RUNNING HEAD: Effects of Inflammation on Social Behavior

Beyond Social Withdrawal: New Perspectives on the Effects of Inflammation on Social Behavior

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Abstract

Decades of research in animals and humans show that inflammation is an important regulator of social behavior. While much research in this area has concluded that inflammation causes a *withdrawal* from social interaction, closer examination of the literature reveals that the effects of inflammation on social behavior are much more nuanced. Indeed, while many studies do show that increases in inflammation lead to social withdrawal, other studies show the exact opposite, finding that inflammation leads to an increase in social *approach* behavior. Critically, whether an organism withdraws or approaches when inflamed may depend on the whether the target of the behavior is a close other or a stranger. In the present paper, we review both animal research and our initial research in humans that has utilized experimental manipulations of inflammation and examined their effects on social approach behavior. We argue, based on complementary theoretical perspectives and supporting evidence from the literature, that there are three critical next steps for translational work examining the effects of inflammation on social behavior: (1) We need to study actual social *behavior*, as expressed toward both close others and strangers; (2) We should examine not just the social behavior of the inflamed individual, but also the behavior of others interacting with an inflamed individual; and (3) We must consider the relative increases in inflammation (i.e., higher vs. lower) as a contributor to social withdrawal vs. approach. Ultimately, we urge the field to move beyond a singular focus on inflammation and social withdrawal so that we can develop a more comprehensive understanding of the effects of inflammation on a variety of social behaviors.

Keywords: Inflammation, social behavior, social withdrawal, social approach, social interactions, cytokines

Word count: 3,761

Beyond Social Withdrawal: A Translational Perspective on the Effects of Inflammation on Social Behavior

Inflammation, a critical component of the innate immune system's response to injury and infection, is an established regulator of social behavior[1–4]. Decades of research in animals and humans show that experimentally-induced inflammation (e.g., in response to infection or vaccination) causes reductions in social approach behavior[5]. These findings have led to the conclusion that social withdrawal is part of the set of hallmark symptoms observed in the face of an inflammatory challenge (i.e., "sickness behaviors"[6]). However, recent empirical work suggests that the effects of inflammation on social behavior may be more nuanced than uniform social withdrawal[1]. In fact, under some circumstances, inflammation causes an increase in social *approach* behaviors in animals and increased neural sensitivity to certain positive social stimuli in humans. The current perspective suggests that we need an updated view on the effects of inflammation on social behavior. In particular, we recommend moving beyond a singular focus on social withdrawal to examine a broader repertoire of social behaviors, directed toward a variety of social targets, to better understand how and when inflammation might influence social behavior in humans.

In the present paper, we provide a selective review of the animal and human literature on the effects of inflammation on social behavior beyond social withdrawal (for more extensive reviews, see[1,3,4,7]). We focus exclusively on studies that utilize experimental manipulations of inflammation to establish causality. Our overarching goal is to provide recommendations for future work in this area, which we argue should: (1) study actual social *behavior*, as expressed toward both close others and strangers; (2) examine not just the social behavior of the inflamed individual, but also the behavior of those interacting with an inflamed individual; and (3)

consider relative increases in inflammation (i.e., higher vs. lower) as a contributor to differential social behavior.

