Brain, Behavior, and Immunity 112 (2023) 246–253

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

The roles of inflammation, affect, and interoception in predicting social perception

Mallory J. Feldman [a,*], Tatum A. Jolink [a], Gabriella M. Alvarez [a], Nicholas J. Fendinger [b], Monica M. Gaudier-Diaz [a], Kristen A. Lindquist [a], Keely A. Muscatell [a,c,d]

[a] University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[b] New York University, New York, NY, USA
[c] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[d] Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

ARTICLE INFO

Keywords:
Inflammation
Affect
Interoception
Social Perception

ABSTRACT

"Sickness behavior" is an orchestrated suite of symptoms that commonly occur in the context of inflammation, and is characterized by changes in affect, social experience, and behavior. However, recent evidence suggests that inflammation may not always produce the same set of sickness behavior (e.g., fatigue, anhedonia, and social withdrawal). Rather, inflammation may be linked with different behavior across contexts and/or across individuals, though research in this area is under-developed to-date. In the present study (n = 30), we evaluated the influence of affective context and individual differences in difficulty detecting bodily sensations (i.e., interoceptive difficulty) on social perception following an inflammatory challenge. Inflammation was induced using the influenza vaccine and inflammatory reactivity was operationalized as changes in circulating levels of interleukin-6 (IL-6) before the vaccine and approximately 24 h later. Twenty-four hours after administration of the influenza vaccine, we manipulated affective context using a well-validated affect misattribution task in which participants made trustworthiness judgments of individuals with neutral facial expressions following the rapid presentation of "prime" images that were positive or negative in affective content. Interoceptive difficulty was measured at baseline using a validated self-report measure. Results revealed significant interactions between inflammatory reactivity to the influenza vaccine and affective context on social perception. Specifically, individuals with greater inflammatory reactivity were more biased by affective context when judging the trustworthiness of neutral faces. In addition, interoceptive difficulty and affective context interacted to predict social perception such that individuals with greater interoceptive difficulty were more biased by affective context in these judgments. In sum, we provide some of the first evidence that inflammation may amplify the saliency of affective cues during social decision making. Our findings also replicate prior work linking interoceptive ability to the use of affect-as-information during social perception, but in the novel context of inflammation.

1. Introduction

"Sickness behavior" is an orchestrated suite of symptoms that commonly occur in the context of inflammation and is characterized by changes in affect, social experience, and behavior. Sickness behavior, including fatigue, anhedonia, and social withdrawal, is thought to be an adaptive response that promotes rest and recuperation (Hennessy et al., 2014). However, recent work suggests that higher levels of inflammation may not *always* lead to the same behaviors. For example, both animal and human work have shown that an inflammatory challenge sometimes leads to social withdrawal (particularly from unknown conspecifics), but other times leads to social approach (particularly toward close others or care providers) (Hennessy et al., 2014; Inagaki et al., 2015; Jolink et al., 2022). These findings suggest that there may not be a one-to-one relationship between increases in inflammation and increases in sickness behavior such as social withdrawal. Rather, inflammation may be associated with different behaviors and experiences across contexts and individuals (Devlin, Smith & Bilbo, 2022). In the present study, we examined whether inflammation influenced social perceptions differently when those perceptions occurred in positive

* Corresponding author.
E-mail address: Mallory.Feldman@unc.edu (M.J. Feldman).

https://doi.org/10.1016/j.bbi.2023.05.011
Received 19 December 2022; Received in revised form 20 April 2023; Accepted 22 May 2023
Available online 30 May 2023

versus negative contexts and by individuals who struggle more or less at detecting changes in their bodily states (i.e., interoceptive difficulty).

It is well established that one's context influences social perception. As an example, expressionless faces are routinely rated as more positive when seen in the context of positive compared to negative stimuli (a phenomenon called "affect misattribution" or "affective realism", e.g., Anderson et al., 2012; Storbeck & Clore, 2008; Wormwood et al., 2018; Feldman et al., 2022; for review, see Wieser & Brosch, 2012). One oft-overlooked context is one's *internal* context: the physiological state of the body. Even small changes in physiological activity can alter social perceptions. For example, Garfinkel and colleagues demonstrated that fearful faces were detected more easily and rated as more intense when presented during cardiac contraction versus relaxation (2014). Critically, one's internal and external context do not function in isolation, but rather *interact* to inform social perceptions. For example, MacCormack & Lindquist (2019) demonstrated that feelings of hunger shift social perceptions in negative, but not neutral contexts. At least one study has demonstrated that inflammation shifts behavior towards affective stimuli under sad but not neutral mood induction (Benson et al 2017). However, to the best of our knowledge, no prior work has examined these types of effects in the context of social judgment. Here, we merge insights from social psychology and psychoneuroimmunology (Muscatell, 2021), to assess for the first-time whether inflammation and affective context interact to inform social perception.

In addition to context, differences between individuals may also impact how internal sensations such as inflammation are experienced and come to influence social perception and behavior. One important individual difference is interoceptive difficulty. Just like "vision" refers to the sensation and perception of light, "interoception" refers to the sensation and perception of signals from the body. When people "*feel*" their heart racing or their stomach fluttering, they are relying on processes of interoception. Importantly, individuals differ in their ability to sense changes to their internal physiological state. Difficulty sensing and perceiving the body (i.e., interoceptive difficulty) is associated with various mental and physical ailments including depression, anxiety, somatic symptom disorders, and neurodegenerative disease (to name a few; Chen et al., 2021; Khalsa et al., 2018). While little work has examined interoception in the context of inflammation, studies that induce inflammation reliably observe neural activation in limbic and paralimbic regions implicated in representing signals from the body (e.g., anterior insula; Kraynak et al., 2018; Savitz & Harrison, 2018) that correlates with both circulating levels of proinflammatory cytokines (Kraynak et al., 2018) and subjective symptom reports following inflammatory induction (Harrison et al., 2009; Lekander et al., 2016). These findings imply a possible role for interoceptive processes in the translation of peripheral inflammation *into* sickness behavior by the brain. To date, there is no research investigating how interoceptive processes may modulate the influence of peripheral inflammation on social perception and behavior. However, prior work evaluating the influence of interoceptive difficulty and *cardiovascular* activity on social perception provides preliminary evidence that individuals experiencing greater physiological reactivity and who report greater interoceptive difficulty may be more biased by affective context when making social judgments (Feldman et al., 2022, Feldman et al., 2023). Given interoception's hypothesized role in translating peripheral inflammation into mental states and inflammation's well-established role in shaping both affect and social behavior, we set out to test whether individual differences in interoceptive difficulty might interact with inflammation and/or affective context to influence social judgement.

In sum, features of contexts and individuals may independently or interactively shape associations between inflammation and social perception, though very little work has explored this possibility. Here, we examined how affective context and individual differences in interoceptive difficulty interact with inflammation to predict social perception. We manipulated the affective context in which social judgments occurred by adapting a well-validated computer task to examine the influence of affect on social perception. Based on findings that the influenza vaccine reliably elicits a mild inflammatory response (Christian et al., 2013; Radin et al., 2021; Segerstrom et al., 2012; Tsai et al., 2006) and drives subtle within-subject changes in affective processes including mood and reward learning (Boyle et al., 2019; Kuhlman et al., 2018), we manipulated the internal context by administering the influenza vaccine and measuring circulating levels of inflammatory marker interleukin-6 (IL-6) approximately 24 h later. Finally, we measured interoceptive difficulty using a validated self-report measure. This design allowed us to examine interactions between affect, inflammation, and interoception in predicting social perceptions.

