Inflammatory Reactivity to the Influenza Vaccine is Associated with Changes in Automatic Social Behavior

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Abstract

Recent evidence suggests differential patterns of social behavior following an inflammatory challenge, such that increases in inflammation may not uniformly lead to social withdrawal. Indeed, increases in inflammation have been associated with *enhanced* self-reported motivation to approach a specific close other, and greater neural sensitivity to positive social cues. However, no known studies have examined the association between inflammation in response to an inflammatory challenge and social *behavior* in humans, nor has past research examined specifically how approach and withdrawal behavior may differ based on whether the target is a close other or stranger. To address this, 31 participants (ages 18-24) received the influenza vaccine to elicit a low-grade inflammatory response. The morning before and approximately 24 hours after the vaccine, participants provided a blood sample and completed a computer task assessing automatic (implicit) approach and withdrawal behavior toward a specific close other and strangers. Greater increases in the inflammatory cytokine interleukin-6 (IL-6) in response to the vaccine were associated with an increase in accuracy in avoiding strangers and a decrease in accuracy in approaching them. Increases in IL-6 were also associated with a decrease in reaction time to approach a close other, but only when controlling for baseline IL-6 levels. There were no associations between change in IL-6 and changes in self-reported motivation to engage in social behavior with either close others, or strangers. Together, these findings reveal that increases in inflammation following the influenza vaccine are associated with automatic social behavior, especially behavior suggesting avoidance of unfamiliar social targets and ease in approaching close others. These data add to the growing literature suggesting that the association between inflammation and social behavior includes both social withdrawal and social approach, depending on the specific target.

Keywords: inflammation, interleukin-6, influenza vaccine, social behavior, close relationships, social approach, social withdrawal

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The release of proinflammatory cytokines in mammals often leads to the "sickness behavior" of social withdrawal (Dantzer, 2001; Dantzer & Kelley, 2007; Dantzer et al., 2008; Kelley et al., 2003; Larson & Dunn, 2001). From an evolutionary perspective, withdrawing when experiencing heighted inflammation (e.g., when ill or infected) allows an organism to conserve metabolic resources in order to rest and recover, and to avoid infecting others. Decades of experimental work using animal models have documented this phenomenon using inflammatory challenge paradigms (for review see Dantzer, 2001; Dantzer & Kelley, 2007; Hart, 1988; Yirmiya, 1996). Similarly, research with humans has shown that social withdrawal often follows an inflammatory challenge. For example, experimentally-induced inflammation predicts greater feelings of social disconnection (Eisenberger et al., 2010), and greater neural activity in response to a variety of social tasks, including viewing socially threatening images (Inagaki et al., 2012), receiving negative social feedback (Muscatell et al., 2016), and being socially rejected (Eisenberger et al., 2009). Findings such as these have led many to conclude that social withdrawal is a hallmark sickness behavior that occurs in response to inflammatory challenge (Dantzer & Kelley, 2007; Raison et al., 2006).

However, recent theoretical and empirical work argues that the effect of inflammation on social behavior may be more nuanced than uniform social withdrawal (Eisenberger et al., 2017; Hennessey et al., 2014; Muscatell & Inagaki, 2021). Indeed, some work shows that inflammation can prompt one to draw *toward* or *approach* close or familiar others, rather than withdraw (Aubert, 1999; Cole, 2006; Hennessy et al., 2014). From an evolutionary lens, it makes sense that individuals may approach close others when experiencing heighted levels of peripheral inflammation, as doing so could facilitate the receipt of comfort and care from them, promoting faster healing and recovery (Eisenberger et al., 2017). Empirical support for the idea that inflammation may sometimes lead to social approach behavior has been most consistently demonstrated in animal models (Aubert, 1999; Dantzer, 2001; Hennessy et al., 2014). Along these lines, rhesus monkeys injected with low doses of lipopolysaccharide (LPS) spent more time passively sitting near a companion for grooming relative to monkeys injected with saline (Willette et al., 2007). Further, LPS-injected lactating mice demonstrated more approach-related maternal behavior (e.g., nest building and pup retrieving) in cold temperatures than saline-injected mothers (Aubert et al., 1997); this effect did not emerge in ambient temperatures, revealing that mammals can prioritize sickness behavior differentially based on situational demands. Further, rats dosed with interleukin-1 beta (IL-1ß) and prairie voles injected with LPS exhibited sustained or faster preference behavior for sexual partners compared to those injected with saline, suggesting greater social approach toward some social targets (Bilbo et al., 1999; Yirmiya et al., 1995). Altogether, this work suggests that, in some cases, social approach behavior is maintained and/or amplified in response to an inflammatory challenge, perhaps particularly when the target of social interactions is a familiar or close other.