1. Theoretical Perspectives on the Effects of Inflammation on Social Behavior

There are compelling theoretical reasons to hypothesize that inflammation might cause an increase in social approach behavior in both the inflamed individual and interacting partner[1,3,8,9]. In particular, the effects of inflammation on social behavior are likely to depend on the social target; inflammation may cause social withdrawal from the majority of social targets, particularly from strangers, but it may also cause social approach toward close others (e.g., family members, romantic partners, other support providers among humans; in animals, a cagemate, littermate, or sexual partner; see Figure 1). The reasons why inflammation may cause social withdrawal from strangers have been well-articulated elsewhere (i.e., it is an adaptive response that conserves metabolic resources, allows for rest/recuperation, and prevents widespread infection[6,10]). From an evolutionary perspective, however, social approach toward close others when experiencing heightened inflammation might also be adaptive. Specifically, when someone is in a vulnerable state, including those states accompanied by acute increases in inflammation (e.g., sickness, social stress), social approach toward close others could trigger help, support, and care for the inflamed individual and further protect them from additional external threats. Indeed, large-scale analyses of social behavior following inflammation suggest social approach toward close others may confer a survival advantage for the inflamed target[11]. The analysis also suggests that behavior of those interacting *with* the inflamed target (i.e., interacting partners) changes in ways that grant a survival advantage, again depending on whether the inflamed target is a close other or not. Thus, both social withdrawal from strangers and approach toward close others could

confer survival benefits for an individual experiencing high levels of inflammation and those in their social networks.

Beyond evolutionary theories, additional theoretical perspectives also offer insight regarding why individuals might approach close others during periods of heightened inflammation. Though not specifically about inflammation, attachment theory originates from behavioral observations of both young children and their caregivers during 'inflamed' periods (i.e., sickness, behavior following social separation) and suggests that social approach can occur during these periods[12–15]. Similarly, theories explaining the relationship between social support and health suggest that social approach is most helpful during times of need, such as during sickness or high-stress periods when inflammation is likely to be elevated[14,16,17]. Taken together, these theories suggest that the default or typical behavior toward close others during acute inflammation might be increased, rather than decreased, social approach behavior. Specifically, inflamed individuals may increase behaviors that increase physical proximity and/or that elicit social connection, care, support, and protection from their close others.

Theories from animal literature make similar suggestions: the effects of inflammation on social behavior depend on the motivational relevance of the target, with approach toward stimuli or targets that meet immediate needs and withdrawal from those who do not[3,8,18]. Interestingly, findings from the animal literature also suggest that the behavior of interacting partners (i.e., those interacting with an inflamed individual) might be altered – though evidence is mixed as to which direction (i.e., approach or withdrawal) behavior might change (see Section 2 for more detail). Thus, theories of both human and animal behavior suggest that inflammation may sometimes cause an increase in social approach behavior, particularly toward close others. We next review the existing empirical literature that supports these theoretical claims.

2. Animal Literature Examining Effects of Inflammation on Social Approach Behavior

The most robust empirical literature showing that inflammation can, under some circumstances, lead to an increase in social approach behavior has utilized non-human animal models. As an early example, the maternal behavior of mice (e.g., pup retrieval, nest building) was measured following injection of lipopolysaccharide (LPS), a bacterial endotoxin that elicits an inflammatory response vs. following injection of saline placebo[19]. A reasonable hypothesis based on the standard conceptualization of sickness behavior is that maternal behavior should decrease among animals exposed to an inflammatory challenge. Instead, maternal behavior was no different between the LPS and placebo conditions. Such effects also extend beyond maternal behavior. A pair of inflammatory challenge studies conducted with rhesus monkeys showed that a relatively low dose of LPS (vs. saline) *increased* close social contact such as clasping arms around another animal[20]. Huddling behavior in rats has also been shown to increase from pre- to post-LPS exposure[21]. And similar effects, with acute inflammatory challenge (vs. placebo) leading to increased or sustained approach behavior, are seen in other species as well (for review see[3]). Thus, there is a sizable animal literature suggesting that, under some circumstances, inflammation leads to social approach behavior, not uniform social withdrawal.