2. Methods

2.1. Participants

A sample of 31 young adults were recruited from the University of North Carolina at Chapel Hill (UNC-CH; 80.65% assigned female at birth; 41.94% White, 25.81% Asian/Asian American, 6.45% Black/African American, 6.45% Latina/(o)/ Chicana/(o)/Latin American, 6.45% Middle Eastern, and 12.9% that identified with none of the races presented; M_{age} = 20.29 years, SD_{age} = 1.4 years). Participants were recruited online via social media and emails to class listservs.

All participants were screened for eligibility prior to their participation. Given prior evidence of changes in inflammation and reactivity to the influenza vaccine with age, eligible participants were limited to those between the ages of 18 and 25 (Freund et al., 2010; Irwin, 2014; Lang et al., 2012; McLean et al., 2015; Piber et al., 2019; Sanada et al., 2018). Participants could not have received the annual influenza vaccine or (to their knowledge) have had the seasonal strain of influenza virus. Participants were excluded if they had current or past-history of major mental or physical illness (including history of anxiety or depression), took mood or immune-altering medications (including anti-inflammatory drugs), were currently ill, were habitual users of tobacco products, had Guillain-Barre syndrome, or were allergic to materials in the influenza vaccine. Data was collected between January and April of 2021 during the COVID-19 global pandemic. Participants were therefore also excluded if they self-reported exposure to or current symptoms of COVID-19 (fever; new or worsening cough; new or worsening sore throat; new shortness of breath; loss of taste or smell in the last 5 days; new onset of vomiting or diarrhea; new onset of repeated shaking with chills not related to another medical condition).

2.2. Procedure

Data were collected as part of a larger study designed to examine the relationship between inflammatory reactivity to the influenza vaccine and social and affective processes (see Jolink et al., 2022). This study was approved by a university institutional review board and procedures were carried out in accordance with the Declaration of Helsinki. Consent forms were reviewed with participants online using the video conferencing platform, Zoom. Consent was then submitted in written form. Participants then completed two study sessions approximately 24 h apart. After their first session and before their second, participants were administered the seasonal influenza vaccine.

During the pre-vaccine session, participants completed several questionnaires and behavioral tasks online administered on Qualtrics and Inquisit Web, respectively. Among the questionnaires was a self-report measure of trait interoceptive difficulty, the Interoception Sensory Questionnaire (ISQ; Fiene et al., 2018), and among the tasks was a behavioral measure assessing the influence of affect on perception of faces, the modified affect misattribution procedure (Payne et al., 2005; see below for more detail).

Following the pre-vaccine online session, participants visited the UNC-CH Clinical and Translational Research Center (CTRC) for a non-fasting blood draw ($Time_{earliest}$ = 9:03 AM; $Time_{latest}$ = 12:30 PM; *M*

= 11:14 AM; *SD* = 0:54). Immediately after the blood draw, all participants received the standardized influenza vaccine for the 2020–2021 flu season, which was a single 0.5 mL dose of GSK's Flulaval Quadrivalent ($Time_{earliest}$ = 9:18 AM; $Time_{latest}$ = 12:47 PM; *M* = 11:37 AM; *SD* = 0:55). This vaccine contained four strains of the influenza virus: A/GuangdongMaonan/SWL1536/2019 (H1N1) CNIC-1909, A/Hong Kong/2671/2019 (H3N2) NIB-121, B/Washington/02/2019 (B-Victoria lineage), and B/Phuket/3073/2013 (B-Yamagata lineage).

The post-vaccine session took place approximately 24 h later ($M_{vaccine\ delay}$ = 23:45, $SD_{vaccine\ delay}$ = 1:36)– when levels of IL-6 have been shown to peak following influenza vaccine administration (Radin et al., 2021). Participants completed the same modified affect misattribution task acquired pre-vaccine during the post-vaccine online session, before again visiting the CTRC for a second non-fasting blood draw ($Time_{earliest}$ = 8:35 AM; $Time_{latest}$ = 2:36 PM; *M* = 11:23 AM; *SD* = 1:15 AM)[1]. Participants were then debriefed and compensated $85 for their time and effort. Additional details about the study protocol can be found in (Jolink et al., 2022).

Open Practices Statement. Data and full code for all analyses and plots are available at [https://osf.io/8hsg9/].

3. Measures

3.1. Inflammatory reactivity

At both blood draws, approximately 6 mL of blood were collected via venipuncture and stored on ice in vacutainer EDTA tubes for the duration of study sessions. Following study sessions, blood samples were centrifuged for 10 min at 1500 RPM to isolate plasma. Once centrifuged, plasma was pipetted into cryovials and stored in a −80C freezer until all data had been collected. One blood sample hemolyzed and so this sample was excluded from all analysis[2]—resulting in a final sample size of 30 participants. Final plasma samples were assayed for IL-6 in triplicate using R&D Systems' ELLA automated assay system for implementing Simple Plex immunoassays. Two samples had undetectably small concentrations of IL-6. Consequently, the value of IL-6 for these samples was replaced with the lower limit of detection for the assay, 0.28 pg/mL IL-6. The intra-assay coefficients of variation were all < 6.55% suggesting good precision of the immunoassay test results. Samples were run on two different plates without controls so inter-assay CVs were unavailable. This prevents us from being able to evaluate our plate-to-plate consistency. However, the impact of any variability on results is partially mitigated given that samples were randomized across plates. Inflammatory reactivity to the vaccine was computed as the change in log-transformed concentrations of circulating IL-6 from pre- to post-vaccine.

4. Trait interoceptive difficulty

Interoceptive difficulty was measured using the 20-item Interoception Sensory Questionnaire (ISQ; Fiene et al., 2018). This questionnaire was originally designed to measure alexisomia in adults on the autism spectrum. Alexisomia reflects the tendency to experience confusion about bodily states unless they are extreme. Example scale items of the ISQ include, "I find it difficult to identify some of the signals that my body is telling me (e.g., If I'm about to faint or I've overexerted myself)" and, "Sometimes, when my body signals a problem, I have difficulty working out what the problem might be." Participants indicated the extent to which each item was true of them on a scale ranging from 1 ("not at all true of me") to 7 ("very true of me"). The ISQ demonstrated excellent internal reliability in our data (*alpha* = 0.96). Responses on all items were summed (*M* = 44.19, *SD* = 21.74), such that higher scores on this scale reflected greater self-reported difficulty identifying bodily sensations.

5. Affective context

To study the influence of affective context on social perception, we used a modified version of the well-validated affect misattribution procedure (AMP; Payne et al., 2005). The AMP is used to study affect misattribution. Affect misattribution occurs when people's affective reactions to a valenced prime "spillover" to influence ratings of a neutral target. In the traditional AMP, participants view affective primes followed by neutral targets (e.g., symbols or inanimate objects). These targets are then rated on their perceptual pleasantness. Importantly, participants are told to ignore affective primes while evaluating the targets. We modified the AMP to better resemble tasks used in prior work interested in affect-based decision-making during social perception by replacing the neutral targets with expressionless (i.e., structurally neutral) faces (Siegel et al., 2018; Wormwood et al., 2018; Feldman et al., 2022). Thus, this task allowed us to assess how participants used incidental affective contextual cues to inform perceptions of structurally neutral faces.

At the beginning of the AMP, participants were given the following instructions: "This is a task examining how people make simple but quick judgments. In a moment, you will see a pair of pictures flashed one after the other, the first one being a random image and the second one being an image of a face. The first image simply serves as a warning signal for the second. *That is, the first image has nothing to do with the second picture of the face*" (italics added here for emphasis).

