysis inefficiently produces energy, cells utilizing this metabolic pathway – such as immune cells during an inflammatory response – monopolize available glucose, constraining the resources available for other bodily functions (e.g., growth, reproduction, etc.; Wang et al., 2019).

Recent theory and research suggest that inflammation and its associated immunometabolic shifts influence a number of psychological and behavioral processes beyond just the hallmark symptoms of sickness behavior (Draper, 2018; Gassen et al., 2019a,b; Gassen & Hill, 2019; Lasselin et al., 2017). For example, previous research finds that elevated inflammatory activity reduces individuals' willingness to expend effort in pursuit of rewards, presumably due to the energy constraints inherent in this context (Draper, 2018; Lacourt et al., 2018; Treadway et al., 2019). Specifically, one study found that participants administered lipopolysaccharide (LPS; a bacterial cell wall component) – which elicits an inflammatory response – were less willing to work for high-effort rewards than the control group administered saline (Draper et al., 2018). In addition to inflammation's effects on effort, others find that low-

grade inflammation (i.e., clinically normal and outside the context of acute illness) promotes impulsivity and a preference for smaller, immediate over larger, delayed rewards (Gassen et al., 2019a,b). This is hypothesized to occur because, when inflammation is elevated, the probability of survival is relatively lower and an individual is thus less likely to realize delayed rewards (Gassen & Hill, 2019). Additionally, given that self-regulation requires effort (Baumeister & Vohs, 2018; Evans, Boggero, & Segerstrom, 2016), one's ability to delay gratification is expected to decline in the context of inflammation as energetic resources are depleted (Metallo et al., 2013; Muehlenbein et al., 2010; O'Neill et al., 2016; Wang et al., 2019).

Although the relationship between inflammation and behavior has been found in a wide variety of animals (e.g., bees: Kazlauskas et al., 2016; lobsters: Behringer et al., 2006; primates: Ghai et al., 2015) and in humans across a range of demographic, social, and health backgrounds (Dantzer, 2001; Draper, 2018; Gassen et al., 2019a,b; Gassen & Hill, 2019; Lacourt et al., 2018; Lasselin et al., 2017), a growing body of research finds that some individuals are more sensitive to inflammation than others (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012). In particular, this research suggests that exposure to early life stress may sensitize individuals to exhibit exaggerated behavioral responses to the release of proinflammatory cytokines. For example, in one study, researchers found that adults reporting higher levels of childhood stress exposure experienced more negative cognitive and mood-related effects in response to experimentally elevated inflammatory activity (i.e., in response to an influenza vaccine) than did those from less stressful environments (Kuhlman et al., 2019). Others who have examined this issue longitudinally have found that the relationship between inflammation and depression is stronger for those who experienced high levels of early life stress that it is for those who have not (Danese, 2008; Miller & Cole, 2012).

Although the precise mechanism through which early life stress sensitizes the central nervous system to shifts in peripheral levels of inflammation has yet to be determined, one possibility is that those exposed to early life stress may exhibit greater transduction of peripheral inflammation into neuroinflammation (Banks, 2005; Banks & Broadwell, 1995). According to this perspective, even though adults from a wide range of childhood environments may exhibit comparable levels of peripheral inflammatory activity, those from stressful childhood environments may express a greater amount of this peripheral inflammatory activity in their brains than what is expressed by those from less stressful environments. This explanation is consistent with animal research finding that exposure to early life stress both increases the permeability of the blood-brain barrier (Gómez-González & Escobar, 2009; Menard et al., 2017) – which may allow for more transport of cytokines into the brain – and increases the density and activity of microglial cells in the brain (Bilbo & Schwarz, 2012; Calcia et al., 2016; Delpech et al., 2016), cells that manufacture and release cytokines in the central nervous system.

A Role for the Immune System in Regulating Cooperation

Research on cooperation predicts that this behavior should increase when the future benefits of cooperating outweigh the current costs and decrease when the opposite conditions are true (Clutton-Brock, 2009; Santos, Pacheco, & Santos, 2016; Taborsky, Frommen, & Riehl, 2016). Given that inflammation reflects an internal, physiological state during which (a) one's probability of surviving to received delayed rewards is diminished (Gassen et al., 2019a,b; Gassen & Hill, 2019) and (b) one's immediate resource needs are elevated (Muehlenbein et al., 2010; Lacourt et al., 2018; O'Neill et al., 2016; Treadway et al., 2019), I predicted that higher inflammatory activity would be associated with reduced investment in cooperative behavior (see Figure 1 for theoretical model).

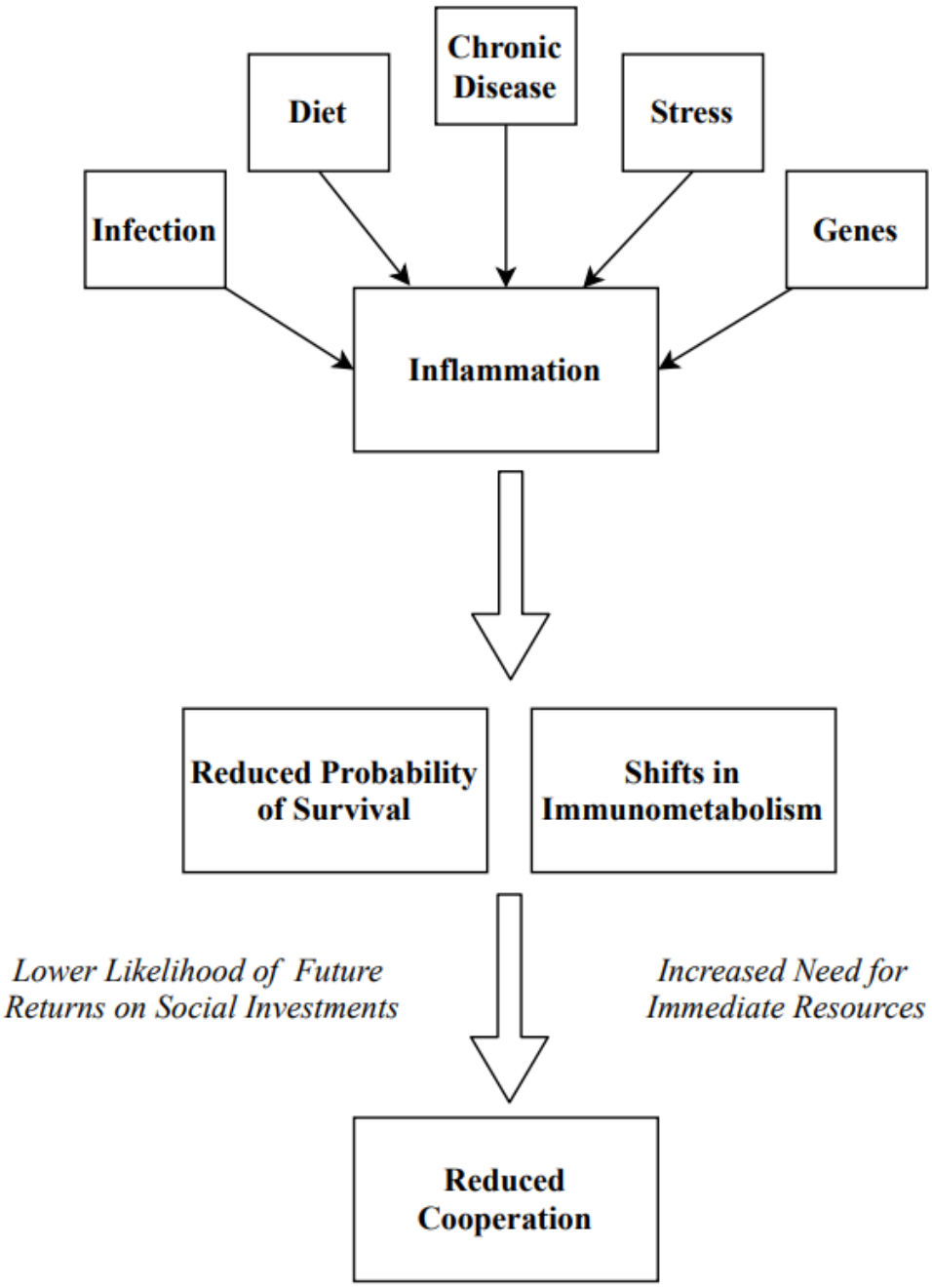

Figure 1. Theoretical model depicting the hypothesized relationship between bodily condition, inflammation, and cooperation. Elevated inflammation indicates a reduced probability of survival to realize delayed social rewards and induces metabolic shifts that increase one's need for immediate resources, which together diminish the returns one can expected on investment in cooperation.

The idea that inflammation may predict reduced cooperation – although it has not yet been tested directly – is supported by extant empirical work. For example, research finds that sickness behavior is often accompanied by marked changes in social motivation (Dantzer, 2001; Dantzer & Kelley, 2007; Medzhitov et al., 2012) in species ranging from rodents (Bluthé et al., 1994), birds (Owen-Ashley & Wingfield, 2006), and insects (Kazlauskas et al., 2016), to species like humans (Perkins et al., 2016) and non-human primates (Ghai et al., 2015). Such research suggests that investment in social relationships – which is a core feature of cooperative behavior (Clutton-Brock, 2009; Santos, Pacheco, & Santos, 2016; Taborsky, Frommen, & Riehl, 2016) – is deprioritized in the context of inflammation.

Additional support for the proposed hypothesis comes from research examining the impact of inflammation on psychological constructs related to cooperation, such as present focus (Harris & Madden, 2002; Stevens & Hauser, 2004) and impulsivity (Crockett et al., 2010). Separate studies have found that higher levels of inflammation – even among young and otherwise healthy participants – are associated with more present-focused decision-making (Gassen et al., 2019a,b). These disparate lines of research together provide evidence of a link between inflammation and psychological factors known to influence cooperative behavior.

Lastly, support for the proposed hypothesis is found in research on the neuroscience of cooperative behavior. Studies using fMRI to explore associations between cooperation and brain activity (e.g., Decety et al., 2004; Emonds et al., 2012; Fett et al., 2012; Rilling et al., 2002) find that cooperation and trust in economic games are associated with increased activation of brain regions involved in reward processing, such as the ventral striatum and orbitofrontal cortex (Fett et al., 2012; Rilling et al., 2002), as well as regions involved in arousal, such as the anterior insula (Decety et al, 2004). Notably, separate research examining the impact of inflammation on

the brain finds that that proinflammatory cytokines alter neural activity in these same regions relevant to cooperative behavior. For example, one study found that experimentally increasing inflammation in humans led to reduced ventral striatum activity (associated with reward processing) in response to rewards (Eisenberger et al., 2010). Another study employing a similar paradigm found that increased inflammation was associated with reduced functional coupling between the insular cortex and other brain regions (Labrenz et al., 2016).

The Current Research

Although this previous research provides preliminary support for the hypothesis that inflammation negatively impacts cooperation, this possibility has yet to be tested directly. In the current research, I tested my hypotheses across three studies by examining relationships between inflammation and cooperation at multiple levels of social organization using a diverse range of methods. In the first study (Study 1), I tested whether individuals' plasma levels of three key proinflammatory cytokines (interleukin-1beta [IL-β], interleukin-6 [IL-6], and tumor necrosis factor-alpha [TNF-α]) predicted cooperation in two gold standard cooperative games: the public goods game (PGG) and the ultimatum game (UG). In Study 2, participants completed the same PGG in groups and levels of the same three cytokines were measured in participants' saliva. I examined whether salivary levels of inflammation predicted cooperation both at the level of individuals (i.e., as in Study 1), as well as at the group level (i.e., do groups with more collective inflammation cooperate less than those with less inflammation). In each of these first two studies, I tested whether relationships between proinflammatory cytokines and cooperative behavior were moderated by exposure to early life stress, a factor previously shown to increase individuals' sensitivity to the psychological and behavioral effects of inflammation (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012). I predicted that at both the individual level

(Studies 1-2) and the group level (Study 2) higher levels of inflammation would predict less cooperation, particularly for those exposed to higher levels of early life stress (i.e., compared to those with less early life stress).

In Study 3, I accessed public, cross-national data to examine relationships between an environmental factor that promotes inflammatory activity (i.e., high vs. low infectious disease prevalence; Ferrucci & Fabbri, 2018; Gattone et al., 2001; Nazmi et al., 2010; Thompson et al., 2014) and nations' investment in two public goods: social welfare and environmental protection. I predicted that countries with higher levels of both historical and contemporary infectious disease prevalence would invest less in social and environmental causes than countries with lower disease prevalence. Further, consistent with my predictions for Studies 1-2, I predicted that these relationships would be moderated by national wealth, with the negative impact of high infectious disease prevalence on public goods investment being greater for poorer countries than for wealthier countries. Study 3 also tested the hypothesis that reduced cooperation in the context of high infectious disease burden would be related to greater sociopolitical instability, a distal outcome related to cooperation (Ftehi-Sedeh & Safizadeh, 1989; Szent-Ivanyi, 2007).