Beyond the effects of inflammation on social behavior of a target animal, a small animal literature has also examined the behavior of conspecifics (i.e., other members of the same species) interacting with an inflamed animal. This is critical, as social interactions necessarily occur between at least two individuals, and there are compelling theoretical reasons why interaction partners might adjust their behavior toward an inflamed target[11]. On the one hand, conspecifics may withdraw from interactions to potentially avoid contracting and spreading an illness, but on the other hand, they may also approach an inflamed individual to provide care and

comfort. One interesting study in this area found that conspecifics behaved similarly toward LPS- and placebo-treated mice: they did not socially withdraw from either[22]. The nature of social interactions did shift, however; those interacting with an LPS-treated animal showed decreased "social information gathering" behavior (i.e., greater muzzle sniffing at the expense of ano-genital sniffing). Such changes in the behavior of the conspecific might be because they were seeking information about the source of inflammation, at the expense of learning about the animal's social status and sexual state. While intriguing, other work adds complexity to the picture. For example, Arakawa and colleagues[23] found no effects of a lower dose of LPS on social exploration by conspecifics, but did observe an increase in "antagonistic behavior" (i.e., decreased sniffing, increased bedding burying) among conspecifics exposed to an LPS-treated mouse. Though small and currently equivocal about directionality, this literature suggests that examining the social behavior of both an inflamed target and those they are interacting with is a promising future direction to further our understanding of the effects of inflammation on behavior in social interactions.

3. Human Literature Examining Effects of Inflammation on Social Approach Behavior

Do the effects of inflammation on social approach behavior observed in animals also translate to humans? Strikingly, very few experimental studies have examined this question, with the exception of preliminary work by authors of this article and colleagues. Our prior work in this area exposed healthy human participants to low dose LPS or placebo prior to completing social tasks in the MRI scanner[24,25]. In one task, participants viewed images of a self-identified close other (e.g., friend, parent) and reported how much they wanted to be around this person; neural responses in motivation-related regions (i.e., the ventral striatum, VS) were also measured[24]. Compared to those in the placebo condition, LPS led to a *greater* desire to be around

the close other, and *greater* VS activity in response to images of their close other, consistent with the animal literature and theories from the human literature. Furthermore, greater increases in the inflammatory cytokine interleukin-6 (IL-6) from baseline to post-LPS administration were associated with higher VS activity to images of the close others, suggesting the acute inflammatory response itself might be driving approach-like neural responses.

In an extension of these initial findings, we found similar effects of LPS on neural responses to positive social feedback, a potential cue of support or care[25]. During another task from the same study, participants received positive, negative, and neutral feedback on a pre-recorded interview from a supposed 'evaluator' who they met in-person prior to the scan (i.e., a confederate). Neural responses to this task were consistent with responses to images of close others, such that LPS led to *greater* neural activity in the VS and ventromedial prefrontal cortex when receiving positive (vs. neutral) feedback. That is, an acute inflammatory challenge enhanced neural responses to receiving positive feedback in regions associated with processing motivationally-relevant outcomes. Thus, inflammation may heighten the motivational relevance of close others and possible care providers (i.e., strangers providing positive feedback), which could ultimately lead to more social approach behavior, rather than social withdrawal.

Beyond our initial work, additional human research that has examined changes in social cognition and behavior in response to inflammation is worth noting. With regard to social cognition, three studies have examined the effects of an inflammatory challenge on emotion recognition; two reported that inflammation caused *decreased* accuracy in recognizing the emotions of others[26,27], while the third found no differences in emotion recognition accuracy among those exposed to LPS vs. placebo[28]. Thus, there is some evidence that inflammation causes a decrease in the ability to accurately identify others' emotions, which could make social

interactions more challenging and thus lead to social withdrawal[26]. However, we note that each of these studies used images of strangers as stimuli (i.e., the standard Reading the Mind in the Eyes task[29]). Given evidence reviewed above suggesting that the effects of inflammation on social behavior may depend on the target, it would be interesting to examine if accuracy in identifying the emotions of close others (vs. strangers) is preserved in the face of an inflammatory challenge, perhaps given the importance of emotion recognition in facilitating communication with care providers[30].