On each trial of the task, participants saw either a positive (e.g., a puppy), negative (e.g., a fire), or neutral (e.g., a paperclip) image for 75 ms, a blank screen for 125 ms, a structurally neutral face for 100 ms, and then a pattern mask consisting of black and white "noise." Participants were then asked to rate the trustworthiness of the face they just saw on a five-point scale ranging from 1 ("very untrustworthy") to 5 ("very trustworthy") (see Fig. 1; task files are available at [https://osf.io/8hsg9/]). Trustworthiness ratings were chosen given that perceived trustworthiness is a good proxy for valence evaluation (Oosterhof & Todorov, 2008; Sutherland et al., 2013) and correlates with general approach and avoidance behaviors (Fenske et al., 2005; Todorov, 2008). To increase ease of interpretation (given that ratings were made on a bipolar scale), responses were converted to a −2 (very untrustworthy) to 2 (very trustworthy) scale after data collection was complete.

Thirty non-social positive, negative, and neutral images were chosen from the Open Affective Standardized Image Set (Kurdi et al., 2017) and the Complex Affective Scene Set (Weierich et al., 2019). Images were chosen to ensure significant differences in normative valence across affective conditions. Image file names, norms, and relevant descriptive and inferential statistics are available at [https://osf.io/8hsg9/]. All face stimuli were White and Female-presenting and were taken from the Chicago Face Database (Ma et al., 2015).

The entire task took about 5 min to complete. Participants saw each affective image once and each face three times: once preceded by a positive image, once preceded by a negative image, and once preceded by a neutral image (n_{trials} = 90). This ensured that any differences in trustworthiness ratings across affective conditions could not be attributed to features of the target faces. Presentation of all prime and target stimuli were randomized and counterbalanced.

[1] Nearly all sessions took place between 6:30 AM and 1 PM to control for diurnal variation in IL-6 levels. On one occasion, a winter storm caused the CTRC to shut down until 1:00 PM. Consequently, one participant provided their blood sample at 2:36 PM. On another occasion, a participant missed their second online session and was rescheduled for 1:15 PM after their second blood draw.

[2] The hemolyzed sample was retained and prepared for analyses but ultimately did not have enough usable plasma for assay.

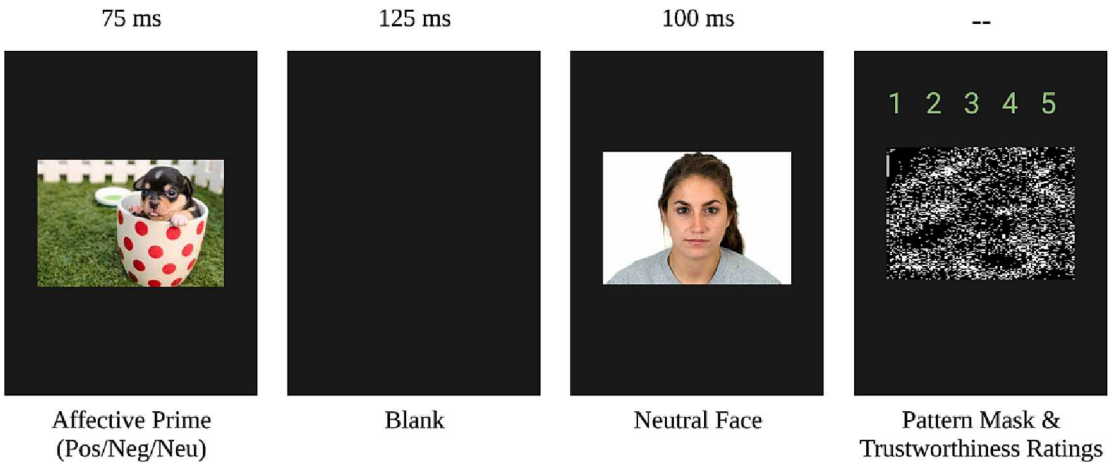

Fig. 1. Example trial from the modified affect misattribution task. Figure made with biorender.com. Example prime taken from the OASIS database (Kurdi et al., 2017). Neutral face used with permission from the Chicago Face Database (Ma et. al., 2015).

5.1. Data analysis

IL-6 was right-skewed and thus log-10 transformed in all analyses. To check whether the influenza vaccine was associated with significant changes in inflammation, we performed a two-tailed paired samples *t*-test assuming unequal variance comparing circulating levels of IL-6 before and after the influenza vaccine. Variance was assumed unequal due to a significant Levene's test for homogeneity of variance; $F(1, 5488) = 65.85$, $p < 0.001$. Because pre-vaccine levels of IL-6 were strongly correlated with IL-6 reactivity ($r = -0.62$), models assessing inflammatory reactivity also controlled for baseline IL-6 (Llabre et al., 1991; O'Connell et al., 2017).

All analyses were conducted using hierarchical linear modeling (HLM), which allowed us to avoid aggregation and to model individual trials nested within the same participant (Baayen et al., 2008). To control for baseline trustworthiness ratings of target faces, trials from the pre-vaccine and post-vaccine sessions were matched within-subject based on prime condition and target face. This allowed us to predict participants' trustworthiness ratings post-vaccine, controlling for pre-vaccine trustworthiness ratings, on a trial-by-trial basis.

Analyses were run using the lme4 package in R (Bates et al., 2015). Note that this package uses the Satterthwaite method for computing denominator degrees of freedom. Standardized betas were computed using the effectsize function from the effectsize package in R (Ben-Shachar et al., 2020). First, we evaluated task data for evidence of an overall affect misattribution effect (i.e., that trustworthiness ratings of faces tracked the valence of affective prime images). Trustworthiness ratings from the post-vaccine session were treated as the criterion variable and participant ID as the random intercept (ICC = 0.12). Affect condition in the modified-AMP (positive vs negative vs neutral) and trustworthiness ratings from the pre-vaccine session were included as level 1 fixed effects. Next, IL6-reactivity and ISQ scores were added as level 2 fixed effects. We tested all two- and three-way interactions between affect condition, IL-6 reactivity, and ISQ. Significant interactions were probed using the *interactions* package (version 1.1.5) in R (Long, 2019). Finally, Body Mass Index (BMI)[3] and Assigned Sex at Birth (ASAB) were added to the model as level 2 covariates (O'Connor et al., 2009). All continuous predictors at levels 1 and 2 were grand mean centered (Enders & Tofighi, 2007). Additional exploratory models were run controlling for (1) time of day for both the pre- and post- vaccine blood draws and (2) time between vaccine administration and post-vaccine blood draw. Effects were robust to the addition of these covariates. Full model summaries for analyses including these covariates can be found in the Supplemental Material (Supplemental Tables S8-S9).

Diagnostics revealed residuals that were approximately normally distributed and homoscedastic, consistent with model assumptions. Robust standard errors are presented in supplementary tables (see supplemental materials).

Power: Independent empirical data was not available for *a priori* power simulations. As such, power simulations were run post hoc using estimated effect sizes. This approach has limitations when it comes to providing accurate power estimates for the data presented herein (Hoenig & Heisey, 2001). However, our data can serve as an independent empirical data source for future research (Hoenig & Heisey, 2001; Lenth, 2007).

Power simulations were run using the mixedpower package in R (Kumle et al., 2021) using the methods described in (Kumle et al., 2021). Mixedpower allowed us to estimate several fixed effects and their interactions simultaneously at different sample sizes. We simulated all fixed effects for sample sizes ranging from 20 to 100 in steps of 10. Five hundred datasets were simulated at each sample size (4,500 simulated datasets in total). Full code for simulations can be found at [https://osf.io/8hsg9/]. Unsurprisingly, fixed effects estimated at level 1 (condition, pre-vaccine trustworthiness ratings) were well powered (βs ranged from 0.87 to 1.00). However, fixed effects at level 2 were underpowered (βs for ISQ and IL-6 reactivity ranged from 0.19 to 0.22). Cross-level interactions achieved slightly higher power (βs ranging from 0.12 to 0.51; full simulation results are available in the supplemental materials).