Does inflammation sometimes also lead to social approach behavior in humans? Thus far, much of the evidence for this link in humans has examined how inflammation affects neural activity in reward-related circuitry in the brain in response to certain positive social experiences or cues of social others (for review, see Eisenberger et al., 2017). For instance, an inflammatory challenge leads to greater neural activity in reward-related brain regions in response to positive social feedback (Muscatell et al., 2016), and greater activity in mentalizing-related regions when viewing others' eye expressions (Kullmann et al., 2014), suggesting that heightened inflammation causes greater activity in neural circuitry that contributes to social cognitive processing or social approach. Only one known study has examined how inflammation affects self-reported motivation to approach a close other. After receiving a low-dose endotoxin, individuals endorsed a greater desire to approach a close other (i.e., they felt "like being around this person right now"), compared to those receiving placebo (Inagaki et al., 2015). Further, the endotoxin group demonstrated greater activity in the ventral striatum, a key reward/motivation-related brain region, when viewing an image of that close other, compared to those on placebo. Taken with the existing animal literature, this initial evidence in humans suggests that sickness behavior in response to experimentally-induced inflammation may extend beyond social withdrawal to also include target-specific approach-oriented behavior.

Despite these strides, no human work to date has examined actual social approach *behavior* (i.e., as opposed to neural responses or self-reports) following an inflammatory challenge, nor has prior work explored whether such behavioral responses differ based on the social *target*. To address these gaps in the literature, the current study evaluates whether inflammatory reactivity in response to a low-grade inflammatory challenge is associated with social behavior, specifically increased approach behavior toward a close other and withdrawal behavior from strangers in an automatic social behavior task. This provides the opportunity to gain insights in how low-grade inflammatory reactivity is related to differential patterns of social behavior toward different social targets.

To measure automatic social behavior toward a close other and strangers, we employed an established stimulus-response compatibility task, the Approach-Avoidance or Manikin Task (De Houwer et al., 2001). Typically used in addiction research to study motivation to approach drug-related stimuli (e.g., alcohol, Field et al., 2004; 2005; tobacco, Mogg et al., 2003; cannabis, Field et al., 2006), work using the Approach-Avoidance Task has consistently shown that faster approach tendencies toward drug-related stimuli are associated with greater attentional focus on the drug and greater cravings for it (Field et al., 2004; 2005; 2006; Mogg et al., 2003). In more recent work, the task has been used to demonstrate automatic motivational behavior toward social others. For example, anxiously attached individuals showed greater approach behavior toward attachment figures when distressed, while avoidantly attached individuals showed less approach behavior (Dewitte et al., 2008). Further, males administered intranasal oxytocin who were in monogamous relationships approached attractive romantic alternatives more slowly on the task (Scheele et al., 2012). Altogether, these findings suggest the Approach-Avoidance Task measures automatic motivation to draw toward – or move away from – valenced stimuli, which has then been linked with behavior toward similar stimuli in real life.

In addition to advancing knowledge about the associations between inflammation and automatic social behavior across different targets, the present study also capitalizes on recent work showing that the influenza vaccine can be utilized to study how low-grade within-person changes in inflammation are associated with psychology and behavior (Boyle et al., 2019; Kuhlman et al., 2018). This is an important step, as past research using inflammatory challenge procedures in humans has largely utilized LPS to induce inflammation (with some work using typhoid vaccine; see Brydon et al., 2008; Harrison et al., 2009; Strike et al., 2004). Given that typical LPS doses lead to a very large increase in levels of circulating inflammatory markers (i.e., ~100 pg/mL of IL-6), these studies are likely modelling the effects of acute sickness on social processes (Muscatell & Inagaki, 2021). However, low-grade changes in inflammation (e.g., analogous to those induced by the influenza vaccine or an acute psychological stressor) are also likely monitored and detected by the brain (Savitz & Harrison, 2018) and thus may also be associated with changes in perception and behavior (Gassen & Hill, 2019; Muscatell 2020). This is because the brain is constantly monitoring and anticipating bodily needs, a process called allostasis (Sterling, 2012). Allostasis serves to align one's perceptions and behavior with present metabolic needs, helping one avoid threats and attain resources (Barrett & Bar, 2009; Siegel et al 2018; Friston et al 2017). As a result, even a low-grade shift in inflammation is likely recognized by the brain, which would then adjust behavior to attain appropriate metabolic resources, including, perhaps, withdrawing from strangers and approaching close others.