Related to communication, only one known study has examined verbal and non-verbal behavior during an inflammatory challenge[31]. In this creative experiment, video recordings of participants' behavior while alone and while interacting with female medical care providers were acquired during exposure to LPS and placebo. Trained coders blind to condition then coded the videos for a variety of behaviors, including verbal complaining and non-verbal cues, such as sighs and moaning. Participants were more likely to moan and verbally complain when exposed to LPS vs. placebo; further, males specifically showed a greater frequency of sighs and deep breaths compared to females when in a state of heightened inflammation. These results suggest that inflammation may cause an increase in behaviors designed to elicit concern and care from others. It would be interesting for future work to examine if these behaviors are particularly upregulated when in the presence of a close other vs. a professional care provider (e.g., doctor, nurse) vs. a stranger not signaling their intent to provide care.

4. Next Steps for Research on the Effects of Inflammation on Social Behavior

As briefly reviewed above, the effects of inflammation on social behavior are more nuanced than singular social withdrawal. Below, we outline key next steps for research in this area that may also clarify the implications of such effects for human social behavior.

4.1. Examining the effects of inflammation on social *behavior* in humans. From our perspective, the most critical next step in translating prior animal research to humans is to examine the effects of an inflammatory challenge on actual social *behavior*[32]. This is particularly important given that all of the human work in this area to-date has relied on self-reports of social connection or other "proxy measures" of social experience (i.e., performance on computer-based tasks; neural activity), but has not examined observable social behavior. As such, it is largely unclear whether the observed effects of inflammation on social behavior of animals will translate to humans. We see at least two ways this knowledge gap could be addressed in future research. First, behavior toward close others should be integrated into studies examining humans, as, apart from our single study[24], no other studies in humans have measured inflammation-induced changes in behavior toward close others. This represents a significant gap in understanding as a large proportion of social interaction occurs among close others. To accomplish this, researchers can capitalize on methods from the sizeable literature in social psychology that has established reliable techniques for eliciting and quantifying social behavior in dyadic interactions in the laboratory[33,34]. Along these lines, participants exposed to an inflammatory challenge or a placebo could engage in real-time, video-recorded, dyadic interactions with a close other and a stranger. A variety of social approach vs. withdrawal behaviors as displayed by both the inflamed individual and their interaction partners could then be coded from the videos to quantify dyadic social behavior. This methodological approach would provide greater insight into the effects of inflammation on observable social behavior across multiple targets (e.g., close others vs. strangers)[35,36], thus expanding our translational knowledge of the effects of inflammation on social interactions and potentially on the effects of inflammation for the maintenance of relationships over time.

A second exciting direction for future research on social behavior is to utilize ecological momentary assessment (EMA) and/or passive sensing techniques to examine the effects of inflammation on social behavior outside of the laboratory. This would allow for even greater nuance in our understanding of the types of social interactions people may withdraw from vs. approach when experiencing inflammation. Further, inflammation's effects on social approach are sometimes specific to a certain type of social behavior. Thus, among the range of social behaviors measured, certain behaviors might show withdrawal, others might show approach, and still others might show no effects of inflammation[8,20,22]. Utilizing EMA methods would allow for a more robust examination of a range of social behaviors.

To date, only one known study has utilized daily diary methods in the context of an inflammatory challenge paradigm[37]. In this study, participants completed reports of their mood, physical symptoms/sleep, and feelings of social disconnection at the end of each day for seven days prior to receiving the influenza vaccine and for seven days following the influenza vaccine. Changes in mood, symptoms, and social disconnection from pre- to post-vaccine were examined. While informative, this paradigm was limited in that it only asked participants to report once per day (vs. multiple times per day at random intervals common in EMA studies), and did not measure social behavior (i.e., just feelings of social disconnection). As such, future research could use a similar paradigm but assess social behavior multiple times a day, for a few days before and a few days after an inflammatory challenge, such as the influenza or typhoid vaccine. Alternatively, researchers could utilize passive sensing technology as employed via smartphone applications to quantify the amount of time participants spend in social interactions vs. alone following exposure to an inflammatory challenge[38]. Both of these approaches would provide a more complete picture of how inflammation affects social behavior in the "real world" and

would thus move us beyond artificial laboratory-based interactions. This is a critical next step in efforts to translate the animal literature on inflammation and social interactions into humans.