Study 1: Inflammation and Individual-Level Cooperation in Economic Games

Study 1 was designed to test the prediction that heightened inflammation would be associated with reduced investment in cooperation using two standard cooperative games: the PGG (Fehr & Gächter, 2000; Fischbacher, Gächter, & Fehr, 2001; Ledyard, 1994) and the UG (Andreoni, 1988; Fehr & Gächter, 2000; O'Gorman et al., 2008; Sasaki et al., 2007). Additionally, in light of recent research finding that early life stress sensitizes individuals to the psychological and behavioral shifts that accompany elevated inflammation (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012), the current study also sought to examine whether

exposure to stress during childhood moderated the relationship between inflammation and cooperation. Childhood SES was selected as a proxy of early life stress because it was one of the strongest predictors of a child's exposure to stressful events, such as financial and food insecurity, neglect, and abuse (e.g., Miller & Chen, 2007; Moffitt et al., 1992; Taylor et al., 2006). I predicted that individuals with higher levels of inflammation would cooperate less in economic games. Further, I predicted that this effect would be greater for individuals reporting a lower childhood SES compared to those reporting a higher childhood SES.

Method

Participants. Participants were 130 healthy college students (86 women; M_{age} = 19.68, SD_{age} = 3.70) recruited from Texas Christian University's research participant pool. Full characteristics of the sample are displayed in Table 1. All participants 1) were without a history of chronic physical or psychological disorders, 2) were free from acute illness for at least two weeks prior to participation, and 3) abstained from steroidal and non-steroidal anti-inflammatory medications, exercise, and alcohol for at least two days prior to the session. Participants were awarded partial course credit in exchange for participation. Additionally, participants had the opportunity to win up to $5.00 across the economic games.

This sample size was determined by conducting an a priori power analysis using G*Power software (version 3.1.9). Based on the smallest effect size (R^2 = .10) found for the relationship between inflammation and an outcome related to cooperation in previous research, present focus (Gassen et al., 2019a), I determined that I would require a total sample size of 120 participants in order to achieve .80 power. This target sample size was increased to 130 to account for potential data loss due to issues with blood collection (e.g., participant having veins that are difficult to find) or sample assaying.

Table 1

Characteristics of the Sample for Study 1 (N = 130)

Variable	***M* (*SD*)**
Age	19.68 (3.70)
Body Mass Index	23.49 (4.55)
Exercise (hrs/week)	5.66 (4.28)
Sleep (hrs/night)	6.98 (1.11)
Hours Since Eaten	5.00 (4.85)
Day Length at Session (hh:mm:ss)	10:27:03 (0:18:48)
Adult SES (1–7)	4.49 (1.59)
Childhood SES (1–7)	4.82 (1.41)

Note. SES = socioeconomic status.

Materials and Procedure

This research was approved as compliant with ethical standards by the Texas Christian University Institutional Review Board (Approval #1920-81-AM1). Upon arrival to their session, participants were escorted to a private, single-person computer room where they provided informed consent. Under the ruse that the purpose of the study was to examine relationships between stress and group behavior, each participant was told that the researchers would be collecting a small blood sample to measure levels of stress biomarkers, after which the participant would be playing a series of games online with students at another university. Next, participants were led to the biological samples collection laboratory, located in the same suite as the private computer room. At this time, an 8mL whole blood sample was collected via venipuncture into EDTA-coated tubes and transported to a separate laboratory for processing. After the blood collection procedure, participants were led back to the computer room and given additional instructions about the games that they were about to play. Upon finishing the games, participants

completed demographic surveys using Qualtrics online survey software (Qualtrics, Provo, UT), were thanked, debriefed, awarded credit, paid the money they earned during the economic games, and dismissed.

Measures of inflammation. After blood collection, samples were immediately centrifuged for 15 minutes at 4-6°C, after which plasma was removed, aliquoted, and frozen at -80°C until assayed for levels of inflammatory markers. Markers of inflammation assayed in plasma samples included a trio of pro-inflammatory cytokines: IL-6, IL-1β, TNF-α. Samples were assayed in duplicate per convention using commercially-available electrochemiluminescence multiplexing kits (Meso Scale Discovery, Rockville, MD) read on a MESO QuickPlex SQ 120 machine. Intra-assay coefficients of variation (CVs) were 3.36% (IL-1β), 2.24% (IL-6), and 4.10% (TNF-α). Inter-assay CVs were 7.21% (IL-1β), 4.85% (IL-6), and 6.23% (TNF-α).

Childhood and adult socioeconomic status. As proxy measures of early life and current stress exposure, childhood and adult SES were measured using previously-validated scales (Griskevicius et al., 2011). Participants reported their childhood SES by responding to three statements about their life before age 12 using a 7-point Likert scale (1: *Strongly disagree*, 7: *Strongly agree*). Scale items included, "My family usually had enough money for things when I was growing up"; "I grew up in a relatively wealthy neighborhood"; and "I felt relatively wealthy compared to other kids in my school." These items together yielded good reliability ($\alpha = .84$) and were formed into a mean composite.

Adult SES was measured using a similar scale. Participants responded to three items regarding their current financial situation: "I have enough money to buy the things I want"; I don't need to worry too much about paying my bills"; and "I feel relatively wealthy these days." These

items also yielded good reliability ($\alpha = .87$) and were formed into a mean composite. For both childhood and adult SES, higher values represented a higher SES.

Measures of cooperation. To assess cooperation, participants played two well-validated cooperative games presented using the SMARTRIQS interactive experimental platform in Qualtrics survey software (Qualtrics, Provo, UT). The first game was a repeated PGG, the gold standard for measuring cooperation in controlled laboratory settings (Fehr & Gächter, 2000; Fischbacher, Gächter, & Fehr, 2001; Ledyard, 1994). Participants were first given detailed written instructions about how to play the game and were required to correctly compute the payoff structure for a hypothetical round before advancing. Participants then completed three practice rounds against the computer to further ensure that they understood the rules of the game. Participants were told that the tokens they accrued in these practice rounds would not count toward their final token total.

Next, participants played 10 rounds of the PGG game against four computer bots (see e.g. Kurzban & Houser, 2005). Token contributions for each of these bots for each round were randomly generated; bots' token contributions were the same for each participant. To support the ruse that participants were playing with real players, they were told that they would be synced into the game online with three students from different universities. A one-minute lobby wait period was programmed into the game to increase the believability of this ruse. Participants were told that they would be playing with the same three partners for the entire duration of the game.

For each round, participants were given 20 tokens (worth 0.5 cents each) and had to decide how to divide them between their private account and the public account. There were no restrictions on the number of these tokens that could be allocated to these two accounts. Participants were instructed that they would keep all tokens banked into their private accounts.

Tokens contributed to the public account, however, were taxed and divided evenly between all players. Specifically, public contributions from all players were summed, multiplied by 1.6 (i.e., marginal per capita return of 0.4), and then re-distributed evenly between the players' private accounts. Although participants were not provided this information, allocating all tokens to the private account (i.e., free-riding) yielded the highest payoff. Throughout the game, participants were shown the amount each player contributed to the public account after each round. Participants were also shown a running total of their private accounts. Cooperation in this game was measured as the number of tokens participants contributed to the public account across rounds, with greater contributions representing higher cooperation.

Upon completion of the PGG, participants completed a one-shot UG (Andreoni, 1988; Fehr & Gächter, 2000; O'Gorman et al., 2008; Sasaki et al., 2007). Participants again played against computer bots programmed to employ a randomly generated strategy; bot responses for each round were the same for each participant. In contrast to the PGG, participants were told that each round they would be playing with a unique partner logged into the game online from another university. For this game, participants played 10 rounds as the "proposer" and 10 rounds as the "responder." As proposer, participants were awarded 20 tokens (worth the same amount as for the PGG) each round and were required to decide how many of those tokens to keep and how many to offer to the responder. The responder could either accept or reject the offer. If the offer was rejected, neither player kept any of the tokens. However, if the offer was accepted, tokens were divided between the two players as offered by the proposer. Computer responders accepted 50% of the offers and rejected 50% of the offers in a pre-determined random order. As responder, participants were offered between 1 and 11 tokens by the computer each round and were given the choice to accept or reject the offers. Two dependent measures of cooperation

were extracted from this data. First, cooperation as proposer was measured by the number of tokens offered to the responder across rounds, with greater offers representing higher cooperation. Second, cooperation as responder was measured as the number of offers accepted, with a greater number of acceptances indicating higher cooperation.

Alternative explanations. To rule out alternative explanations for the relationship between inflammation and cooperation, measures of several variables previously shown to covary with inflammation, cooperation, or both were collected. These included age, sex, body mass index (BMI), day length, physical activity, hours since last eaten (i.e., energy need), sleep, and recent illness (O'Connor et al., 2009). Physical activity was assessed by asking participants to answer the question, "How many hours of exercise do you do in a typical week?" Participants reported their typical sleep pattern by responding to the question, "How many hours of sleep do you get in a typical night?" Finally, acute illness was measured by asking participants three questions: (a) "I am feeling sick today", (b) "I have felt sick within the past week", and (c) "When was the last time you had a cold, flu, or other illness?" with 7-point response scales.

Data Analysis Plan

Descriptive statistics are displayed in Table 2. All data were analyzed using MPlus statistical software (Version 6, Muthén & Muthén, 2012). Data were first inspected for normality. Levels of each proinflammatory cytokine were positively skewed. Given that models were estimated using robust maximum likelihood estimation, a method that is robust to normality violations, whether these variables were to be transformed was determined by model fit statistics. The frequency distributions of all other variables approximated normality. Missing data were minimal (less than 3.2% for any variable) and were handled using maximum likelihood estimation in MPlus. For all models, model fit indices included: the 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). Acceptable 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. All significance tests were two-tailed and effects were considered statistically significant at $p < .05$.

Table 2

Descriptive Statistics for Study 1 (N = 130)

Variable	***M* (*SD*)**
Plasma IL–1β (pg/mL)	.08 (.07)
Plasma IL–6 (pg/mL)	.54 (.40)
Plasma TNF–α (pg/mL)	1.73 (.80)
Avg. Public Contribution per Round (PGG)	5.33 (3.43)
Avg. Offer as Proposer per Round (UG)	7.86 (1.92)
Number of Offers Accepted as Responder (UG)	6.59 (2.28)

Note. IL–1β = interleukin–1beta, IL–6 = interleukin–6, TNF–α = tumor necrosis factor–alpha, pg/mL = picograms per milliliter, PGG = public goods game, UG = ultimatum game. Economic game values reflect performance across all ten rounds of respective game.

Relationships between inflammation, childhood SES, and behavior in each of the economic games were examined using a series of multilevel models, summarized as follows and described in more detail below: (a) the main effects of a latent inflammation factor (see below) and childhood SES, as well as the interaction between these variables, were tested as predictors of each dependent measure (in separate outcome models), (b) similar models were tested, but instead of a latent factor, each cytokine was treated as an independent predictor (i.e., to examine whether effects were driven by any one cytokine; included interactions with each cytokine and

childhood SES), and 3) models *a* and *b* were tested twice more, once controlling for covariates (see Method for full list) and again with adult SES replacing childhood SES as the moderator.

Inflammation was first modeled as a latent factor comprised of levels of each of the three cytokines (IL-1β, IL-6, and TNF-α). Because a confirmatory factor analysis (CFA) model including only this factor would be just-identified and therefore would not yield model fit statistics, CFAs were conducted using models that also included the dependent measure (modeled as a latent factor at level 2). CFAs revealed excellent model fit and factor loadings were moderate to high (see Table 3 for model fit statistics). Model fit statistics supported leaving the cytokine data untransformed. After confirmation of the latent factor structure, primary models were tested.