In sum, the present study examines associations between changes in inflammation in response to the influenza vaccine and social behavior directed toward both close others and strangers. Based on preclinical animal work and a limited number of human studies (Hennessy et al., 2014; Inagaki et al., 2015; Muscatell & Inagaki, 2021), we hypothesized that greater increases in inflammation (i.e., levels of circulating IL-6) following the influenza vaccine would be associated with: (1) greater motivation to approach a specific familiar other (i.e., a support figure), and (2) decreased motivation to approach (and perhaps greater motivation to withdraw from) unfamiliar others. We examine these hypotheses using a standardized computer-based task measuring automatic approach and withdrawal behavior, as well as self-report measures of desire for social interactions with different targets.

Methods

Participants

A convenience sample of thirty-one undergraduate students (*mean* age = 20.29 years, *SD* = 1.40) at the University of North Carolina at Chapel Hill (UNC-CH) participated in the study from January to April of 2021. An *a priori* power analysis (conducted with G*Power) determined that a sample size of N = 34 was needed to detect small-to-medium effects ($f < .25$)

at 80% power. Unfortunately, given the challenge of collecting in-person data during the 2020-2021 COVID-19 global pandemic, we fell slightly short of our recruitment goal and thus may be underpowered. Participants were recruited by posts to email and class listservs and on social media, in which they were first directed to an online eligibility questionnaire. Inclusion criteria were similar to prior studies using the influenza vaccine paradigm (Boyle et al., 2019; Kuhlman et al., 2018); see Supplemental Material (SM) for more information about excluded participants. Specifically, participants had to be between 18 and 25 years of age and could not have received the annual influenza vaccine or had influenza that season. Participants were excluded if they used tobacco products, used mood or immune-altering medications (e.g., anti-depressants), had a current diagnosis of or history of depression, anxiety, or any major medical condition (e.g., diabetes, asthma), had had Guillain-Barre Syndrome (GBS), were allergic to the influenza vaccine or ingredients present in the vaccine (e.g., eggs), or had a current illness. Because the study was conducted during the COVID-19 pandemic, participants were also screened out for self-reported exposure to COVID-19 or current respiratory symptoms[1]. See Table 1 for descriptive characteristics of the sample.

[1] For the pre-session screening questions to assess possible infection with COVID-19, participants had to report if they were currently experiencing any of the following: fever; new or worsening cough; new or worsening sore throat; new shortness of breath; loss of taste or smell in the last 5 days; newly onset vomiting or diarrhea; new onset of repeated shaking with chills not related to another medical condition; exposure to or had COVID-19 in the past two weeks.

Table 1

Sample characteristics

	M (*SD*)	% (*n*)
Age	20.29 (1.40)	
Assigned Female at Birth		81% (25)
Cisgender Female		77% (24)
BMI[1]	23.98 (4.96)	
Race/Ethnicity[2]		
White/Caucasian		48.3% (15)
Asian/Asian American		29.0% (9)
Latina/(o)/Chicana/(o)/Latin American		9.7% (3)
Black/African American		12.9% (4)
Native American		9.7% (3)
Middle Eastern		6.5% (2)
Parental Education		Parent #1 | Parent #2
High school graduation or less		22.5% (7) | 29.1% (9)
Some college		9.7% (3) | 12.9% (4)
Earned a BA/BS degree		48.4% (15) | 29.0% (9)
Masters/professional/doctoral degree		19.3% (6) | 29% (9)

[1]We controlled for BMI based on published recommendations. However, we note that 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, and readers should use caution interpreting this measure. For more information on considerations of BMI metrics, see https://www.cdc.gov/obesity/downloads/bmiforpactitioners.pdf

[2]Groups are not mutually exclusive as participants could endorse more than one race/ethnicity.