6. Results

As reported in Jolink et al 2022, the influenza vaccine was associated with a significant increase in inflammation. Concentrations of log-transformed IL-6 (pg/mL) were significantly higher after ($M = 0.38$, $SD = 0.26$) compared to before the influenza vaccine ($M = 0.11$, $SD = 0.34$; $t(29) = 5.18$, $p < 0.001$). Correlations and density plots for continuous variables can be found in the supplemental materials (Supplemental Figures S1-S2). Full tables for mixed models can also be found in the supplemental materials (Supplemental Tables S2-S7).

We first looked solely at lower-level fixed effects, regressing affect condition (positive vs negative vs neutral) on trustworthiness ratings, controlling for pre-vaccine task performance (Supplemental Tables S2-S3). Replicating the standard affect misattribution effect, analyses

[3] We controlled for BMI based on published recommendations. However, we acknowledge that BMI is a problematic metric. Factors such as age, sex, race/ethnicity, and muscle mass can all influence the extent to which BMI provides an accurate measure of body fat. For more information on the ethical and empirical implications of using BMI, see https://www.cdc.gov/obesity/downloads/bmiforpactitioners.pdf.

revealed a main effect of condition; $F(2, 2668) = 43.821$, $p < 0.001$ (see Supplemental Figure S3). Participants rated structurally neutral target faces as more trustworthy when paired with a positive image compared to when paired with a neutral [$b = 0.25$, $\beta = 0.20$, *95% CI* = [0.12, 0.29], $t(2667) = 4.75$, p < 0.001] or negative [$b = 0.50$, $\beta = 0.40$, *95% CI* = [0.32, 0.49], $t(2669) = 9.36$, $p < 0.001$] image. Likewise, participants rated structurally neutral target faces as more trustworthy when paired with a neutral compared to a negative image; $b = 0.25$, $\beta = 0.20$, *95% CI* = [0.12, 0.29], $t(2667) = 4.71$, $p < 0.001$. Unsurprisingly, we also found a significant main effect of baseline task performance on trustworthiness ratings post-vaccine; $F(1,2695) = 89.77$, $p < 0.001$. That is, participants pre-vaccine trustworthiness ratings positively predicted their post-vaccine trustworthiness ratings; $b = 0.19$, $\beta = 0.18$, *95% CI* = [0.14, 0.21], $t(2695) = 9.48$, $p < 0.001$.

Next, we added focal upper-level fixed effects into the model (Table 1**;** Supplemental Tables S4-S5). The addition of these fixed effects resulted in a significant improvement in model fit; $\chi 2(10) = 24.50$, $p < 0.01$. The main effects of affect condition [$F(2,2662) = 43.42$, $p < 0.01$] and baseline task performance [$F(2,2686) = 87.91$, $p < 0.01$] remained significant. Neither IL6-reactivity (main effect), interoceptive difficulty (ISQ; main effect), nor their two-way interaction significantly predicted trustworthiness ratings (*ps* > 0.28).

The two-way interaction between affect condition and IL6-reactivity was significant; $F(2, 2661) = 4.51$, $p = 0.01$. Specifically, as IL-6 reactivity increased, the difference between trustworthiness ratings in the positive and negative affect conditions [$b = 0.47$, $\beta = 0.10$, *95% CI* = [0.02, 0.19], $t(2661) = 2.27$, $p = 0.02$] and between ratings in the neutral and negative affect conditions [$b = 0.59$, $\beta = 0.13$, *95% CI* = [0.04, 0.21], $t(2661) = 2.84$, $p < 0.01$] grew larger. This suggests that participants with *greater* IL-6 reactivity were *more* biased by any affective image when rating the trustworthiness of structurally neutral target faces. Descriptively, the greatest non-zero slope occurred in the negative condition, suggesting that the interaction between affect condition and IL6-reactivity may have been largely driven by decreases in perceived trustworthiness with increasing IL-6 reactivity in the negative affect condition. A simple slopes depiction of this interactions is given in Fig. 2**.**

The two-way interaction between affect condition and ISQ was also significant; $F(2, 2661) = 3.13$, p = 0.04. Specifically, as interoceptive difficulty increased, the difference between ratings in the positive and negative affect condition grew larger; $b = 0.01$, $\beta = 0.11$, *95% CI* = [0.02, 0.20], $t(2661) = 2.36$, $p = 0.02$. This suggests that participants with *greater* interoceptive difficulty were *more* biased by affective images when rating the trustworthiness of structurally neutral target faces. As before, the greatest non-zero slope occurred in the negative condition, suggesting that the interaction between affect condition and interoceptive difficulty may have been largely driven by decreases in perceived trustworthiness with increasing interoceptive difficulty in the negative affect condition. A simple slopes depiction of this interactions is given in Fig. 2**.**

Finally, the three-way interaction between affect condition, IL-6 reactivity, and ISQ was not significant; $F(2, 2661) = 1.67$, $p = 0.19$; see Supplementary Figure S4.

All effects were robust when covariates were added to the model (Supplemental Tables S6-S7). Neither assigned sex at birth (ASAB) nor BMI were significant predictors of trustworthiness ratings. Further, the addition of these fixed effects did not significantly improve model fit; $\chi^2(2) = 0.31$, $p = 0.86$.

Table 1
Type III Analysis of Variance Table with Satterthwaite's method for fixed effects.

Predictor	Sum Sq	Mean Sq	*DF*	*F*	*P*
Affect Condition (Cond)	**108.84**	**54.42**	**(2, 2661.56)**	**43.42**	**0.00**
IL-6 Reactivity (IL-6 React)	0.00	0.00	(1, 24.77)	0.00	0.98
Interoceptive Difficulty (ISQ)	1.16	1.16	(1, 24.77)	0.93	0.34
Baseline Task Ratings	**110.19**	**110.19**	**(1, 2685.94)**	**87.91**	**0.00**
Baseline IL-6	0.30	0.30	(1, 24.77)	0.24	0.63
Cond × IL-6 React	**11.30**	**5.65**	**(2, 2660.83)**	**4.51**	**0.01**
Cond × ISQ	**7.85**	**3.93**	**(2, 2660.84)**	**3.13**	**0.04**
IL-6 React × ISQ	1.53	1.53	(1, 24.86)	1.22	0.28
Cond × IL-6 React × ISQ	4.20	2.10	(2,2660.88)	1.67	0.19

Note. IL-6 is log transformed with base 10, raw scale in pg/ml. Interoceptive difficulty rated on 1 –7 scale and summed (0 –140). All continuous predictors are grand mean centered. LL and UL indicate the lower and upper limits of a confidence interval, respectively. Significant effects are bolded.

7. Discussion

In the present study, we evaluated the influence of affective context, inflammation, and interoceptive difficulty on social perception in the context of an inflammatory challenge. We replicated the standard affect misattribution effect whereby structurally neutral target faces were perceived as significantly more trustworthy when paired with positive, compared to negative affective images. However, this main effect was contextualized by small but significant interactions with both inflammatory reactivity and interoceptive difficulty, suggesting that increases in inflammation and difficulty perceiving and making sense of bodily sensations each influence the extent to which affect is used to inform social perception. Together, this work advances our knowledge of how individual differences in inflammation and interoceptive difficulty may interact with affective cues in one's external environment to influence social perception.