Note that standard model fit statistics are not provided for models involving random effects (i.e., TYPE = TWOLEVEL RANDOM; ALGORITHM = INTEGRATION in MPlus) as was required to compute the interaction between childhood SES and the latent inflammation factor. Accordingly, Akaike (AIC), Bayesian (BIC), and sample-sized adjusted Bayesian (SABIC) information criterion are listed for these models (see Table 3). For the PGG, at level 1, contributions were regressed on game round as previous research finds that public contributions typically decline at later rounds (Fehr & Gächter, 2000; Fischbacher, Gächter, & Fehr, 2001; Ledyard, 1994). At level 2, the latent intercept representing contributions across rounds was regressed on childhood SES (grand mean-centered), the latent inflammation factor (grand mean-centered), and the interaction between these two variables. Next, a follow-up model was tested to examine whether the two predictors and their interaction term predicted the random slope of contributions across rounds. The primary model was tested a second time controlling for covariates. Finally, the primary model was tested a third time with adult SES specified as a

predictor instead of childhood SES, to examine whether any significant effects of SES (and its interaction with inflammation) were specific to childhood socioeconomic conditions or generalized to adult circumstances. This process was repeated with each cytokine score simultaneously included in the model as an individual predictor, in place of the latent inflammation factor. While cytokine values covaried, a preliminary regression analysis revealed that multicollinearity was low (i.e., variance inflation factors = 2.07-2.99; Hair et al., 2010).

The UG data were analyzed in a similar fashion. At level 1, offers as proposer were regressed on game round. Further, offers acceptances as responder (dummy-coded; 0 = reject, 1 = accept) were regressed on the amount offered by the computer each round. The acceptances dependent measure was analyzed using logistic regression (odds ratio), with higher beta values indicating an increased likelihood of accepting an offer from the computer. The serial model progression was otherwise the same for the UG data as outlined above for the PGG data.

Table 3

Summary of Model Fit Indices for All Models

Model	$\chi^2(df)$	CFI	RMSEA	SRMR	AIC	BIC	SABIC
Study 1							
Inflammation CFA – Log–Transformed	4.25 (2)	.97	.03	.04	7836.331	7902.17	6860.88
Inflammation CFA – Untransformed[1]	3.00 (2)	.99	.02	.02	7684.83	7750.68	7709.38
Latent Factor Model – PGG	–	–	–	–	7673.52	7754.56	7703.74
Separate Cytokine Model – PGG	1.84 (4)	1.00	.00	.04	7184.45	7240.16	7205.22
Latent Factor Model – UG Offers	–	–	–	–	7533.24	7644.23	7610.87
Separate Cytokine Model – UG Offers	1.22 (4)	1.00	.00	.04	6207.86	6253.44	6224.85
Study 2							
Primary Model	.31 (1)	.98	.00	.005	6019.28	6060.95	6016.65
Study 3							
Historical Disease Prevalence: Primary Model	8.46 (1)	.96	.04	.05	5890.52	5935.61	5903.86
Historical Disease Prevalence: Mediation Model	13.38 (5)	.92	.04	.05	7826.30	7889.65	7845.20
Contemporary Disease Prevalence: Primary Model	7.32 (1)	.98	.03	.02	5500.91	5562.83	5541.12
Contemporary Disease Prevalence: Mediation Model	10.38 (5)	.94	.05	.05	7815.32	7880.47	7831.29

Note. CFA = confirmatory factor analysis, χ^2 = chi–square test of model fit, CFI = comparative fit index, RMSEA = root mean square error of approximation, SRMR = standardized root mean square residual, AIC = Akaike information criterion, BIC = Bayesian information criterion, SABIC = sample–sized adjusted BIC, PGG = public goods game, UG = ultimatum game.

Results

Public goods game with inflammation modeled as a latent factor. Consistent with previous research, results revealed that public account contributions decreased as a function of round number, b = -.14, SE = .05, t = -3.05, p = .002. People contributed more on earlier rounds than on later rounds. Neither the main effect of childhood SES, b = -.06, SE = .25, t = -.23, p = .82, nor the main effect of inflammation, b = -5.31, SE = 4.52, t = -1.18, p = .24, reached statistical significance in predicting the latent intercept of contributions. No effects of any predictor on the slope of contributions across time reached significance (ps > .48). However, the interaction between inflammation and childhood SES significantly predicted the intercept of contributions, b = 6.40, SE = .2.06, t = 3.10, p = .002 (see Figure 2 for interaction).

This interaction was unpacked by examining the effects of inflammation on contributions at high (1 SD above the mean) and low (1 SD below the mean) levels of childhood SES. At high childhood SES, there was no significant relationship between inflammation and contributions, b = 3.57, SE = 2.27, t = 1.57, p = .12. However, at low childhood SES, higher inflammation was associated with lower public account contributions, b = -14.33, SE = 7.26, t = -1.97, p = .048. This interaction was not examined within levels of inflammation due to limitations on re-centering latent variables in the available version of MPlus (version 6). See 'Public goods game with individual cytokine values" for further interaction decomposition.

Next, the primary model was tested a second time while controlling for significant covariates. Age and energy need were the only covariates that approached significance. Specifically, older participants contributed more to the public account, b = .22, SE = .06, t = 4.05, p < .001, as did participants who had gone longer without eating prior to participating (marginally significant), b = .13, SE = .07, t = 1.83, p = .067. Importantly, controlling for these

and all other covariates did not change the pattern or significance of the results (interaction between childhood SES and inflammation: b = 6.17, SE = 2.58, t = 2.39, p = .02). A final follow-up model tested whether a similar pattern of results were found when replacing childhood SES with adult SES as the moderator. Neither the main effect of adult SES, nor the interaction between adult SES and inflammation, reached significance (ps > .12).

Public goods game with individual cytokine values. An additional series of models were tested to examine whether the pattern of relationships between inflammation, childhood SES, and cooperation varied by cytokine. Non-significant interactions were removed from the model such that meaningful main effects could be reported and interpreted. Neither the interaction between childhood SES and IL-6 levels (p = .57), nor the interaction between childhood SES and TNF-α levels (p = .97), were significant. The main effects of childhood SES, b = -.09, SE = .24, t = -.36, p = .72, levels of IL-1β, b = -2.60, SE = .4.59, t = -.57, p = .57, levels of IL-6, b = .77, SE = .62, t = 1.25, p = .21, and levels of TNF-α, b = -.03, SE = .02, t = -1.24, p = .21, were also non-significant. However, there was a significant interaction between childhood SES and IL-1β levels, b = 5.88, SE = 1.97, t = 3.49, p < .001 (see Figure 2 for interaction).

Unpacking this interaction revealed that, at high childhood SES, IL-1β did not significantly predict public goods contributions, b = 6.96, SE = 6.12, t = 1.14, p = .26. However, at low childhood SES, higher levels of IL-1β predicted lower contributions, b = -12.30, SE = 4.46, t = -2.76, p = .006. This pattern was similar to what was observed when inflammation was modeled as a latent factor. Next, this interaction was probed by examining the impact of CSES on contributions at high and low levels of IL-1β. Results revealed that, at high levels of IL-1β, those with a higher childhood SES tended to contribute more than those with a lower childhood SES, b = .35, SE = .21, t = 1.63, p = .10. At low levels of IL-1β, those with a higher childhood

SES tended to contribute less than those with a lower childhood SES, b = -.50, SE = .32, t = -1.58, p = .11, However, neither of these simple effects reached statistical significance.

The pattern and significance of these results did not change when covariates were controlled for (interaction between childhood SES and IL-β levels: b = 7.33, SE = 1.98, t = 3.70, p < .001), nor were they found for adult SES (all main effects and interactions: ps > .14). The effects of childhood SES, levels of IL-1β, and their interaction explained approximately 7.5% of the variance in public contributions across rounds.

Ultimatum game with inflammation modeled as a latent factor. Results revealed that proposers' offers declined as the game progressed, b = -.15, SE = .04, t = -3.97, p < .001. Further, the odds of accepting an offer were positively predicted by the amount of the offer, b = 1.14, SE = .09, t = 12.72, p < .001.

Proposer behavior. Results revealed that, while playing as proposers, the latent intercept of the amount of participants' offers was not significantly predicted by either the main effect of childhood SES, b = .06, SE = .15, t = .41, p = .68, or the main effect of inflammation, b = -3.70, SE = 1.97, t = -1.89, p = .06, although the latter effect was marginally significant. No effect significantly predicted the slope of offer amount across rounds (ps > .10). There was, however, a significant interaction between childhood SES and inflammation on offer size, b = 2.79, SE = .72, t = 3.87, p < .001 (see Figure 2 for interaction).

As with the PGG data, this interaction was probed at high (1 SD above mean) and low (1 SD below mean) levels of childhood SES. Results revealed that at high childhood SES, inflammation did not significantly predict offer amounts, b = .37, SE = 1.52, t = .24, p = .81. However, at low childhood SES, higher inflammation predicted reduced offer amounts, b = -7.59, SE = 2.82, t = -2.69, p = .007.

Next, the model was tested again while controlling for covariates. Only age and energy need emerged as significant predictors of offer amounts, with older participants, b = .06, SE = .03, t = 2.60, p = .009, and those who had eaten more recently, b = -.10, SE = .04, t = -2.73, p = .006, offering larger shares. A final follow-up model tested whether a similar pattern of results would be found when replacing childhood SES with adult SES as the moderator. Neither the main effect of adult SES, b = .06, SE = .12, t = .55, p = .58, nor the interaction between adult SES and inflammation, b = 2.00, SE = 1.32, t = 1.51, p = .13, reached significance.

Responder behavior. Neither inflammation, b = -1.43, SE = 3.19, t = -.45, p = .65, nor childhood SES, b = -.16, SE = .21, t = -.77, p = .44, significantly predicted likelihood of offer acceptance. The interaction between childhood SES and inflammation was also not significant, b = .80, SE = .1.51, t = .53, p = .60. No effect significantly predicted the slope of acceptance likelihood across different offer amounts (ps > .10). The pattern and significance of these results were not changed by controlling for covariates (all ps > .20). Further, neither adult SES, nor the interaction between adult SES and inflammation, predicted likelihood of offer acceptance (ps > .31).

Ultimatum game with individual cytokine values. As with the PGG data, a series of models were tested to examine whether the pattern of results varied by cytokine.

Proposer behavior. Results revealed that no main effects reached significance: childhood SES, b = .09, SE = .15, t = .57, p = .57, IL-1β levels, b = -3.17, SE = 2.04, t = 1.56, p = .12, IL-6 levels, b = .30, SE = .21, t = 1.38, p = .17, TNF-α levels, b = -.004, SE = .02, t = -.22, p = .83. Neither the interaction between childhood SES and IL-6 levels, nor the interaction between childhood SES and TNF-α levels reached significance (ps > .16). However – similar to what was

observed with the PGG – there was a significant interaction between childhood SES and IL-1β levels on offer amounts, $b = 2.45$, $SE = .88$, $t = 2.80$, $p = .005$ (see Figure 2 for interaction).

Unpacking this interaction revealed that at high childhood SES, IL-1β levels did not significantly predict offer amounts, $b = .24$, $SE = 1.36$, $t = .18$, $p = .86$. However, at low levels of childhood SES, higher levels of IL-1β predicted decreased offer amounts, $b = -6.63$, $SE = 3.09$, $t = -2.15$, $p = .03$. Unpacked another way, childhood SES did not significantly predict offer amounts at either high levels of IL-1β, $b = .19$, $SE = .15$, $t = 1.25$, $p = .21$, or low levels of IL-1β, $b = -.11$, $SE = .16$, $t = -.67$, $p = .50$. The pattern and significance of these results did not change when covariates were controlled for (interaction between childhood SES and IL-1β levels: $b = 2.68$, $SE = .96$, $t = 2.80$, $p = .005$), nor were they found for adult SES (all main effects and interactions: ps > .32). Overall, childhood SES, levels of IL-1β, and their interaction explained approximately 5.4% of the variance in offer amounts across rounds.

Responder behavior. No main effects of any predictor on acceptance likelihood reached significance: childhood SES, $b = -.13$, $SE = .21$, $t = .64$, $p = .53$, IL-1β levels, $b = -.98$, $SE = 4.16$, $t = -.24$, $p = .82$, IL-6 levels, $b = -.30$, $SE = .54$, $t = -.55$, $p = .58$, TNF-α levels, $b = -.14$, $SE = .40$, $t = -.35$, $p = .72$. Further, no interactions between any cytokine and childhood SES reached significance (ps > .14). The pattern and significance of these results were not changed by controlling for covariates (all ps > .18). Further, neither adult SES, nor the interaction between adult SES and inflammation, predicted likelihood of offer acceptance (ps > .55).

Taken together, the results of Study 1 suggest that one's childhood experiences – specifically early life SES – interact with current levels of inflammation to influence cooperation. Specifically, the current study found that, across both economic games, higher levels of inflammation were associated with reduced cooperative behavior for participants who

reported a relatively low childhood SES. Follow-up analyses revealed that this effect was driven specifically by levels of IL-1β, a key proinflammatory cytokine. No relationship between inflammation and cooperation was found for participants reporting a relatively high childhood SES. These results both provide support for a role of the immune system in regulating cooperative behavior and also add to the growing body of research suggesting that early life stress sensitizes individuals to the effects of peripheral inflammation on psychology and behavior (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012).