Procedure

Informed consent was obtained using the video conferencing platform Zoom. After consenting to participate, participants scheduled their two study sessions (i.e., pre- and post-vaccine), which occurred over two consecutive days approximately 24 hours apart. Before the pre-vaccine session, participants were instructed to submit five photos of a specific close other they identified as a consistent support figure in their lives (see below for more detail). For the pre-vaccine session, participants attended a morning online session with an experimenter during which they completed questionnaires and behavioral tasks on Inquisit Web. They then visited the UNC-CH Clinical and Translational Research Center (CTRC) for a blood draw ($\text{Time}_{\text{earliest}}$ = 9:03 AM; $\text{Time}_{\text{latest}}$ = 12:30 PM; *Mean* = 11:14 AM; *SD* = 0:54). After providing a blood sample, participants were escorted to a pharmacy where they received the influenza vaccine ($\text{Time}_{\text{earliest}}$ = 9:18 AM; $\text{Time}_{\text{latest}}$ = 12:47 PM; *Mean* = 11:37 AM; *SD* = 0:55). The post-vaccine session took place approximately 24 hours later, with participants first completing another questionnaire and set of Inquisit tasks during an online session with an experimenter, and then returning to the CTRC for a second blood draw ($\text{Time}_{\text{earliest}}$ = 8:35 AM; $\text{Time}_{\text{latest}}$ = 2:36 PM; *Mean* = 11:23 AM; *SD* = 1:25)[2]. The post-vaccine blood draw occurred 20.5-28 hours after the vaccination ($\text{M}_{\text{vaccine delay}}$ = 23:45, $\text{SD}_{\text{vaccine delay}}$ = 1:36). We specifically aimed for participants to complete the post-vaccine tasks and blood draw 24 hours after the vaccine, given prior work showing that IL-6 levels following the influenza vaccine peak at approximately 24 hours post-vaccine (Radin et al., 2021). Levels of IL-6 were not correlated with the time of day the blood was drawn (pre-vaccine: $r = -.10$, $p = .60$; post-vaccine: $r = -.08$, $p = .67$). Further, change in IL-6 in response to the vaccine was not significantly correlated with either the amount of time that passed between blood draws ($r = -.30$, $p = .10$) or the amount of time that lapsed between the vaccine and post-vaccine blood draw ($r = -.31$, $p = .09$).

The influenza vaccine administered to all participants was a 0.5-mL single-dose of GSK's Flulaval Quadrivalent, which was standardized for the 2020–2021 flu season and included the following four influenza virus strains: 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).

Participants were compensated $85 for participating and offered reimbursement for parking.

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[2] With the exception of two participants, all sessions took place between the hours of 6:30 AM and 1 PM to control for diurnal variation in IL-6 levels. One participant had to visit the CTRC for their blood draw at 2:36 PM due to a winter storm that kept the CTRC closed until 1 PM. Another participant missed their second online session and had to complete it at 1:15 PM *after* their second blood draw.

Support Figure Photo Submission and Quality Check. Participants were told that they would be asked questions about one specific support figure during the course of the study and were asked to provide five photos of that person. Participants were told the support figure should be "someone in your life you can go to for help or for comfort" (i.e., a family member, close friend, roommate or romantic partner). The submitted photos could only depict this person and no one else. Because participants could select their choice of a support figure, the selections spanned various relationship types. The majority of participants chose a close friend (*n*=11, 35.5% of the sample) or a romantic partner (*n*=9, 29%). Five participants selected a sibling (16.1%), and three participants picked their parent/guardian (9.7%). The remaining participants picked a roommate (*n*=2, 6.5%) or another familial relative (*n*=1, 3.2%). Based on these categories, relationship type was recoded into a 3-point ordinal variable: close friend/roommate (*n*=13), romantic partner (*n*=9), or family member, i.e., parent, sibling, or another familial relative (*n*=9). This 3-point variable was used as a covariate in analyses involving the data that utilized images of the close others (see below for more detail).

Finally, in line with past research (Inagaki et al., 2015), we included two items to confirm that the chosen person indeed met the criteria of a "support figure". During the pre-vaccine session, participants responded to the following items about the person in the photographs on a scale from 1 (*not at all*) to 7 (*a lot*): "Can you rely on this person for help if you have a serious problem?"; "Can you really count on this person to help you feel better when you are feeling generally down-in-the-dumps?" Responses to the two items were averaged (= .83). Participants rated their support figure as highly supportive (*M* = 6.47, *SD* = 0.78, *median* = 7, *range* = 4-7), suggesting that participants were compliant in following instructions to select a specific person who provides them support.

Measures

Inflammation. IL-6 was used as the measure of inflammation in the study, as it demonstrates consistent increases following the influenza vaccine (Christian et al., 2013; Segerstrom et al., 2012; Tsai et al., 2005) and has been examined in prior work looking at within-subject changes in inflammation in response to the influenza vaccine (Boyle et al., 2019; Kuhlman et al., 2018; 2020; Radin et al., 2021). Approximately 6 mL of blood was drawn by venipuncture and collected into EDTA tubes, held on ice, centrifuged for 10 minutes, aliquoted for plasma, and stored in a -80C freezer until study completion. Hemolysis occurred to one pre-vaccine blood sample, and that participant was thus excluded from analysis. Samples were assayed in triplicate using the high-sensitivity ELLA immunoassay platform (R&D Systems). The lower limit of detection for the assay was 0.28 pg/mL. The values in our sample ranged from 0.28 – 6.17 pg/mL pre-vaccine and 0.99 – 8.4 pg/mL post-vaccine; two values were undetectable and were replaced with the lower limit of detection (i.e., 0.28 pg/mL). Intra-assay CVs were <6.55%. No inter-assay CV was calculated because samples were run on two different plates and no control sample was used.