While the main effect of inflammatory reactivity on trustworthiness ratings was non-significant, inflammatory reactivity interacted with affective context such that individuals with greater inflammatory reactivity to the influenza vaccine were *more* biased by affective context. This is consistent with research linking inflammation to sensitivity toward both rewarding and threatening social stimuli (e.g., both positive *and* negative feedback; (Muscatell et al., 2016; Irwin & Eisenberger, 2017). Although the slope of the negative affect condition did not differ significantly from zero, descriptively, effects appeared particularly potent for faces presented in a negative affective context. This observation is consistent with previous work demonstrating a "negativity bias" following inflammatory induction using experimental endotoxemia and typhoid vaccine (e.g., Hansson et al 2021; Harrison et al 2009; Harrison et al 2016; Benson et al 2017).

Our findings extend this work to show that inflammatory reactivity may interact with affective cues, more generally, to influence whether others are seen as socially threatening or affiliative. If individuals are more sensitive to affective information when experiencing higher levels of inflammation, this may suggest that affect is a more proximal mechanism driving other context-dependencies in sickness behavior. For example, experiences of positive and negative affect reliably motivate approach and avoidance behaviors, respectively (Phaf et al., 2014). If social support figures are perceived more positively or are more often encountered in positive environments and if strangers are perceived more negatively or are more often encountered in uncertain or negative environments – then this may help explain *why* inflammation draws humans toward social support figures and away from strangers (Jolink et al., 2022; Muscatell & Inagaki, 2021). Future research should explore this possibility directly by manipulating the affective context that strangers and support figures are encountered in.

Contrary to our hypotheses, neither the main effect of interoceptive difficulty nor the interaction between inflammatory reactivity and interoceptive difficulty achieved statistical significance. However, we did find evidence that individuals with greater self-reported interoceptive difficulty were *more* biased by affective information. Again, descriptively, this effect seemed particularly potent for faces presented

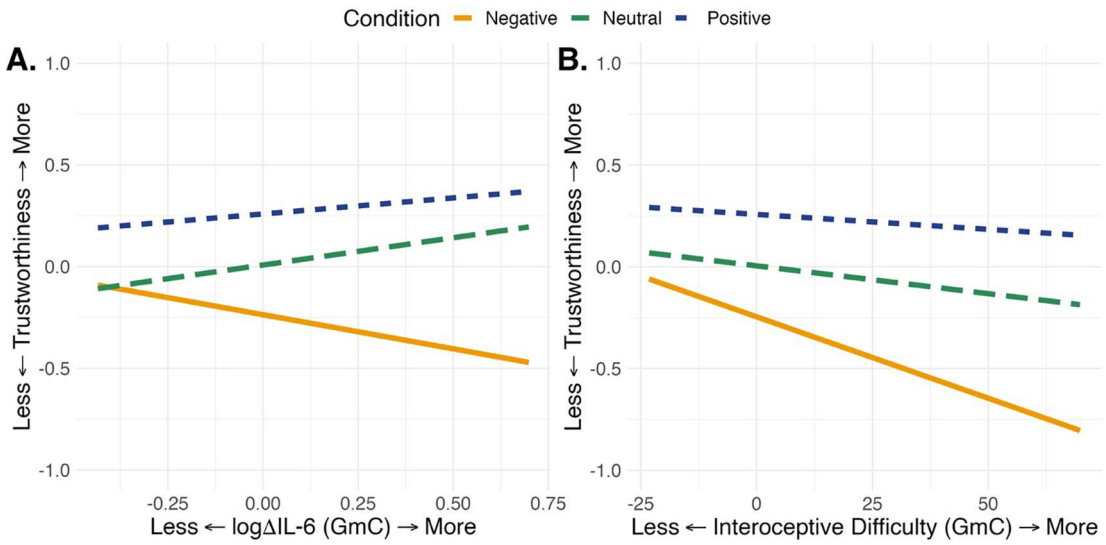

Fig. 2. Two-way interactions between log transformed IL-6 reactivity (raw scale in pg/ml) and affect condition (**panel A**) and between interoceptive difficulty (possible range = 0–140) and affect condition (**panel B**). Continuous predictors are grand mean centered (GmC). Trustworthiness ratings ranged from −2 ('very untrustworthy') to 2 ('very trustworthy'). Dashed lines along the × axes indicate variable distributions.

in a negative affective context. The evidence linking interoceptive ability and emotion is somewhat mixed—with most evidence supporting a role for interoceptive ability in the experience of arousal (activation versus deactivation) but not valence (pleasantness versus unpleasantness; Barrett, 2004). However, some studies have reported evidence for a "negativity effect" such that individuals higher in interoceptive ability experience more general levels of intense negative (but not positive) affect (Critchley et al (2004). More research is needed to better elucidate the boundary conditions of these effects.

Generally, the fact that individuals with greater self-reported interoceptive difficulty were more biased by affective information in our sample is consistent with prior research on interoception in the context of affect misattribution. According to the Misattribution Hypothesis (Payne et al., 2005), affect misattribution occurs when individuals struggle to disentangle their affective responses to incidental affective cues in the environment from their affective responses to a social target. Consistent with this idea, affect misattribution effects are amplified when either source ambiguity or target ambiguity are increased (Oikawa et al., 2011; Payne et al., 2016; Ruys et al., 2012). It is possible that individuals with greater interoceptive difficulty experience greater difficulty disentangling the source of their own affective responses and thus are more biased by affective context during social perception. This is further supported by evidence tying selfhood to the neural monitoring of visceral and tissue functions (Allen & Tsakiris, 2018; Bebo-Rebelo & Tallon-Baudry, 2018). Specifically, individuals with greater interoceptive difficulty may be more likely to classify sensations as being world- vs self- generated. For example, in one study researchers found that individuals with lesser sensitivity to changes in heartbeat sensations were more likely to confound their own affective state with another's during social judgment (von Mohr et al., 2021). The present results contribute to this growing body of literature suggesting that interoceptive difficulty may exacerbate the extent to which individuals use "affect as information" during social decision making.

While this study contributes meaningfully to our nascent understanding of the relationship between inflammation and socio-affective processes, it is not without limitations. First, this was a preliminary study, and our small sample size decreased our power to detect small effects such as potential three-way interactions. Other larger studies have reported significant three-way interactions between affective context, cardiovascular reactivity, and objective measures of interoceptive difficulty such as a heartbeat detection task (Feldman et al., 2023). Here we did not use an objective measure of interoceptive difficulty and instead had participants self-report interoceptive difficulty on the ISQ. The ISQ has good predictive validity (Fiene et al., 2018), however it is not uncommon for self-report measures of interoception to diverge from behavioral measures of interoceptive sensitivity such as heartbeat detection tasks (Garfinkel et al., 2015). Sensitivity for subtle physiological changes (such as those induced by a mild inflammatory challenge) may thus be better captured using behavioral measures that tap ability below reportable awareness. Unfortunately, there currently is no "objective" measure of inflammatory interoception, as most of the research on interoceptive ability has focused on cardiovascular sensitivity. Future research should work to create objective measures of inflammatory interoceptive ability. Additionally, the ISQ is a *trait* measure of interoceptive ability. Several studies have demonstrated that state-based changes in interoception can occur (Schandry et al., 1993; Wittkamp et al., 2018)– including within the context of inflammation (Zheng et al., 2021). This evidence motivates future work using state-based measurement of interoceptive ability in the context of inflammation.

Second, demographic specificities of our sample limit its generalizability. Given well-established age differences in levels of inflammation and reactivity to vaccines, our sample was constrained to individuals ages 18–25. Our sample also skewed Female (81%) and White (42%) and consisted largely of undergraduate college students from the southern United States. Future work must replicate these effects in a larger and more representative sample. Relatedly, our affect misattribution procedure only used White and Female-presenting faces as stimuli. A homogenous face set was chosen for this pilot study to increase experimental control. However, this choice undeniably reduces the ecological validity and generalizability of our findings. Future studies should use samples and stimuli with greater diversity.