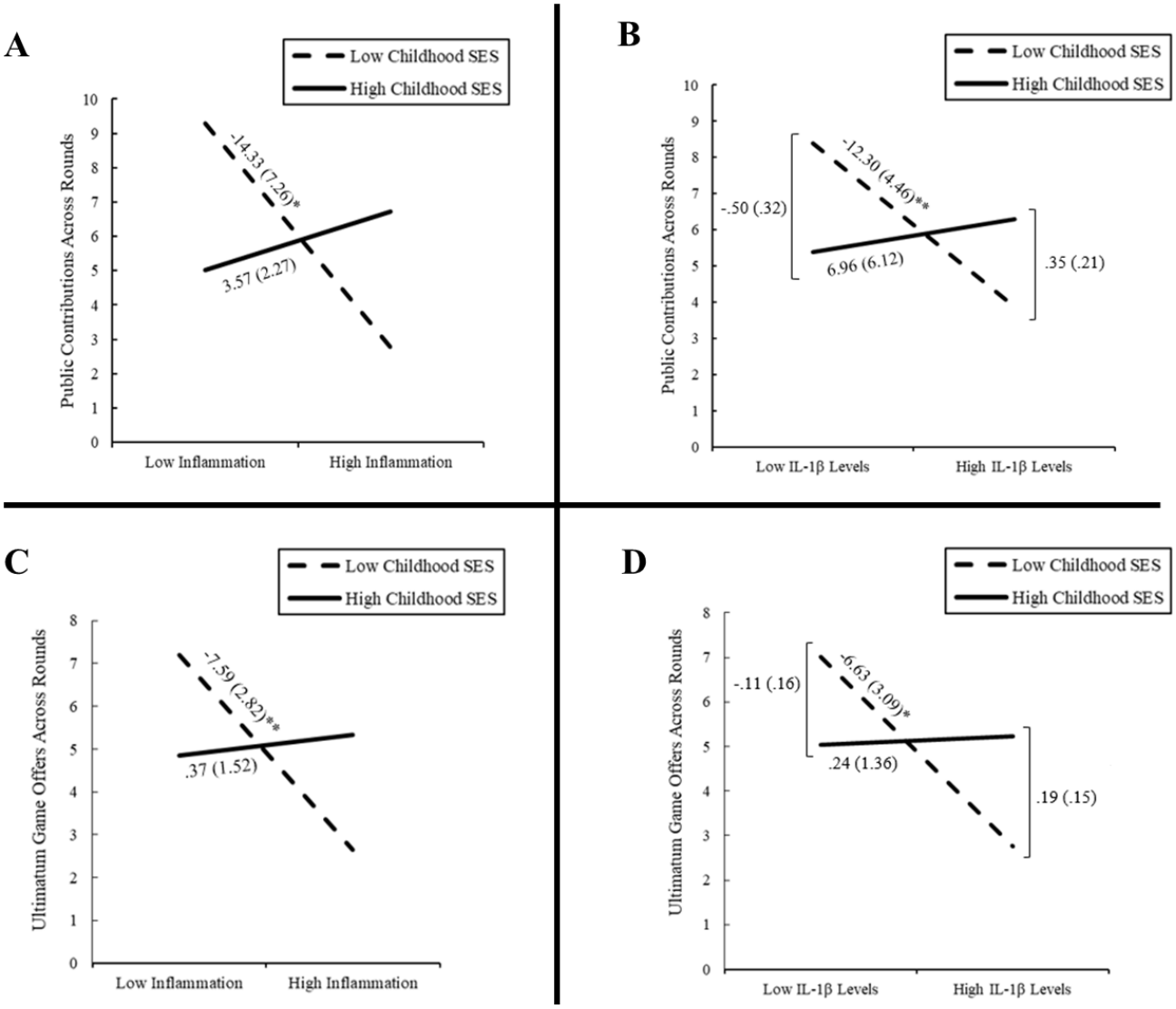

Figure 2. Graphs of interactions between inflammation and childhood socioeconomic status (SES) found in Study 1. "High" childhood SES refers to one standard deviation above the mean of this variable; "low" refers to one standard deviation below the mean. Panel A displays an interaction between the latent inflammation factor and childhood SES predicting the latent intercept of public goods contributions across rounds. Panel B displays an interaction between levels of interleukin–1β (IL–1β) and childhood SES predicting this same outcome. Panel C displays an interaction between the latent inflammation factor and childhood SES predicting the latent intercept of ultimatum game offer amounts across rounds. Panel D displays an interaction between levels of IL–1β and childhood SES predicting this same outcome. ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

Study 2: Inflammation and Group-Level Cooperation in the Public Goods Game

Study 2 was designed to conceptually replicate and extend the results of Study 1 by examining relationships between childhood SES, inflammation, and cooperation in the PGG at both the individual- and group level. The method and procedures for the second study differed from those of the first in three key ways. First, proinflammatory cytokines were measured in saliva, instead of plasma (i.e., as was done in Study 1). Collecting saliva instead of whole blood, in addition to being less invasive than venipuncture, also allowed me to examine whether relationships between inflammation and cooperation generalized across sample types. Second, instead of only playing with programmed computer bots, participants played the PGG with each other in groups of 2-4. Additionally, participants also played for hypothetical, rather than monetary, rewards. Previous research suggests that behavior in the PGG is not typically affected by whether real or hypothetical rewards are used (Gillis & Hettler, 2007; Kahneman & Ritov, 1994). Lastly, because Study 2 PGG data were structured such that individuals were nested within groups, I was able to examine relationships between inflammation and cooperation at both the individual level and group level. I predicted that at each level of social organization, higher levels of inflammation would predict diminished cooperative behavior. Further, I predicted that, consistent with the results of Study 1 and recent research finding that exposure to early life stress increases one's sensitivity to elevated inflammation (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012), the relationship between heightened inflammation and reduced cooperation would be specific to those reporting a relatively low childhood SES (compared to those reporting higher childhood SES).

Method

Participants. Participants were 207 healthy college students (149 women; M_{age} = 19.77, SD_{age} = 2.43) recruited from Texas Christian University's research participant pool. Full characteristics of the sample are displayed in Table 4. All participants 1) were without a history of chronic physical or psychological disorders, 2) were free from acute illness for at least two weeks prior to participation, 3) abstained from steroidal and non-steroidal anti-inflammatory medications, exercise, and alcohol for at least two days prior to the session, and 4) did not have any dental work done for 48 hours prior to participating. Participants were awarded partial course credit in exchange for participation.

This sample size was determined by conducting an a priori power analysis using G*Power software (version 3.1.9). Based on the smallest effect size found for the relationship between inflammation and cooperation in Study 1 (R^2 = .075), I determined that I would require a total sample size of 320 participants in order to achieve .80 power to detect a significant session-level relationship between inflammation and cooperative behavior. Note that, because data collection was suspended due to the ongoing COVID19 pandemic, the final sample size was underpowered to examine relationships between these variables at the session level. Accordingly, I only report the results of analyses at the individual- and group levels in this document.

Table 4

Characteristics of the Sample for Study 2 (N = 207)

Variable	***M* (*SD*)**
Age	19.77 (2.43)
Body Mass Index	23.51 (5.14)
Exercise (hrs/week)	5.21 (3.66)
Sleep (hrs/night)	7.13 (1.18)
Hours Since Eaten	5.55 (5.18)
Day Length at Session (hh:mm:ss)	11:31:06 (0:08:54)
Adult SES (1–7)	4.57 (1.62)
Childhood SES (1–7)	5.11 (1.36)

Note. SES = socioeconomic status.

Materials and Procedure

This research was approved as compliant with ethical standards by the Texas Christian University Institutional Review Board (Approval #1920-81-AM1). Participants entered the computer laboratory in groups of 6-10. After signing in, participants sat at individually partitioned computer terminals and provided informed consent. Participants were then escorted one-by-one to the biological samples collection laboratory to give a 4mL saliva sample via passive drool into scintillation vials. These samples were immediately transferred to a separate laboratory for processing. Next, participants returned to the computer laboratory and a researcher accurately explained to participants that they would be playing a game with three other players in the room. However, the identity of the other players would not be revealed. They were further told that, in the event that they were randomly selected to be in a group with less than four total players, computer bots responding randomly would replace the missing players. Participants were explicitly told if any of their partners were bots. Participants were then required to correctly

compute the payout structure for a hypothetical round of the PGG, followed by three practice rounds against the computer. When all participants had finished their practice rounds, they were randomly synced to play a 10-round PGG game in groups of 4 (with computer bots filling in any missing group members). After finishing the game, participants completed demographic surveys using Qualtrics online survey software (Qualtrics, Provo, UT), were debriefed, thanked, awarded credit, and dismissed.

Measures of inflammation. After saliva collection, samples were immediately stored at -80°C until assayed for inflammatory markers. At the time of assaying, samples were thawed and centrifuged for 15 minutes. As in Study 1, markers of inflammation assayed were IL-6, IL-1β, and TNF-α. Samples were assayed in duplicate per manufacturer instructions using commercially-available electrochemiluminescence multiplexing kits (Meso Scale Discovery, Rockville, MD) read on a MESO QuickPlex SQ 120 machine. Intra-assay CVs were 2.21% (IL-1β), 1.78% (IL-6), and 2.98% (TNF-α). Inter-assay CVs were 4.31% (IL-1β), 5.01% (IL-6), and 3.93% (TNF-α).

Childhood and adult socioeconomic status. Childhood and adult SES were measured using the same validated scales utilized in Study 1 (Griskevicius et al., 2011). The items for each scale together yielded good reliability (childhood SES: $\alpha = .82$; adult SES: $\alpha = .85$).

Measures of cooperation. To assess cooperation, participants played 10 rounds of a PGG presented using the SMARTRIQS interactive experimental platform in Qualtrics survey software (Qualtrics, Provo, UT). As with Study 1, participants were given detailed instructions about how to play the game and completed a series of practice trials. In contrast to the PGG played in Study 1, participants played against each other in groups of 2-4, synced into the game using SMARTRIQS. Computer bots employing random strategies filled in whenever a group had fewer than four players. Whether or not a group played with a mixture of real players and bots vs. only

real players did not influence cooperative behavior (p = .70). The structure of the game (i.e., number of rounds, token amounts, and marginal per capital return) was otherwise identical to the game played in Study 1. Individual-level cooperation was operationalized as a participant's average contribution to the public account across rounds. Group-level cooperation was measured as a group's average contribution to the public account across rounds. Contributions from bots were not included in these averages.

Alternative explanations. For Study 2, the same covariates were collected as in Study 1. These measures were identical to those collected in the first study (see Study 1 Method). Covariates included age, sex, BMI, day length, physical activity, hours since last eaten (i.e., energy need), sleep, and recent illness (O'Connor et al., 2009).

Data Analysis Plan

Descriptive statistics are displayed in Table 5. All data were again analyzed using MPlus statistical software (Version 6, Muthén & Muthén, 2012). Although positively-skewed, levels of each proinflammatory cytokine were entered into the model untransformed to remain consistent with the data analysis strategy for Study 1. Again, models were estimated using robust maximum likelihood estimation, which is robust to normality violations. The frequency of all other variables approximated normality. Missing data were minimal (less than 2.1% for any variable) and were handled using maximum likelihood estimation in MPlus. For all models, model fit indices included: the χ^2 test of model fit, CFI, RMSEA, and SRMR. Acceptable 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. All significance tests were two-tailed and effects were considered statistically significant at $p < .05$.

Table 5

Descriptive Statistics for Study 2 (N = 207)

Variable	***M* (*SD*)**
Salivary IL–1β (pg/mL)	124.97 (125.70)
Salivary IL–6 (pg/mL)	4.20 (8.34)
Salivary TNF–α (pg/mL)	3.09 (4.15)
Avg. Individual Contributions per Round	5.33 (3.96)
Avg. Group Contributions per Round	5.65 (4.48)

Note. IL–1β = interleukin–1beta, IL–6 = interleukin–6, TNF–α = tumor necrosis factor–alpha, pg/mL = picograms per milliliter. Contribution values reflect average contributions to public account per round across 10 rounds of game.

I again examined relationships between inflammation, childhood SES, and cooperation in the PGG using a series of multilevel models. In MPlus, including random between-level interactions involving a latent factor (i.e., between the latent inflammation factor and childhood SES) requires advanced numerical integration (ALGORITHM = INTEGRATION). When using this command, variables are not allowed to vary randomly across model levels. As a result, I could not simultaneously examine relationships between inflammation, childhood SES, and public contributions at both the individual- and group-level if inflammation was modeled as a latent factor. Thus, for Study 2, levels of each cytokine were included in the model simultaneously as independent predictors. As in Study 1, results of a preliminary analysis revealed minimal multicollinearity (variance inflation factors: 1.45-2.41).