Physical Symptoms. Because studies have shown changes in subjective physical symptoms following an inflammatory challenge (Cohen et al., 2006; Eisenberger et al., 2009; 2010), participants reported the extent to which they felt a constellation of six common physical symptoms – feeling sick, headache, joint aches, muscle aches, chills, and fatigue – on a 7-point scale from 1 (*not at all*) to 7 (*extremely*), during both sessions. These physical symptom items were different from the pre-session symptom screening questions used to screen for acute infection (e.g., COVID-19), which were just used for exclusion.

Self-Reported Motivation to Foster Social Connection. Participants completed the State Motivation to Foster Social Connections Scale (Bernstein et al., 2019) at both sessions to measure self-reported motivation to engage in different affiliative social behaviors. The 10-item scale is comprised of two 5-item subscales: motivation to foster connection with new relationships (e.g., "Right now, I would like to meet new people") and motivation to foster connection with existing relationships (e.g., "Right now, I'd like to be around friends"), measured from 1 (*strongly disagree*) to 7 (*strongly agree*) for each item. Items from each subscale were averaged to form a composite measure of motivation to foster connection with new relationships ($_{\text{pre-vaccine}}$ = .96, $_{\text{post-vaccine}}$ =.94) and motivation to foster connection with existing relationships ($_{\text{pre-vaccine}}$ = .87, $_{\text{post-vaccine}}$ =.93).

Automatic Approach/Withdrawal Behavior Toward Support Figure and Strangers. To measure automatic approach and withdrawal behavior toward different social targets, we used the Approach-Avoidance or Manikin Task (De Houwer et al., 2001), which has been used primarily in addiction and recovery research (Field et al., 2006; 2011; Mogg et al., 2003). Some studies (e.g., Dewitte et al., 2008; Mogg et al., 2005; Scheele et al., 2012) have used only reaction times (latency) on different trials from the task to index approach and avoidance motivation, and used accuracy to discard trials in which participants made errors. Here we were interested in *both* latency and accuracy, as distinct automatic behavior measures.

In the present study, the task measured approach and withdrawal behavior toward a close other and separately, toward strangers (i.e., vaguely familiar celebrities). The task consisted of two blocks, which were counterbalanced across participants. In each block, there were 8 practice trials and 56 experimental trials, presented in random order for each participant. On each trial, an image depicting either the participant's close other, or a stranger, was presented in the center of the screen. A small figure (manikin) was displayed either above or below the image. Participants pressed an up or down key to move the manikin either toward or away from the picture in the center. In one of the two blocks, participants were instructed to move the manikin *toward* their close other and *away* from the stranger as quickly and accurately as possible. For example, in this block, if the manikin was displayed above the image of the close other, the participant needed to press the 'down' response to move the manikin down toward the image. In the other block, participants needed to move the manikin *away* from their close other and *toward* the stranger. For any incorrect response, a red 'X' was displayed across the image. Accuracy (proportion correct) and latency (reaction time) of participants' responses were recorded for each trial and each averaged to form both accuracy and latency scores for approach behavior toward close other, approach behavior toward strangers, withdrawal behavior from close other, and withdrawal behavior from strangers, respectively.

One participant indicated inattentive or rushed responding to the task based on accuracy scores that were barely above chance both pre-vaccine (54%) and post-vaccine (55%). Their latency scores were also at the lower threshold of response (less than 250 ms) at 246 ms and 207 ms, on average, pre- and post-vaccine, respectively. This participant was thus excluded from analyses. With that participant excluded, average accuracy across all trials was 94% pre-vaccine and 94% post-vaccine (SDs = .05) and average latency was 831 ms pre-vaccine (SD = 225 ms) and 802 ms post-vaccine (SD = 218 ms). Paired-samples t-tests did not show evidence of significant practice effects, such that between the pre-vaccine and post-vaccine sessions across all trials of the task, participants did not get more accurate, $t(27) = .28$, $p = .78$, $d = .05$, or faster, $t(27) = 1.73$, $p = .10$, $d = .33$.

Data Analysis

Analyses were conducted using R. IL-6 values were right-skewed, so values were log-transformed. IL-6 reactivity to the vaccine was computed as a change score (log-transformed post-vaccine IL-6 minus log-transformed pre-vaccine IL-6), with higher values signifying a greater increase in circulating IL-6 following the influenza vaccine. Any extreme values (i.e., greater than 3 SDs away from the mean) of these variables (of which there were five total outlying values across eight variables) were winsorized and retained in the data. Results held with and without winsorizing these values: table of exact outlying variables and results including those outliers can be found in SM.