Finally, future work in this area should consider how differences between individuals and characteristics of relationships may moderate associations between inflammation and social behavior, particularly that directed toward close others. For example, some prior work has shown that there are sex differences in the effects of an inflammatory challenge on feelings of social disconnection (which are heightened in females compared to males)[39,40] and perceptions of social standing (which are reduced in males compared to females)[41]. To our knowledge, very little work has examined sex differences in social *behavior* among humans, which will be critical to consider moving forward. Further, an area ripe for future investigation is the consideration of how relationship factors may influence whether an individual approaches vs. withdraws from a close other when inflamed[42]. Along these lines, characteristics of the attachment bond may be an important moderator of the effects of inflammation on behavior toward a close other[43], such that individuals in a securely attached relationship might approach a close other while inflamed, while those with an avoidant bond might withdraw from that close other. Perceived partner responsiveness, or whether someone expects to receive the responsive care and support they need from a close other[44], may also moderate the effects of inflammation on approach vs. withdrawal behavior. To our knowledge, all of these moderators are yet untested in research utilizing inflammatory challenge protocols and examining impacts on social behavior, leaving many exciting opportunities for future studies to incorporate knowledge from relationship science and add greater clarity to the effects of inflammation on social behavior.

4.2. Examining the social behavior of both inflamed individuals and their interaction partners.

A second major next step for research in this area is to examine not only the social behavior of those experiencing heightened inflammation, but also the behavior of the interacting partners (see Figure 2). Some animal research suggests that the behavior of conspecifics is altered when interacting with an LPS-exposed animal[22,23], and a small body of human literature shows that people can detect those exposed to LPS through both visual (images) and olfactory (body odor) cues[45–47]. However, to our knowledge no human work has explored if individuals change their behavior when interacting with a person experiencing heightened inflammation. This is an important avenue for future research, as the implications are that there may be situations in which people withdraw from interactions with an inflamed individual or, in the reverse direction, approach and behave in either antisocial (e.g., aggressive behavior to prevent contracting an illness or prevent someone from spreading an illness), or prosocial (e.g., to provide care and comfort) ways. Future work could utilize the dyadic interaction paradigm discussed in Section 4.1, and code the behavior of the (non-inflamed) interaction partner, noting if behavior is different depending upon if the interaction partner is a close other or a stranger. These are empirical questions in need of examination.

4.3. Considering the magnitude of the inflammatory response. A final, relatively nuanced methodological point to be addressed in future research and that should be considered when taking stock of the literature writ large is that the magnitude of the inflammatory response itself may lead to differential effects on social behavior. For example, animal studies with rhesus monkeys show that in some cases, higher (40 ng/kg of body weight) vs. lower (4 ng/kg of body weight) doses of LPS lead to different magnitude of inflammatory response and thus different patterns of social behavior (relative to placebo)[20]. Our prior work in humans utilized a relatively low-dose of LPS (.8 ng/kg of body weight), but even this low dose leads to a roughly 100-fold

increase in inflammatory cytokines (i.e., ~100 pg/mL of IL-6 at peak[39]). This can be contrasted with vaccination models, which lead to a smaller increase in inflammatory cytokines (i.e., ~1 pg/mL of IL-6 at peak for typhoid vaccination; ~.5 pg/mL of IL-6 at peak for influenza vaccine[37,48,49]). We believe this is an important issue to address moving forward because experimental models for examining the effects of acute illness vs. more low-grade inflammation may need to be developed separately. In other words, changes in social behavior in response to LPS are more likely to map on to how social behavior is influenced by sickness, whereas vaccination models and other lower-grade inflammatory challenge protocols (e.g., rhinovirus[50]) likely map on to how social behavior is influenced by subtle, but meaningful, "everyday" changes in inflammation elicited by stress[51,52]. However, to our knowledge, no studies in humans to date integrate multiple doses of inflammatory challenge within the same study, so that social behavior of participants experiencing high levels of inflammation (i.e., elicited by LPS) vs. lower levels of inflammation (i.e., elicited by influenza vaccine) vs. placebo (i.e., saline) can be compared (though this is a common approach in the animal literature). This is a critical next step because it is feasible that a particular pattern of social behavior (e.g., approach toward close others and withdrawal from strangers) might be adaptive during an acute sickness, but might not occur in response to everyday fluctuations in inflammation.