The iterative model testing procedure was the same as for Study 1. First, the effects of each cytokine (grand mean-centered), childhood SES (grand mean-centered), and the interactions between childhood SES and each cytokine were included as predictors of average individual

contributions (level 1) and average group contributions (level 2). Non-significant interactions were removed from the final models. This model was then tested a second time (a) controlling for covariates and (b) with adult SES replacing childhood SES as the moderator.

Results

Individual-level cooperation in the public goods game. Model fit statistics revealed good model fit (see Table 3 for model fit statistics). Results revealed that, at the individual level (i.e., within-groups), average contributions were not predicted by the main effects of childhood SES, b = .37, SE = 5.34, t = .07, p = .95, IL-1β levels, b = .01, SE = .05, t = .27, p = .78, IL-6 levels, b = -.05, SE = .06, t = -.74, p = .46, or TNF-α levels, b = .97, SE = 1.88, t = .52, p = .61. Neither the interaction between childhood SES and IL-1β levels, nor the interaction between childhood SES and TNF-α levels reached significance (ps > .28). However, results did reveal a significant interaction between childhood SES and IL-6 levels, b = .11, SE = .04, t = 3.13, p = .002.

This interaction was first unpacked at high (1 SD above the mean) and low (1 SD below the mean) levels of childhood SES (see Figure 3 for interaction). Results revealed that at high childhood SES, there was no significant relationship between IL-6 levels of average contribution amount, b = .07, SE = .09, t = .73, p = .47. However, at low childhood SES, higher levels of IL-6 predicted lower average contributions to the public account, b = -.24, SE = .08, t = -3.10, p = .002. Unpacked another way, at high levels of IL-6, those with a higher childhood SES, on average, contributed more to the public account than those with a lower childhood SES, b = 1.24, SE = .42, t = 2.98, p = .003. In contrast, at low levels of IL-6, higher childhood SES predicted lower average contributions, b = -.66, SE = .30, t = -2.20, p = .03. The pattern and significance of these results did not change when covariates were controlled for (interaction between childhood

SES and IL-6: b = .13, SE = .05, t = 2.6, p = .009). A second follow-up model revealed that neither the main effect of adult SES nor any interaction between this variable in cytokine levels were significant (ps > .35). Overall, the effects of childhood SES, IL-6, and the interaction between these two variables explained approximately 9.8% of the variance in average individual contributions across rounds.

Group-level cooperation in the public goods game. At the group level, the main effects of childhood SES, b = 2.04, SE = 4.52, t = .45, p = .65, IL-1β levels, b = .03, SE = .04, t = .90, p = .37, and TNF-α levels, b = .53, SE = 1.53, t = .35, p = .73, were not significant. However, the main effect of IL-6 levels was significant, b = -1.12, SE = .38, t = -2.95, p = .003, with groups having higher collective IL-6 levels contributing less in the PGG compared to groups with lower IL-6 levels. No interactions reached significance (ps > .54). The pattern and significance of these results did not change when controlling for covariates (main effect of IL-6: b = -1.25, SE = .63, t = -2.00, p = .046). Further, neither the main effect of adult SES, nor any interactions involving this variable reached significance (ps > .40). Overall, the main effect of IL-6 explained approximately 7.6% of the variance in average group-level contributions across rounds.

The results of Study 2 found that, for individuals reporting a lower (compared to higher) childhood SES, higher IL-6 levels predicted reduce contributions to the public account. At group level, higher levels of IL-6 were associated with reduced contributions across each level of childhood SES. The results of the current study were similar to those of Study 1, which found that among those reporting a relatively low childhood SES, higher plasma levels of the cytokine IL-1β predicted reduced cooperation in both a PGG, as well as a UG. Notably, the proinflammatory cytokine that interacted with childhood SES to predict cooperative behavior differed between the two studies (i.e., Study 1: IL-1β; Study 2: IL-6). While there are a number

of potential explanations for this finding, most salient among them is differences in the sample type collected between the two studies. In Study 1, proinflammatory cytokines were measured in plasma. Levels of IL-1β in plasma are tightly regulated and much lower than other proinflammatory cytokines because of the central that role this protein plays in initiating inflammatory cascades (Dinarello, 1997, 2011, 2018). Accordingly, high levels of plasma IL-1β may be more indicative of elevated systemic inflammation than high levels of either IL-6 of TNF-α in this medium. The same might be said for levels of IL-6 in saliva. Salivary IL-6 levels are typically much lower than other proinflammatory cytokines because IL-6 is a relatively large molecule that does not pass easily into saliva (Mozaffari et al., 2018). On the other hand, salivary IL-1β levels are typically much higher than plasma levels (see e.g., Tables 2 and 4). Thus, in saliva, high IL-6 levels may provide a better index of elevated inflammation (given limitations on transport of this protein into saliva) than high IL-1β levels. This possibility, however, is speculative and future research is necessary to examine whether the link between levels of a given cytokine and systemic inflammatory processes depends on the medium in which the cytokine is measured.

Nonetheless, the results of Study 2 conceptually replicated those of Study 1, providing additional support both for the relationship between proinflammatory cytokines and cooperation, as well as for a role of early life stress in sensitizing an individual's behavior to shifts in peripheral inflammation.

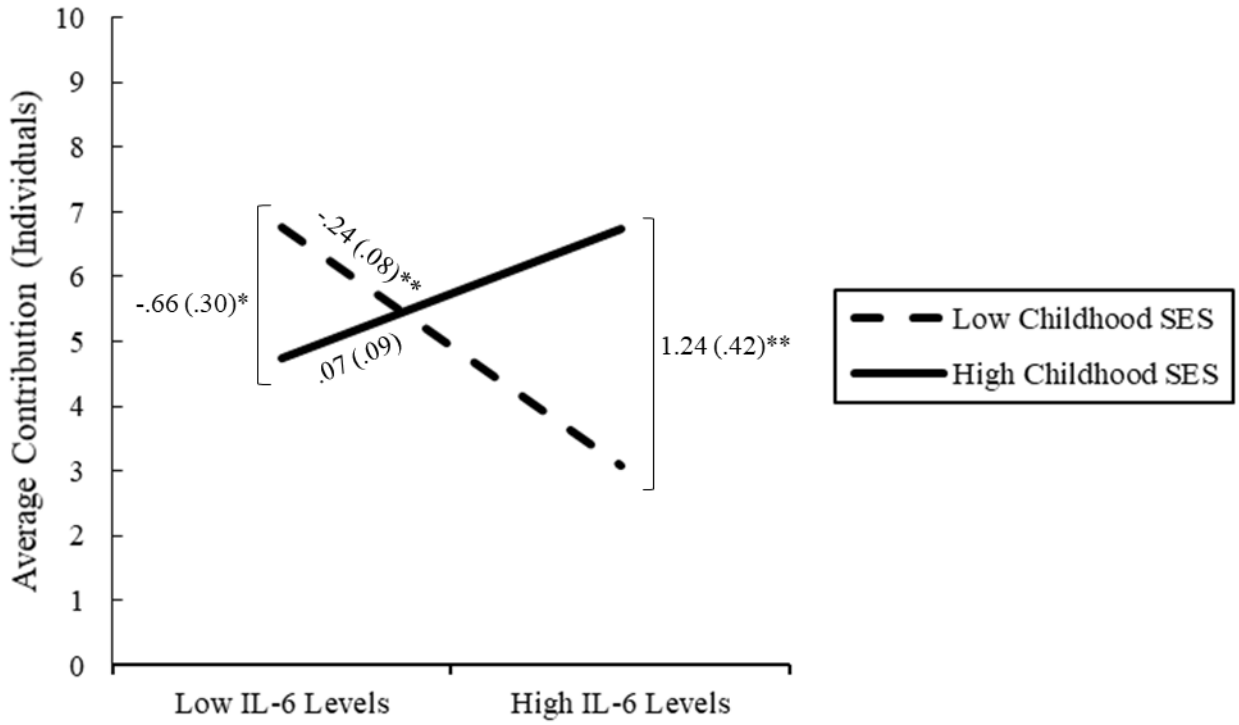

Figure 3. Interaction between childhood socioeconomic status (SES) and levels of interleukin–6 (IL–6) predicting individuals' average contributions to the public account across rounds in Study 2. "High" childhood SES refers to one standard deviation above the mean of this variable; "low" refers to one standard deviation below the mean. ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

Study 3: Worldwide Differences in Infectious Disease and Cooperative Behavior

Study 3 was designed to build on the findings of Studies 1-2 by assessing, at the country-level, whether environmental conditions that elicit an immune response reduce a nation's investment in cooperative structures. Further, it sought to examine whether differences in investment in a nation's cooperative structures emerging from immunologically-relevant environmental conditions may impact sociopolitical instability, which is a measure that impacts a wide range of critical social (REFS), economic (REFS), and geopolitical (REFS) outcomes. Specifically, Study 3 examined cross-national relationships between infectious disease

prevalence – both historical and contemporary – and (a) the percent of a country's total gross domestic product (GDP) invested in social welfare (i.e., intra-national public goods) and (b) a country's investment in environmental protection (i.e., Environmental Performance Index [EPI]; international public goods). Next, Study 3 tested (c) whether reduced investment in public goods mediated the relationship between infectious disease prevalence and sociopolitical instability (i.e., Fragile States Index [FSI]). Each of these measures has been used in similar cross-national research (e.g., Bradshaw, Giam, & Sodhi, 2010; Hilamo & Glantz, 2015; Salamon & Anheier, 1998; Taylor, Perez-Ferrer, Griffiths, & Brunner, 2014). Given that the results of the first two studies found that the relationship between the activities of the immune system and cooperation as moderated by childhood SES, I also examined whether national income interacted with infectious disease prevalence to predict the target outcomes. I predicted that countries with higher levels of infectious disease would invest less in social welfare programs and environmental protection policies, and as a result, would experience more sociopolitical instability.

Method

Historical infectious disease prevalence. All measures used in Study 1, as well as the original published source for this information, are displayed in Table 6. To assess historical infectious disease prevalence, I used a 7-item index originally developed by Murray and Schaller (2010). This index has high internal reliability ($\alpha = .75$; Murray & Schaller, 2010) and is currently the gold standard measure used in research examining relationships between regional infectious disease prevalence and cross-cultural differences in psychological characteristics (e.g., Fincher & Thornhill, 2012; Murray et al., 2013; Murray, Trudeau, & Schaller, 2011). To compute the index, the researchers combined and standardized data from epidemiological atlases

(see Murray and Schaller, 2010 for full description of methodology) which provided information about the prevalence of seven infectious diseases in 230 geopolitical regions prior to 1961. These diseases included leishmanias, schistosomes, trypanosomes, malaria, typhus, filariae, and dengue.

Contemporary infectious disease prevalence. To measure contemporary disease prevalence, I accessed public data from the World Health Organization (WHO) bearing on the disability-adjusted life years (DALYs) associated with infectious disease in 183 WHO member nations. The DALY metric involves a complex computation (for full description see World Health Organization, 2019) that corresponds to the average number of healthy years lost to both mortality and disability from a given disease across the population in a given geographical region. For my analyses, contemporary disease prevalence was operationalized as the combined average annual DALYs from all parasitic and infectious diseases on which the WHO collects these data. These diseases include tuberculosis, syphilis, chlamydia, gonorrhea, trichomonas's, genital herpes, unclassified sexually-transmitted diseases, human immunodeficiency virus, diarrheal diseases, whooping cough, diphtheria, measles, tetanus, meningitis, encephalitis, hepatitis, malaria, African trypanosomiasis, Chagas, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis, cysticercosis, echinococcosis, dengue, trachoma, yellow fever, rabies, leprosy, ascariasis, trichuriasis, hookworm, food-borne trematodes, and other unclassified infectious diseases. These data were available for the years 2000, 2010, 2015, and 2016.

National wealth. To measure national wealth, I accessed public data from The World Bank (2019) reporting each country's gross domestic product (GDP) per capita for the years 2000, 2010, 2015, and 2016. This measure has been used in several previous studies as an index of a country's overall socioeconomic development and standard of living (e.g., Akachi &

Canning, 2015; Stecker, 2008; Swift, 2011). Higher GDP per capita indicated greater overall economic development and a higher standard of living.

Investment in social welfare. To measure the extent to which a given country invests in social programs that provide public benefits, I used annually published aggregate data from The World Bank on the percent of national GDP a country spends on social safety nets and social assistance, including unconditional cash transfers, conditional cash transfers, social pensions, school feeding, in-kind transfers, fee waivers, public works, and other social assistance (for full description of methods see The World Bank, 2019). Data was available for 124 countries and were downloaded for the years 2000, 2010, 2015, and 2016. Higher values represented greater investment in intra-national public goods.