All analyses controlled for sex and BMI (O'Connor et al., 2009), and for relationship type in analyses examining performance on the approach/avoid task when the target was the close other, but not when the target was strangers or for any self-report measure. We also ran ancillary analyses identical to those outlined above, but that additionally adjusted for pre-vaccine IL-6 levels (Boyle et al., 2019; Kuhlman et al., 2018). Because changes in inflammation following the influenza vaccine are relatively small (on average, a 1.16 pg/mL change) and do not reflect starting (baseline) levels, it is possible that a participant's baseline level of IL-6 could be important, as an increase of 1 pg/mL might be experienced differently for someone who has an IL-6 level of 1 pg/ml at baseline vs. someone who has an IL-6 level of 4 pg/mL at baseline. Studies on the efficacy of anti-inflammatory medication use on depressive symptoms offer another empirical example of this point, finding that treatment effects are contingent on participant's basal inflammation levels (Kohler et al., 2016; Miller et al., 2009; Raison et al., 2013). In a similar vein, we wanted to account for baseline IL-6 levels in the present study in ancillary analyses.[3]

We fit linear regression models testing the association between vaccine-induced IL-6 change scores and changes in two self-report measures of social affiliative behavior – motivation to foster connection with new relationships and existing relationships – and changes in automatic approach and withdrawal behavior toward both the support figure and strangers. *Positive* changes in accuracy signify that participants' accuracy improved during the post-vaccine session; *negative* changes signify that accuracy worsened during the post-vaccine session. *Positive* change in latency indicates slower responding during the post-vaccine session, while *negative* changes indicate faster responding during the post-vaccine session.

Results

Table 2 reports descriptive statistics for critical study variables both pre- and post-vaccine, as well as change scores. All zero-order bivariate correlations for all study variables (i.e., pre-vaccine values, post-vaccine values, and change scores) can be found on this osf page: https://osf.io/5e3uc/.

[3] For those interested, correlations between pre-vaccine IL-6 values and social behavior task performance at baseline are reported in the SM.

Table 2

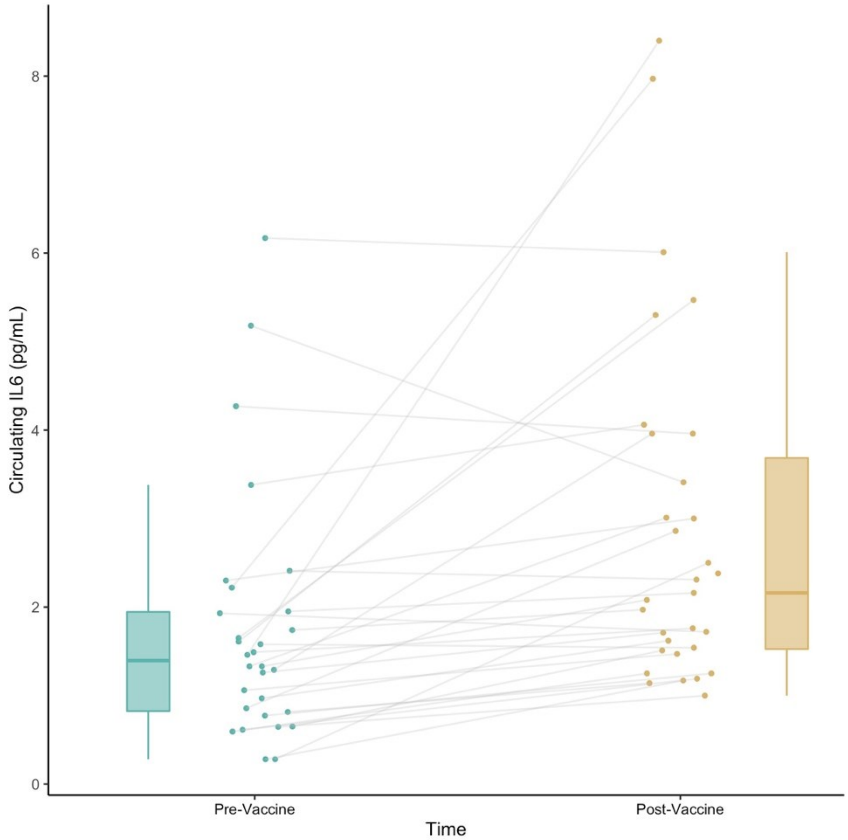
Means, standard deviations and changes scores of pre-vaccine and post-vaccine measures