5. Concluding Comments

In sum, we need to move beyond a singular focus on social withdrawal in the study of the effects of inflammation on social behavior. Future research should consider the whole repertoire of social behaviors that humans engage in, including social approach behaviors, and attend to how inflammation differentially patterns behavior depending on the interaction target (i.e., close other vs. stranger), whether the behavior is carried out by the inflamed individual or their social

interaction partners, and whether the challenge used to elicit an inflammatory response is a model of acute sickness (e.g., LPS) or a model of more everyday change in inflammation (e.g., typhoid/influenza vaccine). These advancements will move us toward a more complete understanding of the effects of inflammation on social behavior, a critical undertaking given the important role that social relationships play in contributing to physical and mental health[53,54]. Translational research of this sort may also ultimately shed light on how subtle but meaningful changes in activation of the immune system shape behavior in close relationships and among new acquaintances alike, adding greater depth to our understanding of the myriad factors that contribute to social well-being.

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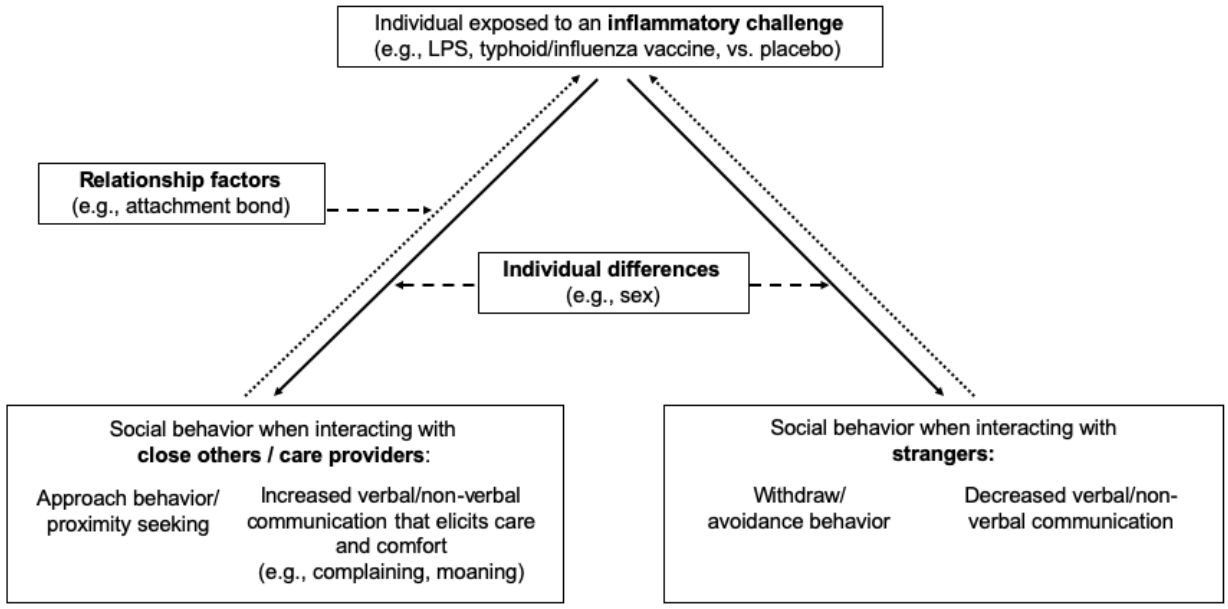