Finally, by using the influenza vaccine to induce inflammation, we also limited the range of inflammatory reactivity in our sample compared to other inflammatory challenge paradigms (e.g., Lipopolysaccharide or LPS). Additionally, because this study used a within-subjects design without placebo control, we are unable to tease out causal effects within versus between subjects. Future studies should replicate these effects using other inflammatory challenge models and placebo controls to elicit greater increases in inflammation and enable more precise causal inference.

In conclusion, we found evidence that both inflammation and interoceptive difficulty independently interact with affective context to

predict social perceptions. This provides some of the first evidence that inflammation may amplify experiences of affective realism – heightening sensitivity to both positive and negative affective cues— during social judgment. In this way, inflammatory cues from the body may interact with affective cues from the environment to serve as a biological compass – moving us towards social resources (i.e., social allies or social support figures) and diverting us away from possible social threats.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data and full code for all analyses and plots are available at [https://osf.io/8hsg9/]

Acknowledgements

The authors would like to thank the participants who generously gave their time.

Author Contributions

MJF and KAM developed the research idea. MJF, TAJ, NJF, GMA, MMG, and KAM developed the experimental design and collected the data. MJF analyzed the data. MJF, KAL, and KAM cowrote the article with input from other authors.

Funding

This work was supported by the Ann Rankin Cowan Award for High Impact Research awarded to Dr. Muscatell. The composition of this manuscript was supported by a National Science Foundation CAREER Grant (BCS2047344 awarded to Dr. Muscatell) and National Science Foundation Graduate Research Fellowships (DGE-189302 awarded to Nicholas Fendinger and Gabriella Alvarez). Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation. Furthermore, the authors would like to thank the staff and support of UNC-CH's Clinical and Translational Research Center, which is supported by the National Center for Advancing Translational Sciences (NCATS; UL1TR002489).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.05.011.

References

Allen, M., Tsakiris, M., 2018. The body as first prior: Interoceptive predictive processing and the primacy of self-models. In: Tsakiris, M., Preester, H.D. (Eds.), The Interoceptive Mind: From Homeostasis to Awareness. Oxford University Press.

Anderson, E., Siegel, E., White, D., Barrett, L.F., 2012. Out of sight but not out of mind: Unseen affective faces influence evaluations and social impressions. Emotion 12 (6), 1210–1221. https://doi.org/10.1037/a0027514.

Baayen, R.H., Davidson, D.J., Bates, D.M., 2008. Mixed-effects modeling with crossed random effects for subjects and items. Journal of Memory and Language 59 (4), 390–412. https://doi.org/10.1016/j.jml.2007.12.005.

Barrett, L.F., 2004. Feelings or Words? Understanding the Content in Self-Report Ratings of Experienced Emotion. Journal of Personality and Social Psychology 87 (2), Article 2. https://doi.org/10.1037/0022-3514.87.2.266.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting Linear Mixed-Effects Models Using lme4. En 67 (1), 1–48. https://doi.org/10.18637/jss.v067.i01.

Bebo-Rebelo, M., Tallon-Baudry, C., 2018. Interoceptive signals, brain dynamics, and subjectivity. In: Tsakiris, M., De Preester, H.D. (Eds.), The Interoceptive Mind: From Homeostasis to Awareness. Oxford University Press.

Ben-Shachar, M.S., Lüdecke, D., Makowski, D., 2020. effectsize: Estimation of Effect Size Indices and Standardized Parameters. Journal of Open Source Software 5 (56), 2815. https://doi.org/10.21105/joss.02815.

Benson, S., Brinkhoff, A., Lueg, L., Roderigo, T., Kribben, A., Wilde, B., Witzke, O., Engler, H., Schedlowski, M., Elsenbruch, S., 2017. Effects of acute systemic inflammation on the interplay between sad mood and affective cognition. *Translational*. Psychiatry 7 (12). https://doi.org/10.1038/s41398-017-0043-0.

Boyle, C.C., Kuhlman, K.R., Dooley, L.N., Haydon, M.D., Robles, T.F., Ang, Y.-S., Pizzagalli, D.A., Bower, J.E., 2019. Inflammation and dimensions of reward processing following exposure to the influenza vaccine. Psychoneuroendocrinology 102, 16–23. https://doi.org/10.1016/j.psyneuen.2018.11.024.

Chen, W.G., Schloesser, D., Arensdorf, A.M., Simmons, J.M., Cui, C., Valentino, R., Gnadt, J.W., Nielsen, L., Hillaire-Clarke, C.S., Spruance, V., Horowitz, T.S., Vallejo, Y.F., Langevin, H.M., 2021. The Emerging Science of Interoception: Sensing, Integrating, Interpreting, and Regulating Signals within the Self. Trends in Neurosciences 44 (1), 3–16. https://doi.org/10.1016/j.tins.2020.10.007.

Christian, L.M., Porter, K., Karlsson, E., Schultz-Cherry, S., Iams, J.D., 2013. Serum Proinflammatory Cytokine Responses to Influenza Virus Vaccine among Women during Pregnancy versus Non-Pregnancy. Am J Reprod Immunol 70 (1), 45–53.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nature Neuroscience 7 (2), 189–195. https://doi.org/10.1038/nn1176.

Devlin, B.A., Smith, C.J., Bilbo, S.D., 2022. Sickness and the Social Brain: How the Immune System Regulates Behavior across Species. Brain, Behavior and Evolution 97 (3–4), 197–210. https://doi.org/10.1159/000521476.

Enders, C.K., Tofighi, D., 2007. Centering predictor variables in cross-sectional multilevel models: A new look at an old issue. Psychological Methods 12 (2), 121–138. https://doi.org/10.1037/1082-989X.12.2.121.

Feldman, M.J., Siegel, E., Barrett, L.F., Quigley, K.S., Wormwood, J.B., 2022. Affect and Social Judgment: The Roles of Physiological Reactivity and Interoceptive Sensitivity. Affective Science 3 (2), 464–479. https://doi.org/10.1007/s42761-022-00114-9.

Feldman MJ, MacCormack JK, Bonar AS, Lindquist KA. Interoceptive ability moderates the effect of physiological reactivity on social judgment. Emotion. 2023 Mar 23. doi: 10.1037/emo0001210. Epub ahead of print. PMID: 36951718.

Fenske, M.J., Raymond, J.E., Kessler, K., Westoby, N., Tipper, S.P., 2005. Attentional inhibition has social-emotional consequences for unfamiliar faces. Psychological Science 16 (10), 753–758.

Fiene, L., Ireland, M.J., Brownlow, C., 2018. The Interoception Sensory Questionnaire (ISQ): A Scale to Measure Interoceptive Challenges in Adults. Journal of Autism and Developmental Disorders 48 (10), 3354–3366. https://doi.org/10.1007/s10803-018-3600-3.

Freund, A., Orjalo, A.V., Desprez, P.Y., Campisi, J., 2010. Inflammatory networks during cellular senescence: causes and consequences. Trends in molecular medicine 16 (5), 238–246.

Garfinkel, S.N., Seth, A.K., Barrett, A.B., Suzuki, K., Critchley, H.D., 2015. Knowing your own heart: Distinguishing interoceptive accuracy from interoceptive awareness. Biological Psychology 104, 65–74. https://doi.org/10.1016/j.biopsycho.2014.11.004.

Hansson, L.S., Axelsson, J., Petrovic, P., Paues Göranson, S., Olsson, M.J., Lekander, M., Lasselin, J., 2021. Regulation of emotions during experimental endotoxemia: A pilot study. Brain, Behavior, and Immunity 93, 420–424. https://doi.org/10.1016/j.bbi.2021.01.013.