	M (*SD*)		*Change (Post – Pre)*
	Pre-Vaccine	Post-Vaccine	
IL-6 (pg/ml)	1.74 (1.38)	2.89 (1.98)	1.155
Physical Symptoms (1 – 7)	1.95 (.87)	1.82 (.66)	-0.13
Self-Reported Motivation to Foster Social Connection With New Relationships (1 – 7)	4.50 (1.71)	4.49 (1.71)	-0.01
Self-Reported Motivation to Foster Social Connection with Existing Relationships (1 – 7)	5.77 (1.22)	5.73 (1.37)	-0.04
Approach Behavior Toward Support Figure			
Accuracy	96% (.07)	95% (.05)	-0.005
Latency	775.14 (328.19)	721.18 (197.60)	-46.518
Withdrawal Behavior Away from Support Figure			
Accuracy	94% (.08)	93% (.08)	-0.004
Latency	881.17 (217.68)	846.54 (224.00)	-34.47
Approach Behavior Toward Strangers			
Accuracy	92% (.06)	92% (.10)	0.000
Latency	851.23 (238.47)	846.07 (280.53)	-5.154
Withdrawal Behavior Away from Strangers			
Accuracy	94% (.06)	94% (.06)	0.003
Latency	827.11 (242.69)	797.08 (213.60)	-33.506

Inflammation Before and After Influenza Vaccine

Circulating levels of IL-6 were significantly higher 24-hours after the influenza vaccine (M = 2.89, SD = 1.98) compared to before the vaccine (M = 1.74, SD = 1.38), $F(27) = 6.63$, p =.016, ^{2}= .20, controlling for sex assigned at birth and BMI. Twenty-four out of 30 participants (80%) showed an increase in IL-6 from pre- to post-vaccine, and the average increase was 1.16 pg/mL (SD = 1.83, range = -1.77 – 6.94 pg/mL). See Figure 1 for pre- and post-vaccine IL-6 levels across participants.

Figure 1



Note. IL-6 levels at pre-vaccine and post-vaccine administration for each participant based on raw (not log-transformed) IL-6 values. Box and whisker plots depict the mean and distribution of IL-6 scores for both pre-vaccine (left-side) and post-vaccine (right-side).

Physical Symptoms Before and After Influenza Vaccine

Physical symptoms did not significantly differ pre- to post- influenza vaccine, $F(30) = 0.86$, $p = .36$, $^2 = .03$. This is consistent with other studies suggesting that the influenza vaccine paradigm is not modelling the effects of acute sickness on psychology and behavior (Kuhlman et al., 2018), but rather low-grade changes that mimic more everyday fluctuations in inflammation.

Change in Inflammation and Self-Reported Motivation to Foster Social Connection

Change in IL-6 from pre- to post-vaccine was not associated with self-reported change in motivation to foster connection with someone new (*B* = -.13, *b* = -.40, *p* = .54) or with existing relationships (*B* = .02, *b* = .07, *p* = .92). Results were the same when controlling for pre-vaccine levels of IL-6. Table 3 has full results for both outcomes.

Conclusions also held when controlling for time between blood draws; full results of those models are reported in the SM.

Table 3

Regression model results predicting change in motivation to foster connection with new and existing relationships from change in IL-6

Predictor	*B*	*b*	*SE*	*t*	95% CI	
					Lower	Upper
Predicting change in motivation to foster connection with new relationships						
Change IL-6	-.13	-.40	.64	-.63	-1.71	0.91
Sex	.09	.17	.41	.42	-0.67	1.02
BMI	-.17	-.03	.04	-.77	-0.10	0.05
Predicting change in motivation to foster connection with existing relationships						
Change IL-6	.02	.07	.63	.10	-1.24	1.37
Sex	.18	.37	.41	.90	-0.47	1.21
BMI	.27	.05	.04	1.28	-0.03	0.12
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels						
Predicting change in motivation to foster connection with new relationships						
Change IL-6	-.17	-.51	.78	-.65	-2.12	1.10
Sex	.11	.22	.46	.48	-0.72	1.15
BMI	-.12	-.02	.05	-.39	-0.13	0.08
Pre-vaccine IL-6	-.08	-.22	.86	-.25	-2.00	1.56
Predicting change in motivation to foster connection with existing relationships						
Change IL-6	.11	.35	.77	.45	-1.25	1.94
Sex	.12	.25	.45	.57	-0.67	1.18
BMI	.15	.02	.05	.50	-0.08	0.12
Pre-vaccine IL-6	.22	.56	.85	.65	-1.20	2.31

Note. BMI = Body Mass Index. $^{\dagger}p < .06$. $^{*}p < .05$.