Investment in environmental protection. Given that investment in environmental protection policies often involves assuming economic costs for long-term local and global benefits, I used a country's Environmental Performance Index (EPI) as another measure of cooperation. The EPI was developed as part of a collaborative effort between Yale University, Columbia University, the World Economic Forum, and the European Commission to quantify, in a data-driven manner, countries' current and prospective environmental sustainability. This index combines data on environmental health (e.g., air quality and water quality), as well as ecosystem vitality (e.g., tree cover loss and sustainable nitrogen management) to determine how close 180 countries are to meeting international environmental standards for the 10 years prior to data release (for full description of methodology see Yale Center for Environmental Law & Policy, 2019). These data were accessed for the year 2018. Higher values represented greater investment in international public goods.

Sociopolitical instability. To measure sociopolitical instability, I used the Fragile States Index (FSI), developed by The Fund for Peace to quantify 178 countries' fragility based on four categories of indicators: cohesion (security apparatus, factionalized elites, and group grievances), economic (economic decline, human flight, and uneven economic development), political (public services, human rights, and state legitimacy), and social (refugees, external intervention, and demographic pressures). Data were downloaded for the years 2000, 2010, 2015, and 2016 (for full description of methodology see Fund for Peace, 2019).

Alternative Explanations. To test whether the relationship between regional infectious disease prevalence and cooperative behavior was robust to controlling for variables that may influence a country's levels of cooperation or infectious disease prevalence, I collected information on several other country-level variables. These included each country's level percent urbanicity, ethnic fractionalization, and latitude/longitude. See Table 6 for the sources of these data.

Table 6

Sources of Data for Study 3

Measure	**Source**
Historical Infectious Disease Prevalence	(Murray & Schaller, 2010)
Contemporary Infectious Disease Prevalence	(World Health Organization, 2019)
Social Welfare Spending GDP per Capita	(The World Bank, 2019)
Investment in Environmental Protection	(Yale Center for Environmental Law & Policy, 2019)
Sociopolitical Instability (FSI)	(Fund for Peace, 2019)
Percent Urbanicity	(The Central Intelligence Agency, 2018)
Latitude and Longitude	https://www.latlong.net/
Ethnic Fractionalization	(Fearon, 2003)

Note. GDP = gross domestic product, FSI = Fragile States Index.

Data Analysis Plan

Descriptive statistics are displayed in Table 7. All data were analyzed using MPlus statistical software (Version 6, Muthén & Muthén, 2012). Data were first inspected for normality. Historical infectious disease prevalence, contemporary infectious disease prevalence, and GDP were positively skewed. These variables were log-transformed, as models did not converge when untransformed. The frequency distributions of all other variables approximated normality. Missing data were again handled using maximum likelihood estimation in MPlus. The number of countries missing data differed by variable, so sample size for each analysis are reported in the Results section. For all models, model fit indices included: the χ^2 test of model fit, CFI, RMSEA, and SRMR. Acceptable 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. All significance tests were two-tailed and effects were considered statistically significant at $p < .05$.

Table 7

Descriptive Statistics for Study 3 (N = 230)

Variable	***M* (*SD*)**
Historical Infectious Disease Prevalence	.03 (.63)
Contemporary Infectious Disease Prevalence	.11 (.17)
GDP Per Capita ($)	13,868.71 (21,945.92)
Social Welfare Spending (% of GDP)	19.88 (5.87)
Environmental Protection (EPI) (0–100)	56.44 (12.92)
Sociopolitical Instability (FSI; 0–115)	70.54 (23.90)
Percent Urban	58.28 (24.27)
Ethnic Fractionalization (0–1)	.47 (.26)

Note. See Table 6 for references for each variable. GDP = gross domestic product. EPI = Environmental Protection Index. FSI = Fragile States Index. Missing data varied by measure; see Results section of Study 3 for analysis–specific sample size.

Two sets of multilevel models were used to examine relationships between each (a) historical infectious disease prevalence and (b) contemporary infectious prevalence and the target dependent measures. Specifically, models were tested using the follow progression: (1) the two dependent cooperation measures were regressed on infectious disease prevalence (grand mean-centered), GDP (grand mean-centered), and the interaction between these two variables, (2) a mediation model was tested to examine whether the cooperation measures mediated relationships between the predictors and the distal outcome of sociopolitical instability (if analysis 1 yielded significant results), and finally, (3) the mediation model was tested a second time controlling for covariates (see Study 3 Method for full list). Variables measured at all time points (2000, 2010, 2015, and 2016) were allowed to vary randomly across levels 1 and 2 of the model, such that the level 2 random intercept for each variable represented a latent factor of that measure across time. These variables included contemporary infectious disease prevalence, GDP, social welfare spending, and sociopolitical instability. Random slopes representing change over time were not included for these variables, as they were not found to vary across the measured time points (regression of variables on time scores: *p*s > .33). Historical infectious disease prevalence and the EPI variable were only measured at a single time point and were thus entered into the model exclusively at level 2.

Results

Historical infectious disease prevalence. Model fit statistics revealed good model fit. The number of countries with data for these variables was 167. For social welfare spending, results revealed that the main effect of national wealth was significant, $b = 3.19$, $SE = .84$, $t = 3.811$, $p < .001$, but the main effect of historical infectious disease prevalence was not, $b = -1.16$, $SE = 1.45$, $t = -.80$, $p = .42$. However, these results were qualified by a significant interaction

between these two variables, $b = 4.93$, $SE = 1.70$, $t = 2.91$, $p = .004$ (see Figure 4 for interaction). Unpacking this interaction at different levels of national wealth revealed that disease prevalence did not significantly predict social welfare spending for wealthier nations (1 SD above mean of GDP per capita), $b = 2.63$, $SE = 2.41$, $t = 1.09$, $p = .28$. However, for poorer nations (1 SD below mean of GDP per capita), higher historical infectious disease prevalence predicted reduced social welfare spending, $b = -4.96$, $SE = 1.33$, $t = -3.73$, $p < .001$. Unpacking this interaction at high and low levels of historical infectious disease prevalence revealed that, at high levels of disease prevalence, wealthier nations spent a greater percentage of their GDP on social welfare than poorer nations, $b = 5.84$, $SE = 1.44$, $t = 4.05$, $p < .001$. However, national wealth did not predict social welfare spending at low levels of disease prevalence, $b = .55$, $SE = .99$, $t = .56$, $p = .58$.

For environmental protection, the main effect of historical infectious disease prevalence was significant, $b = -10.45$, $SE = 2.07$, $t = 3.37$, $p = .001$, with higher infectious disease burden predicting lower investment in such programs. Neither the main effect of national wealth, $b = -.64$, $SE = .62$, $t = -1.03$, $p = .30$, nor the interaction between national wealth and historical infectious disease prevalence ($p = .36$) reached significance.

Next a mediated moderation model was tested to examine whether reduced cooperation in the context of infectious disease prevalence was associated with greater sociopolitical instability. Results of this model are shown in Figure 5. As in the previous model, the interaction between historical infectious disease prevalence and national wealth on social welfare spending remained significant ($p < .001$), as did the main effect of infectious disease prevalence on investment in environmental protection ($p < .001$). Both lower investment in social welfare and lower investment in environmental protection predicted greater sociopolitical instability (ps < .001). The indirect effects of historical infectious disease prevalence on sociopolitical instability

through each mediator were significant (*p*s < .001), as was the direct effect ($p < .001$), suggesting partial mediation. Controlling for covariates did not change the pattern or significance of these results (these results also included in Figure 5). Overall, historical infectious disease prevalence, national wealth, and the interaction between these two variables uniquely explained approximately 25.6% of the variance in social welfare spending. Historical infectious disease prevalence uniquely accounted for approximately 22.2% of the variance in environmental protection investment. Altogether, the mediation model accounted for approximately 55.8% of the variance in sociopolitical instability.

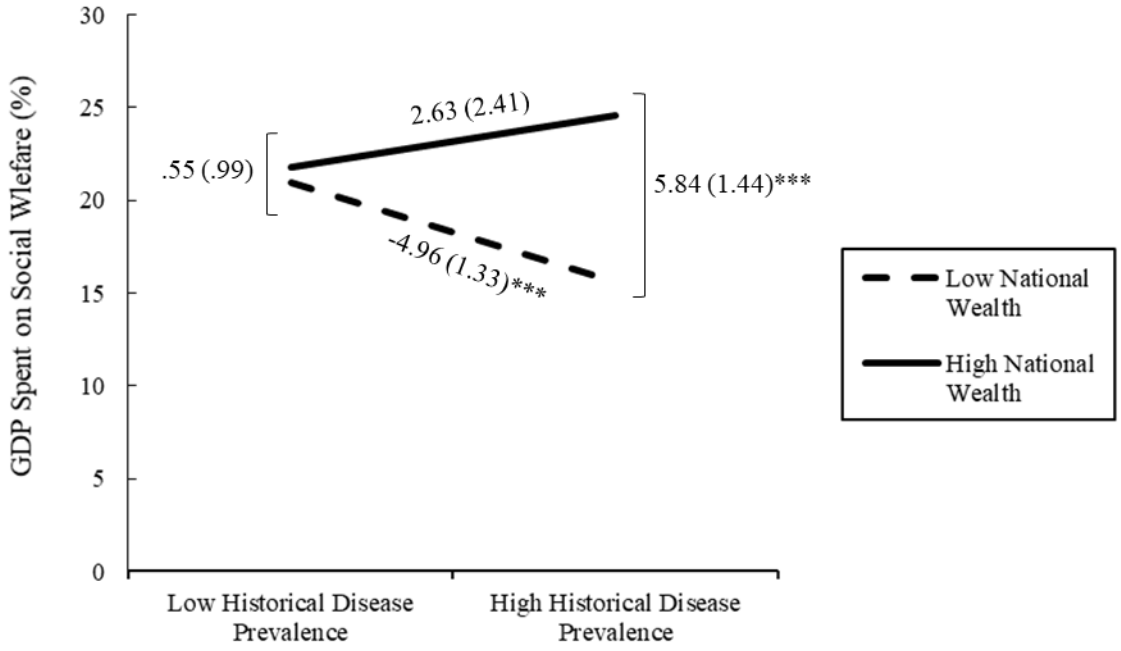

Figure 4. Interaction between historical infectious disease prevalence and national wealth (nation's gross domestic product per capita [GDP]) predicting percent GDP per capita spent on social welfare programs (Study 3). High and low national wealth refer to one standard deviation above and below the mean of GDP per capita, respectively. ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

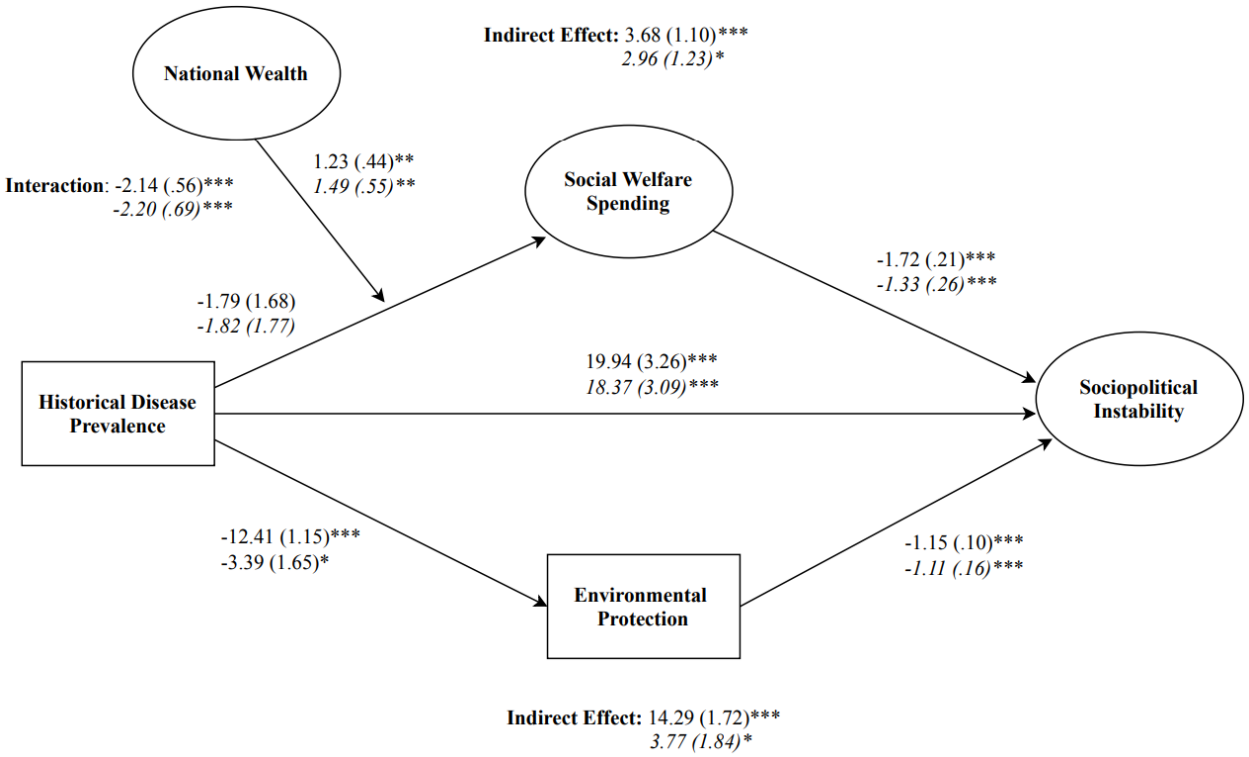

Figure 5. Path model displaying mediation of relationship between historical infectious disease prevalence and sociopolitical instability through social welfare spending and investment in environmental protection. Ovals represent latent level 2 intercepts of variable across years 2000, 2010, 2015, and 2016; Squares represent single measurements of variable. ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