Harrison, N.A., Brydon, L., Walker, C., Gray, M.A., Steptoe, A., Critchley, H.D., 2009. Inflammation Causes Mood Changes Through Alterations in Subgenual Cingulate Activity and Mesolimbic Connectivity. Biological Psychiatry 66 (5), 407–414. https://doi.org/10.1016/j.biopsych.2009.03.015.

Harrison, N.A., Voon, V., Cercignani, M., Cooper, E.A., Pessiglione, M., Critchley, H.D., 2016. A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. Biological Psychiatry 80 (1), 73–81. https://doi.org/10.1016/j.biopsych.2015.07.018.

Hennessy, M.B., Deak, T., Schiml, P.A., 2014. Sociality and sickness: Have cytokines evolved to serve social functions beyond times of pathogen exposure? Brain, Behavior, and Immunity 37, 15–20. https://doi.org/10.1016/j.bbi.2013.10.021.

Hoenig, J.M., Heisey, D.M., 2001. The Abuse of Power. The American Statistician 55 (1), 19–24. https://doi.org/10.1198/000313001300339897.

Inagaki, T.K., Muscatell, K.A., Irwin, M.R., Moieni, M., Dutcher, J.M., Jevtic, I., Breen, E.C., Eisenberger, N.I., 2015. The role of the ventral striatum in inflammatory-induced approach toward support figures. Brain, Behavior, and Immunity 44, 247–252. https://doi.org/10.1016/j.bbi.2014.10.006.

Irwin, M.R., 2014. Sleep and inflammation in resilient aging. Interface Focus 4 (5), 20140009.

Irwin, M.R., Eisenberger, N.I., 2017. Context-Dependent Effects of Inflammation: Reduced Reward Responding is Not an Invariant Outcome of Sickness. Neuropsychopharmacology 42 (4), 785–786. https://doi.org/10.1038/npp.2016.245.

Jolink, T.A., Fendinger, N.J., Alvarez, G.M., Feldman, M.J., Gaudier-Diaz, M.M., Muscatell, K.A., 2022. Inflammatory reactivity to the influenza vaccine is associated with changes in automatic social behavior. Brain, Behavior, and Immunity 99, 339–349. https://doi.org/10.1016/j.bbi.2021.10.019.

Khalsa, S.S., Adolphs, R., Cameron, O.G., Critchley, H.D., Davenport, P.W., Feinstein, J.S., Feusner, J.D., Garfinkel, S.N., Lane, R.D., Mehling, W.E., Meuret, A.E., Nemeroff, C.B., Oppenheimer, S., Petzschner, F.H., Pollatos, O., Rhudy, J.L., Schramm, L.P., Simmons, W.K., Stein, M.B., Stephan, K.E., Van den Bergh, O., Van Diest, I., von Leupoldt, A., Paulus, M.P., Ainley, V., Al Zoubi, O., Aupperle, R., Avery, J., Baxter, L., Benke, C., Berner, L., Bodurka, J., Breese, E., Brown, T., Burrows, K., Cha, Y.-H., Clausen, A., Cosgrove, K., Deville, D., Duncan, L.,

Duquette, P., Ekhtiari, H., Fine, T., Ford, B., Garcia Cordero, I., Gleghorn, D., Guereca, Y., Harrison, N.A., Hassanpour, M., Hechler, T., Heller, A., Hellman, N., Herbert, B., Jarrahi, B., Kerr, K., Kirlic, N., Klabunde, M., Kraynak, T., Kriegsman, M., Kroll, J., Kuplicki, R., Lapidus, R., Le, T., Hagen, K.L., Mayeli, A., Morris, A., Naqvi, N., Oldroyd, K., Pané-Farré, C., Phillips, R., Poppa, T., Potter, W., Puhl, M., Safron, A., Sala, M., Savitz, J., Saxon, H., Schoenhals, W., Stanwell-Smith, C., Teed, A., Terasawa, Y., Thompson, K., Toups, M., Umeda, S., Upshaw, V., Victor, T., Wierenga, C., Wohlrab, C., Yeh, H.-W., Yoris, A., Zeidan, F., Zotev, V., Zucker, N., 2018. Interoception and Mental Health: A Roadmap. Biological Psychiatry. Cognitive Neuroscience and Neuroimaging 3 (6), 501–513.

Kraynak, T.E., Marsland, A.L., Wager, T.D., Gianaros, P.J., 2018. Functional neuroanatomy of peripheral inflammatory physiology: A meta-analysis of human neuroimaging studies. Neuroscience and Biobehavioral Reviews 94, 76–92. https://doi.org/10.1016/j.neubiorev.2018.07.013.

Kuhlman, K.R., Robles, T.F., Dooley, L.N., Boyle, C.C., Haydon, M.D., Bower, J.E., 2018. Within-subject associations between inflammation and features of depression: Using the flu vaccine as a mild inflammatory stimulus. Brain, Behavior, and Immunity 69, 540–547. https://doi.org/10.1016/j.bbi.2018.02.001.

Kumle, L., Võ, M.-L.-H., Draschkow, D., 2021. Estimating power in (generalized) linear mixed models: An open introduction and tutorial in R. Behavior Research Methods 53 (6), 2528–2543. https://doi.org/10.3758/s13428-021-01546-0.

Kurdi, B., Lozano, S., Banaji, M.R., 2017. Introducing the Open Affective Standardized Image Set (OASIS). Behavior Research Methods 49 (2), 457–470. https://doi.org/10.3758/s13428-016-0715-3.

Lang, P.O., Mendes, A., Socquet, J., Assir, N., Govind, S., Aspinall, R., 2012. Effectiveness of influenza vaccine in aging and older adults: comprehensive analysis of the evidence. Clinical interventions in aging 7, 55.

Lekander, M., Karshikoff, B., Johansson, E., Soop, A., Fransson, P., Lundström, J.N., Andreasson, A., Ingvar, M., Petrovic, P., Axelsson, J., Nilsonne, G., 2016. Intrinsic functional connectivity of insular cortex and symptoms of sickness during acute experimental inflammation. Brain, Behavior, and Immunity 56, 34–41. https://doi.org/10.1016/j.bbi.2015.12.018.

Lenth, R.V., 2007. Statistical power calculations. Journal of Animal Science 85 (13 Suppl), E24–E29. https://doi.org/10.2527/jas.2006-449.

Llabre, M.M., Spitzer, S.B., Saab, P.G., Ironson, G.H., Schneiderman, N., 1991. The reliability and specificity of delta versus residualized change as measures of cardiovascular reactivity to behavioral challenges. Psychophysiology 28 (6), 701–711. https://doi.org/10.1111/j.1469-8986.1991.tb01017.x.

Long, J. (2019). *Interactions: Comprehensive, user-friendly toolkit for probing interactions* (R package version 1.1.0). https://cran.r-project.org/package=interactions.

Ma, D.S., Correll, J., Wittenbrink, B., 2015. The Chicago face database: A free stimulus set of faces and norming data. Behavior Research Methods 47 (4), 1122–1135. https://doi.org/10.3758/s13428-014-0532-5.

McLean, H.Q., Thompson, M.G., Sundaram, M.E., Kieke, B.A., Gaglani, M., Murthy, K., Piedra, P.A., Zimmerman, R.K., Nowalk, M.P., Raviotta, J.M., Jackson, M.L., Jackson, L., Ohmit, S.E., Petrie, J.G., Monto, A.S., Meece, J.K., Thaker, S.N., Clippard, J.R., Spencer, S.M., Fry, A.M., Belongia, E.A., 2015. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. The Journal of infectious diseases 211 (10), 1529–1540.