Figure 1. Working conceptual model highlighting the predicted effects of an inflammatory challenge on social behavior, depending on interaction partner. Inflammation is typically understood to induce social withdrawal, but the current perspective urges a more nuanced understanding of the effects of inflammation on social behavior beyond social withdrawal. Solid lines represent relationships for which there is established causal evidence in both animals and humans; dotted lines indicate relationships for which there is currently evidence in animals only and a need for future translational work; dashed lines represent hypothesized moderators in need of study in future research in humans. We highlight that moving forward, researchers studying the effects of inflammation on social behavior should consider if the target of behavior is a close other/care provider, or a stranger. We hypothesize that, based on animal literature and preliminary findings in humans, increases in inflammation (vs. placebo) will cause an increase in approach behavior toward close others, and withdrawal from strangers. This hypothesis should be tested in future research utilizing dyadic interaction paradigms from social psychology in the laboratory setting, and ecological momentary assessment (EMA) methods outside of the laboratory. We also note the bi-directionality of the relationship between an inflamed individual and their interaction partner, and call for future research that examines the behavior of interaction partners, both close others and strangers, when they are interacting with an individual exposed to an inflammatory challenge. Future work should also consider the effects of different types of inflammatory challenge (e.g., LPS, which elicits a large increase in inflammation, vs. typhoid/influenza vaccine, which elicits a smaller increase in inflammation) on social behavior. Finally, we need to examine both individual differences (e.g., sex) and relationship factors (e.g., characteristics of the attachment bond) as moderators of social behavior during an inflammatory challenge for a complete understanding of the effects of inflammation on social behavior. LPS = lipopolysaccharide.

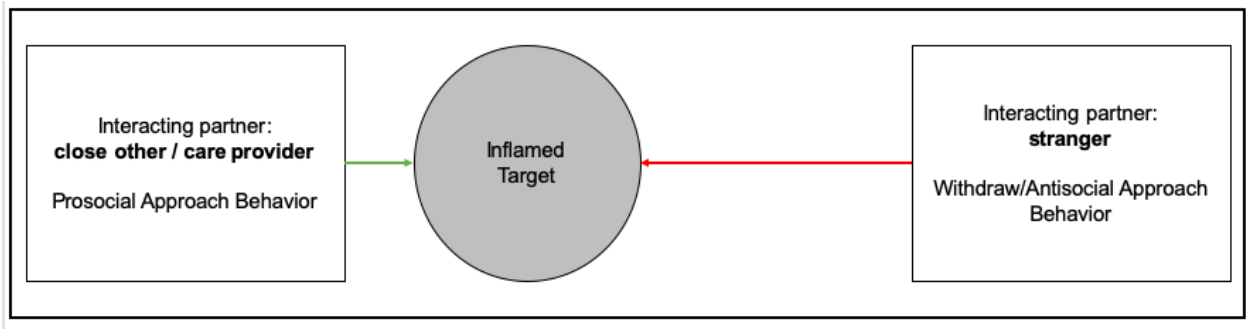

Figure 2. Preliminary hypotheses for future research to test the effects of inflammation on behavior of interacting partners. Although findings from the animal literature are equivocal as to which direction the behavior of those interacting with an inflamed target (i.e., interacting partners) might move, the current theoretical perspective suggests that close others and care providers might *approach* inflamed targets, whereas strangers might *withdraw*, or show *antisocial approach*-type behaviors. That is, close others, including family, romantic partners, or close friends, and care providers might approach an individual exposed to an inflammatory challenge in order to provide the inflamed target with care, protection, support, or connection. Simultaneously, strangers may avoid an inflamed target, or behave antisocially toward them, in order to avoid contracting an illness and/or spreading an illness through a network. Other patterns may emerge for strangers depending on contextual factors, such as the degree to which the inflamed target appears sick. As additional research on the effects of inflammation on interacting partners emerges in humans, the simplistic model pictured above will likely evolve.