Contemporary infectious disease prevalence. Model fit statistics revealed good model fit (see Table 3). The number of countries with data for these variables was 178. For social welfare spending, the main effect of contemporary infectious disease prevalence was significant, b = -3.06, SE = 1.53, t = -2.00, p = .045, and the main effect of national wealth was marginally significant, b = 1.80, SE = .98, t = 1.85, p = .06. However, these results were qualified by a significant interaction between these two predictors, b = 4.20, SE = 1.49, t = 2.82, p = .005 (see Figure 6 for interaction). Unpacking this interaction at different levels of national wealth revealed that disease prevalence did not significantly predict social welfare spending for

wealthier nations, b = .17, SE = 1.86, t = .09, p = .93. However, for poorer nations, higher contemporary infectious disease prevalence predicted reduced spending on social welfare programs, b = -6.30, SE = 1.96, t = -3.21, p = .001. Unpacking this interaction within levels of contemporary infectious disease prevalence revealed that, at high levels of disease prevalence, wealthier nations spent a greater percentage of their GDP on social welfare than poorer countries, b = 3.61, SE = 1.06, t = 3.42, p = .001. National wealth did not significantly predict social welfare spending at low levels of disease prevalence, b = -.001, SE = 1.27, t = -.001, p = .99.

For environmental protection, the main effect of contemporary infectious disease prevalence was significant, b = -6.49, SE = .44, t = -14.77, p < .001, with higher infectious disease burden predicting lower investment in environmental protection. Neither the main effect of national wealth, b = -.36, SE = .26, t = -1.26, p = .21, nor the interaction between national wealth and historical infectious disease prevalence (p = .17) reached significance.

Results of the mediated moderation model (see Figure 7 for full results) revealed, again, that the interaction between contemporary infectious disease prevalence and national wealth on social welfare spending was significant (p < .001), as was the main effect of disease prevalence on investment in environmental protection (p < .001). As in the historical disease prevalence model, both lower investment in social welfare and lower investment in environmental protection significantly predicted greater sociopolitical instability (ps < .001). The indirect effects of contemporary infectious disease prevalence on sociopolitical instability were significant for each mediator (ps < .001), as was the direct effect, suggesting partial mediation. The pattern and significance of the results did not change when controlling for covariates (see Figure 7). Contemporary infectious disease prevalence, national wealth, and the interaction

between these two variables uniquely explained approximately 27.9% of the variance in social welfare spending. Contemporary infectious disease prevalence uniquely accounted for approximately 17.7% of the variance in environmental protection investment. Altogether, the mediation model accounted for approximately 38.6% of the variance in sociopolitical instability.

These results suggest that nations with higher rates of infectious diseases – both currently and in the past – invest less in public goods than those with lower rates of disease. For social welfare spending specifically, the link between high infectious disease burden and diminished cooperation was only found for less wealthy countries (compared to middle- and high-income countries). This pattern of results mirrors those of the first two studies, which found that higher levels of inflammation predicted less cooperative behavior among those reporting a lower childhood SES, but not those reporting a higher childhood SES. The results of Study 3 also suggest that the negative impact of infectious disease prevalence on cooperation may have consequences for sociopolitical stability. Specifically, higher disease prevalence, both directly and via reduced cooperation, predicted greater instability across countries. Together, these findings further support the hypothesis that the activities of the immune system play a role in regulating cooperation and suggest that the relationship between these processes may have important sociopolitical implications.

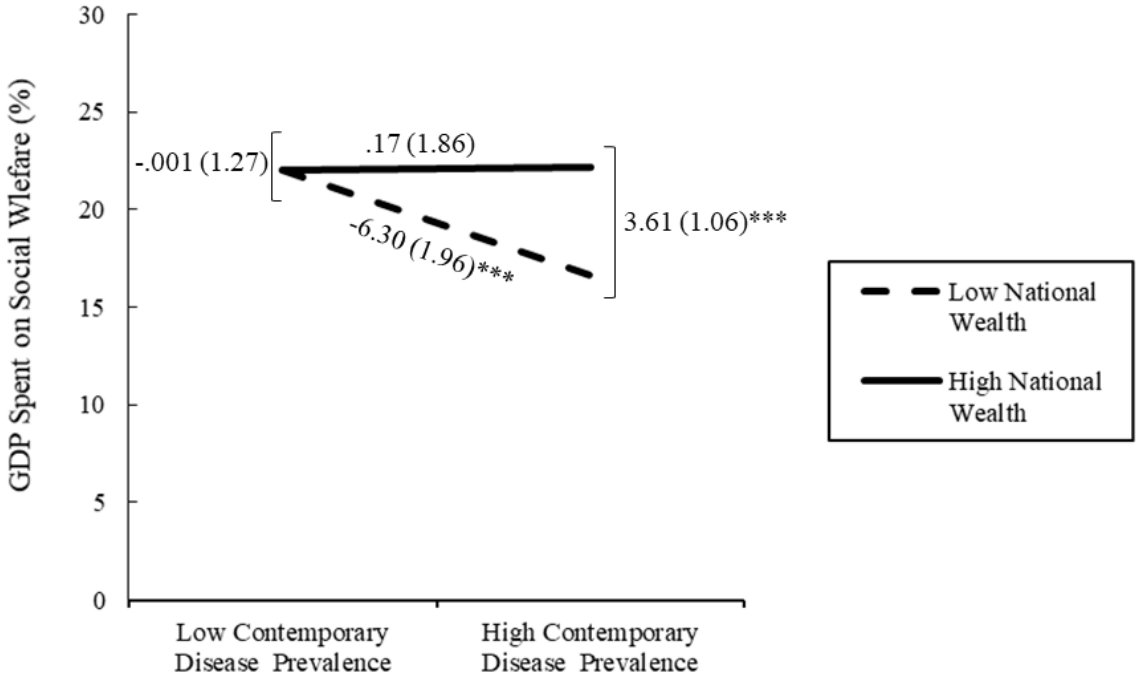

Figure 6. Interaction between contemporary infectious disease prevalence and national wealth (nation's gross domestic product per capita [GDP]) predicting percent GDP per capita spent on social welfare programs (Study 3). High and low national wealth refer to one standard deviation above and below the mean of GDP per capita, respectively. ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

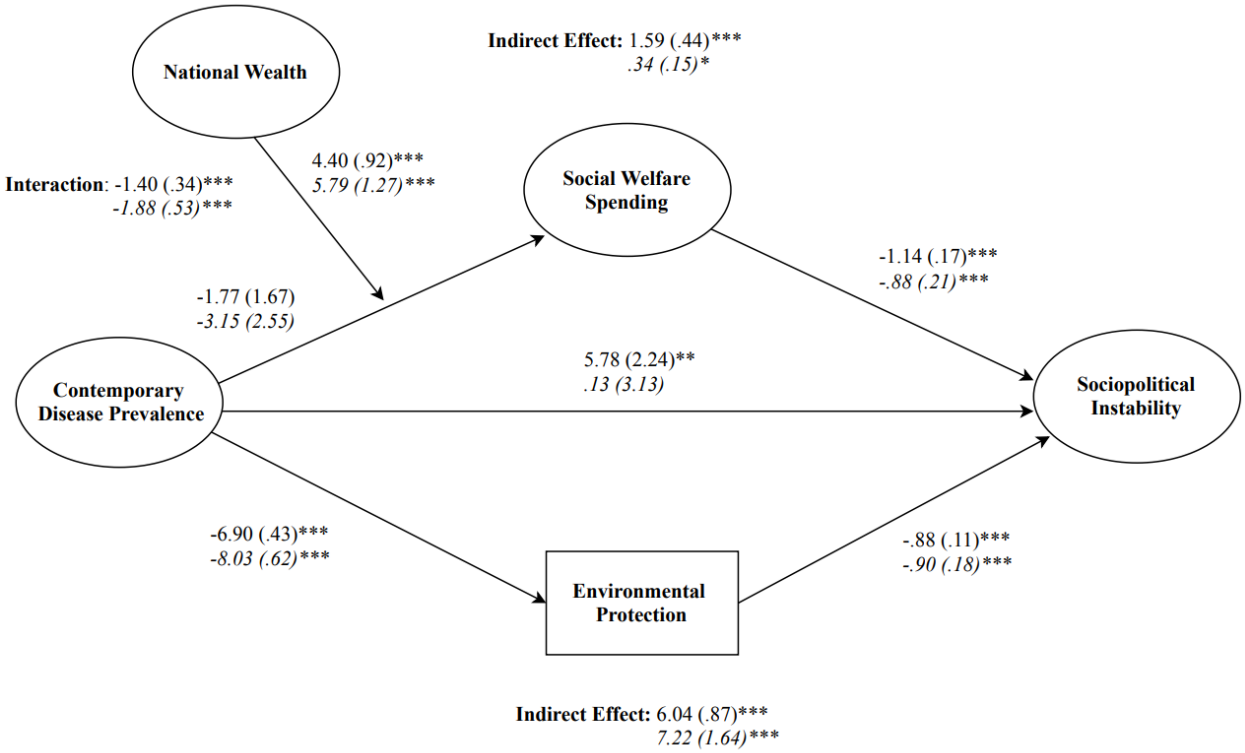

Figure 7. Path model displaying mediation of relationship between contemporary infectious disease prevalence and sociopolitical instability through social welfare spending and investment in environmental protection. Ovals represent latent level 2 intercepts of variable across years 2000, 2010, 2015, and 2016; Squares represent single measurements of variable. ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

Discussion

In the current research, I investigated the role that activities of the immune system – and inflammation in particular – plays in regulating cooperative behavior. Building on evolutionary theory, as well as research in experimental economics and psychoneuroimmunology, I predicted that cooperation would decrease in the context of elevated inflammation. I hypothesized that this would occur because in the context of heightened inflammation (a) the delayed benefits associated with cooperation are lower as one's probability of survival is diminished (Gassen et al., 2019a,b; Gassen & Hill, 2019) and (b) the costs associated with cooperation are higher as the

immunometabolic shifts that accompany this context increase one's immediate resource needs (Lacourt et al., 2018; O'Neill et al., 2016; Treadway et al., 2019). I further predicted that, consistent with research finding that early life stress sensitizes the central nervous system to fluctuations in peripheral inflammatory activity (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012), heightened inflammation would more negatively impact cooperation for those with a lower childhood SES – a key proxy for early life stress exospure – compared to those with a higher childhood SES. Lastly, I predicted that at the population level, higher levels of infectious disease prevalence would be associated with reduced investment in public goods, especially for poorer (compared to wealthier) nations.

Support for these predictions was found across three studies. Study 1 revealed that in the PGG, higher levels of inflammation predicted reduced public goods contributions for individuals reporting a lower childhood SES, but not those reporting a higher childhood SES. A similar pattern of results was found for the UG, whereby offer amounts as proposer decreased as a function of inflammation, only for those reporting a low childhood SES. However, neither inflammation, nor childhood SES, predicted participants' behavior as responder. Study 2 conceptually replicated and extended the results of Study 1, finding that at both the individual level and the group level, average contributions in the PGG were predicted by a significant interaction between levels of IL-6 and childhood SES. Again, among those reporting a lower childhood SES, higher levels of IL-6 predicted reduced cooperation. This relationship was not found among those reporting a higher childhood SES. Together, these results suggest that inflammation and socioeconomic conditions interact to influence cooperative behavior, with higher levels of inflammation predicting reduced cooperation among those who experienced stresfful early life circumstances.