Muscatell, K.A., Inagaki, T.K., 2021. Beyond social withdrawal: New perspectives on the effects of inflammation on social behavior. Brain, Behavior, & Immunity - Health 16, 100302. https://doi.org/10.1016/j.bbih.2021.100302.

Muscatell, K.A., Moieni, M., Inagaki, T.K., Dutcher, J.M., Jevtic, I., Breen, E.C., Irwin, M. R., Eisenberger, N.I., 2016. Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. Brain, Behavior, and Immunity 57, 21–29. https://doi.org/10.1016/j.bbi.2016.03.022.

Muscatell KA. Social psychoneuroimmunology: Understanding bidirectional links between social experiences and the immune system. Brain Behav Immun. 2021 Mar; 93:1-3. doi: 10.1016/j.bbi.2020.12.023. Epub 2020 Dec 28. PMID: 33383146.

O'Connell, N.S., Dai, L., Jiang, Y., Speiser, J.L., Ward, R., Wei, W., Carroll, R., Gebregziabher, M., 2017. Methods for Analysis of Pre-Post Data in Clinical Research: A Comparison of Five Common Methods. Journal of Biometrics & Biostatistics 8 (1), 1–8. https://doi.org/10.4172/2155-6180.1000334.

O'Connor, M.-F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., Hoyt, M.A., Martin, J.L., Robles, T.F., Sloan, E.K., Thomas, K.S., Irwin, M.R., 2009. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. Brain, Behavior, and Immunity 23 (7), 887–897. https://doi.org/10.1016/j.bbi.2009.04.005.

Oikawa, M., Aarts, H., Oikawa, H., 2011. There is a fire burning in my heart: The role of causal attribution in affect transfer. Cognition and Emotion 25 (1), 156–163. https://doi.org/10.1080/02699931003680061.

Oosterhof, N.N., Todorov, A., 2008. The functional basis of face evaluation. Proc. Natl. Acad. Sci. U.S.A. 105 (32), 11087–11092.

Payne, B.K., Cheng, C.M., Govorun, O., Stewart, B.D., 2005. An inkblot for attitudes: Affect misattribution as implicit measurement. Journal of Personality and Social Psychology 89 (3), 277–293. https://doi.org/10.1037/0022-3514.89.3.277.

Payne, B.K., Brown-Iannuzzi, J.L., Loersch, C., 2016. Replicable effects of primes on human behavior. Journal of Experimental Psychology: General 145 (10), 1269–1279. https://doi.org/10.1037/xge0000201.

Phaf, R.H., Mohr, S.E., Rotteveel, M., Wicherts, J.M., 2014. Approach, avoidance, and affect: A meta-analysis of approach-avoidance tendencies in manual reaction time tasks. Frontiers in Psychology 5. https://www.frontiersin.org/articles/10.3389/fpsyg.2014.00378.

Piber, D., Olmstead, R., Cho, J.H.J., Witarama, T., Perez, C., Dietz, N., Irwin, M.R., 2019. Inflammaging: age and systemic, cellular, and nuclear inflammatory biology in older adults. The Journals of Gerontology: Series A 74 (11), 1716–1724.

Radin, A.S., Kuhlman, K.R., Boyle, C.C., Haydon, M.D., Bower, J.E., 2021. Using the influenza vaccine as a mild, exogenous inflammatory challenge: When does inflammation peak? Brain, Behavior, & Immunity - Health 13, 100239. https://doi.org/10.1016/j.bbih.2021.100239.

Ruys, K.I., Aarts, H., Papies, E.K., Oikawa, M., Oikawa, H., 2012. Perceiving an exclusive cause of affect prevents misattribution. Consciousness and Cognition 21 (2), 1009–1015. https://doi.org/10.1016/j.concog.2012.03.002.

Sanada, F., Taniyama, Y., Muratsu, J., Otsu, R., Shimizu, H., Rakugi, H., Morishita, R., 2018. Source of chronic inflammation in aging. Frontiers in cardiovascular medicine 5, 12.

Savitz, J., Harrison, N.A., 2018. Interoception and Inflammation in Psychiatric Disorders. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 3 (6), 514–524. https://doi.org/10.1016/j.bpsc.2017.12.011.

Schandry, R., Bestler, M., Montoya, P., 1993. On the relation between cardiodynamics and heartbeat perception. Psychophysiology 30 (5), 467–474. https://doi.org/10.1111/j.1469-8986.1993.tb02070.x.

Segerstrom, S.C., Hardy, J.K., Evans, D.R., Greenberg, R.N., 2012. Vulnerability, distress, and immune response to vaccination in older adults. Brain, Behavior, and Immunity 26 (5), 747–753. https://doi.org/10.1016/j.bbi.2011.10.009.

Siegel, E.H., Wormwood, J.B., Quigley, K.S., Barrett, L.F., 2018. Seeing What You Feel: Affect Drives Visual Perception of Structurally Neutral Faces. Psychological Science 29 (4), 496–503. https://doi.org/10.1177/0956797617741718.

Storbeck, J., Clore, G.L., 2008. Affective Arousal as Information: How Affective Arousal Influences Judgments, Learning, and Memory. Social and Personality Psychology Compass 2 (5), 1824–1843. https://doi.org/10.1111/j.1751-9004.2008.00138.x.

Sutherland, C.A.M., Oldmeadow, J.A., Santos, I.M., Towler, J., Michael Burt, D., Young, A.W., 2013. Social inferences from faces: Ambient images generate a three-dimensional model. Cognition 127, 105–118. https://doi.org/10.1016/j.cognition.2012.12.001.

Todorov, A., 2008. Evaluating Faces on Trustworthiness. Annals of the New York Academy of Sciences 1124 (1), 208–224. https://doi.org/10.1196/annals.1440.012.

Tsai, J.L., Knutson, B., Fung, H.H., 2006. Cultural variation in affect valuation. Journal of Personality and Social Psychology 90 (2), 288–307. https://doi.org/10.1037/0022-3514.90.2.288.

von Mohr, M., Finotti, G., Villani, V., Tsakiris, M., 2021. Taking the pulse of social cognition: Cardiac afferent activity and interoceptive accuracy modulate emotional egocentricity bias. Cortex 145, 327–340. https://doi.org/10.1016/j.cortex.2021.10.004.

Weierich, M.R., Kleshchova, O., Rieder, J.K., Reilly, D.M., Vazire, S., Vazire, S., 2019. The Complex Affective Scene Set (COMPASS): Solving the Social Content Problem in Affective Visual Stimulus Sets. *Collabra*. Psychology 5 (1). https://doi.org/10.1525/collabra.256.

Wieser, M.J., Brosch, T., 2012. Faces in Context: A Review and Systematization of Contextual Influences on Affective Face Processing. Frontiers in Psychology. https://doi.org/10.3389/fpsyg.2012.00471.

Wittkamp, M.F., Bertsch, K., Vögele, C., Schulz, A., 2018. A latent state-trait analysis of interoceptive accuracy. Psychophysiology 55 (6), e13055.

Wormwood, J.B., Siegel, E.H., Kopec, J., Quigley, K.S., Barrett, L.F., 2018. You are what I feel: A test of the affective realism hypothesis. Emotion 19 (5), 788–798. https://doi.org/10.1037/emo0000484.

Zheng, H., Smith, R., Burrows, K., Kuplicki, R., Bodurka, J., Teague, T.K., Paulus, M., Khalsa, S., Savitz, J., 2021. Inflammation is Associated With Abnormal Interoceptive Processing in Major Depressive Disorder. Biological Psychiatry 89 (9), S190–S191. https://doi.org/10.1016/j.biopsych.2021.02.483.