The final study found continued support for the hypothesized relationship between inflammation and cooperation. Results revealed that, similar to the pattern of results found for the first two studies, higher infectious disease prevalence, both historically and contemporaneously, predicted less investment in social welfare spending for poorer countries, but not wealthier countries. There was also a main effect of infectious disease prevalence on investment in environmental protection, such that countries with higher disease prevalence invested less in this outcome at each level of wealth. Further, higher infectious disease prevalence predicted greater sociopolitical instability, both through and independently of reduced investment in social welfare and environmental protection. These results suggest that infectious disease burden compromises large-scale cooperation and the integrity of sociopolitical institutions, providing further support for a role of the immune system in regulating cooperation and intergroup psychology.

Together, the present results add to a growing body of research finding that inflammation, even at relatively low levels in otherwise healthy adults, plays a role in regulating important psychological and behavioral processes (Draper et al., 2018; Gassen & Hill, 2019; Lacourt et al., 2018; Lasselin et al., 2017). For example, previous research finds that those with higher levels of inflammation tend to engage in more present-focused decision-making than those with lower levels (Gassen et al., 2019a,b). Given that separate research has linked such decision-making patterns to reduced cooperation (Harris & Madden, 2002; Stevens & Hauser, 2004), it is possible that increased present focus partially mediates the relationship between elevated levels of inflammation and diminished cooperative behavior. Future research is needed to explore this possibility and examine other possible mediators of the link between inflammation and cooperation.

Another potential mediator predicted by the proposed theoretical framework is willingness to expend effort. While cooperation is not typically thought of as requiring effort, it involves exercising self-control to forgo immediate rewards in favor of later benefits, a process that is cognitively taxing (Baumeister & Vohs, 2018; Evans et al., 2016) and that is regulated by energetically costly prefrontal cortical structures (Hyder et al., 2013). Additionally, cooperative relationships are not static, but rather require constant investment to maintain their integrity (Axelrod & Hamilton, 1981; Boyd & Richerson, 2009; Clutton-Brock, 2009; Nowak, 2006; Riolo et al., 2001). For example, a friendship may dissolve if one party does not meet the other's expected investment of time, resources, etc. Given these demands of building and maintaining cooperative relationships, those less willing to expend effort may also be less willing to invest in cooperation. Accordingly, the immunometabolic constraints imposed by elevated inflammatory activity may then decrease cooperation through disincentivizing effortful behaviors (Lacourt et al., 2018; Treadway et al. 2019). Such a possibility is consistent with recent research finding that, in the context of inflammation, individuals are less willing to work for rewards that require high amounts of effort to obtain (Draper et al., 2018).

The results of the current research also contribute to the growing body of work finding that certain individuals are more sensitive to the psychological and behavioral sequelae of inflammation than others (Danese, 2008; Kuhlman et al., 2019; Miller & Cole, 2012). Those exposed to higher levels of early life stress, in particular, appear to exhibit increased sensitivity to the effects that proinflammatory cytokines in the periphery have on mood, learning, and as was found in the current research, cooperation (Kuhlman et al., 2019; Miller & Cole, 2012). While the there is a paucity of research on the mechanisms underlying individual differences in sensitivity to inflammation, differences in blood-brain barrier permeability and density of

microglia in certain brain regions likely play a role (Bilbo & Schwarz, 2012; Calcia et al., 2016; Delpech et al., 2016; Gómez-González & Escobar, 2009; Menard et al., 2017).

An alternative, but not mutually exclusive, explanation is that growing up in a harsh, unpredictable environments engenders lasting metabolic dysregulation that is in some way exacerbated by the immunometabolic shifts induced by inflammation. For example, early life stress may promote greater general reliance on inefficient glucose utilization pathways (e.g., glycolysis), leaving those reared in stressful environments (compared to those raised in less stressful environments) with less cellular energy availability. This stress-dependent gap in cellular energy availability may widen in the context of inflammation, when reliance on glycolysis is further elevated (O'Neill et al., 2016; Wang et al., 2019). Accordingly, individuals exposed to harsh, unpredictable childhood environments may be especially prone to forgoing cooperation when inflammation is elevated, as their need retain available resources is greater than for individuals who grew up in more mild environments. Although speculative, this possibility is consistent with research finding that growing up poor leads to dysregulated eating behavior (Hill et al., 2016; Proffitt Leyva & Hill, 2018) and is prognostic of increased metabolic disorder risk in adulthood (Lehman et al., 2005; Tamayo et al., 2010)

The present results also contribute to recent research into the neurobiology underlying cooperative behavior (e.g., Decety et al., 2004; Emonds et al., 2012; Fett et al., 2012; Rilling et al., 2002). While previous work in this area has focused on the effects that hormones like testosterone (Van Honk et al., 2012) and cortisol (Pfattheicher & Keller, 2014) have on cooperation, the current research suggests that the immune system may also play a role in regulating cooperative behavior. Future research is needed to unravel the complex web of relationships between hormones and immunological signaling proteins that undoubtedly

characterizes individual differences in cooperation. Such research would also benefit from including functional brain imaging measures. In addition to delineating how neuroendocrine and neuroimmune axes contribute to cooperative behavior, studies combining cutting-edge biological and neuroscientific methods also hold promise to yield novel insights into relationships between the body and brain more broadly.

This research has important limitations that should be considered. First, all studies were cross-sectional, limiting the causal conclusions that can be drawn from their results. Firmly establishing that inflammation mechanistically reduces investment in cooperative behavior will require future research utilizing experimental, and ideally, within-subjects designs. This future work may find that the relationship between proinflammatory cytokines and cooperation is path-dependent, such that whether or not cooperation decreases in the context of inflammation depends on the type of inflammation-eliciting stimulus. For example, inflammation induced by a stress manipulation may impact cooperation differently than inflammation induced by vaccination or administration of endotoxin. This question of path dependence could not be answered by the current research.

Future studies are also needed to examine whether changes in infectious disease prevalence precede individual countries' changes in public goods expenditure (i.e., as in Study 3). There was minimal within-country change in these variables of interest across the time points measured in the current. Accordingly, I was unable to apply statistical models useful for uncoupling within- and between-country variability to examine whether changes in a given predictor precede changes in a given outcome (e.g., autoregressive latent trajectory models, latent change score models). Future work investigating time-dependent relationships between

infectious disease prevalence and cooperative investment will thus need to procure data for a longer time range.

Another limitation of the current research is that, between Studies 1 and 2, different proinflammatory cytokines were found to drive the relationship between inflammation and cooperation among those reporting a low childhood SES. Specifically, in Study 1, only significant effects of IL-1β were found (in addition to the significant effects of the latent inflammation factor), and in Study 2, only significant effects of IL-6 were found. The most notable difference between the two studies that may help explain these results is that cytokines were assayed in plasma (i.e., from whole blood) in the first study, and saliva in the second. In plasma, levels of IL-1β are typically much lower than other proinflammatory cytokines because of its important role in initiating inflammatory cascades (Dinarello, 1997, 2011, 2018). Accordingly, elevations in plasma levels of this cytokine may provide a better index of systemic inflammation than levels of either IL-6 or TNF-α. In contrast, salivary levels of IL-6 are typically lower than either TNF-α or IL-1β for a completely different reason. IL-6 is rather large protein relative to the other two cytokines and does not pass easily into saliva (Mozaffari et al., 2018). Thus, large quantities of IL-6 may only accumulate in saliva when plasma levels are exceptionally high, such that IL-6 is a more useful salivary marker of systemic inflammation than the other cytokines. This explanation, however, is merely speculative and additional research is needed to compare the utility of different markers of systemic inflammation measured in different mediums.

These differences in relationships between certain cytokines and cooperation across the two studies also highlight that the current research was limited in that only three cytokines were measured. Immune function is incredibly complex (for a review see Janeway et al., 2005) and

there are many different types of cytokines, each of which have pleiotropic effects (Beneveniste, 1992; Dinarello, 2011, 2018; Medzhitov, 2008). For example, anti-inflammatory cytokines, which promote the resolution of inflammation (see Opal & DePalo, 2000 for review), were not measured in this study. Additional research is needed to investigate how the balance between levels of pro- and anti-inflammatory cytokines influences cooperation, and behavior more generally.

Despite these limitations, the results of the current research suggest that the activities of the immune system may play a role in regulating cooperative behavior. Further, the present results suggest that relationships between inflammation and cooperation may have implications for how nations distribute social goods. The current set of studies lays the groundwork for future research to further examine how social environments and the internal condition of the body interact to influence social cohesion and the coordination of collective action.

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Appendix A

Socioeconomic Status (SES) Scales

Please rate your agreement or disagreement with each statement below:

	Strongly Disagree (1)	Disagree (2)	Somewhat Disagree (3)	Neither Agree Nor Disagree (4)	Somewhat Agree (5)	Agree (6)	Strongly Agree (7)
I grew up in a relatively wealthy neighborhood.	❍	❍	❍	❍	❍	❍	❍
My family usually had enough money for things when I was growing up.	❍	❍	❍	❍	❍	❍	❍
I felt relatively wealthy compared to the other kids in my school.	❍	❍	❍	❍	❍	❍	❍

Please rate your agreement or disagreement with each statement below:

	Strongly Disagree (1)	Disagree (2)	Somewhat Disagree (3)	Neither Agree nor Disagree (4)	Somewhat Agree (5)	Agree (6)	Strongly Agree (7)
I felt relatively poor compared to the other kids at my school.	❍	❍	❍	❍	❍	❍	❍
My parents had significant financial struggles while I was growing up.	❍	❍	❍	❍	❍	❍	❍
There were times in my childhood when I qualified for reduced cost or free lunch at school.	❍	❍	❍	❍	❍	❍	❍

Appendix B

Covariate Measures

Physical Activity

How many hours of exercise do you do in a typical week? (numeric entry)

Energy Need

How many hours has it been since you last had something to eat? (numeric entry)

Sleep

How many hours of sleep do you get in a typical night? (numeric entry)

Recent Illness

Please respond to the following items using the 7-point scale provided:

"I am feeling sick today."

1	2	3	4	5	6	7
Strongly Disagree	Disagree	Somewhat Disagree	Neither Agree Nor Disagree	Somewhat Agree	Agree	Strongly Agree

"I have felt sick within the past week."

1	2	3	4	5	6	7
Strongly Disagree	Disagree	Somewhat Disagree	Neither Agree Nor Disagree	Somewhat Agree	Agree	Strongly Agree

"When was the last time you had a cold or the flu?"

1	2	3	4	5	6	7
Today	A Couple Days Ago	A Week Ago	A couple Weeks Ago	A Month Ago	A Few Months Ago	A Year or More Ago

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 under the mentorship of Dr. Sarah E. Hill, where he received a Master of Science degree in Experimental Psychology in 2017.

Personal Background	Jeffrey William Gassen Born May 4, 1989 in Bakersfield, California Son of Kelly Gassen and Nancy Gassen Married to Alissa Kolm in June 2019
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ABSTRACT

INFLAMMATION, EARLY LIFE STRESS, AND COOPERATION: FROM INDIVIDUALS TO SOCIETIES

by Jeffrey Gassen, M.S., 2017
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Dissertation Advisor: Sarah E. Hill, PhD, Associate Professor of Psychology

In the current research, I combined insights from the evolutionary sciences, experimental economics, and psychoneuroimmunology to examine the relationship between inflammation and cooperation at the individual, group, and population levels. I hypothesized that cooperation would decrease in the context of heightened inflammation because inflammation delineates a bodily context in which an individual's immediate resource needs are relatively high and the likelihood of realizing returns on investment in building social capital is diminished. Further – because previous research finds that early life stress increases sensitivity to the psychological and behavioral sequelae of inflammation – I predicted that the impact of inflammation on cooperation would be greatest for those from more stressful early life environments. Consistent with these predictions, Studies 1-2 both found that for individuals reporting a lower childhood socioeconomic status (SES) – a proxy measure of early life stress exposure – higher inflammation predicted less cooperation. These differences were not found for those reporting a higher childhood SES. Additionally, Study 2 also found that groups with higher collective levels of inflammation cooperated less, regardless of collective exposure to early life stress. Finally, the results of Study 3 revealed that countries with higher infectious disease prevalence – an

environmental context that is linked to elevated inflammatory activity – invested less in public goods and were less sociopolitically stable than countries with lower infectious disease burden. Together, these results provide evidence for the immune system playing a role in regulating cooperative behavior, which may have broader implications for social cohesion and the distribution of public goods.