Change in Inflammation and Automatic Approach and Withdrawal Behavior Toward the Support Figure

Change in IL-6 was not related to a change in the proportion of trials on the Approach-Avoidance task that participants responded to correctly when approaching their support figure (B = .12, b = .02, p = .61), nor did change in IL-6 predict a change in the speed at which participants approached the support figure (B = -.35, b = -262.44 p = .11). Controlling for pre-vaccine levels of IL-6 did not alter results for changes in accuracy in approaching a close other; however, change in IL-6 was associated with decreased reaction times to approach the support figure (B = -.54, b = -411.64, p = .03) when accounting for pre-vaccine IL-6. See Figure 2. Specifically, those who demonstrated a greater increase in IL-6 following the vaccine showed decreased reaction times on trials when they approached their support figure. Change in IL-6 was not associated with changes in accuracy (B = -.25, b = -.07, p = .25) or latency (B = .06, b = 32.62, p = .80) in withdrawal behavior from the support figure, and results did not change when controlling for pre-vaccine IL-6. See Table 4 for full model results.

All conclusions held when controlling for time between blood draws (see SM).

Table 4

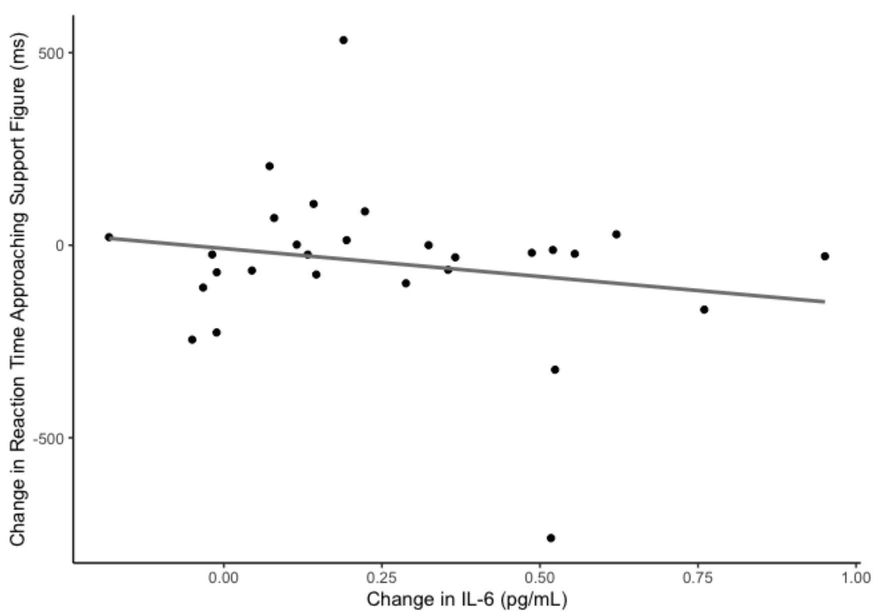
Model results predicting change in automatic approach and withdraw behavior toward the support figure from change in IL-6

Predictor	*B*	*b*	*SE*	*t*	95% CI	
					Lower	Upper
Predicting change in accuracy in approach behavior toward support figure						
Change IL-6	.12	.02	.04	.52	-.07	.11
Sex	.19	.03	.03	.78	-.04	.10
BMI	.18	.002	.003	.72	-.004	.01
Relationship type	.30	.02	.01	1.36	-.01	.05
Predicting change in latency in approach behavior toward support figure						
Change IL-6	-.35	-262.44	158.67	-1.65	-590.67	65.80
Sex	-.30	-160.23	120.35	-1.33	-409.19	88.73
BMI	-.34	-14.02	9.47	-1.48	-33.60	5.56
Relationship type	-.37	-91.77	51.61	-1.78	-198.54	15.00
Predicting change in accuracy in withdrawal behavior away from support figure						
Change IL-6	-.25	-.07	.06	-1.18	-.19	.05
Sex†	-.45	-.09	.04	-1.99	-.18	.003
BMI	-.20	-.003	.003	-.87	-.01	.004
Relationship type	-.27	.02	.02	-1.29	-.06	.01
Predicting change in latency in withdrawal behavior away from support figure						
Change IL-6	.06	32.62	126.19	.26	-228.41	293.66
Sex	.34	137.76	95.71	1.44	-60.24	335.75
BMI	.41	13.01	7.53	1.73	-2.56	28.58
Relationship type	.20	38.10	41.05	.93	-46.81	123.01
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels						
Predicting change in accuracy in approach behavior toward support figure						
Change IL-6	.15	.03	.05	.57	-0.08	0.14
Sex	.16	.02	.04	.59	-0.06	0.10
BMI	.12	.001	.004	.34	-0.01	0.01
Relationship type	.29	.02	.02	1.27	-0.01	0.05
Pre-vaccine IL-6	.09	.02	.06	.26	-0.11	0.14
Predicting change in latency in approach behavior toward support figure						
Change IL-6*	**-.54**	**-411.64**	**178.01**	**-2.31**	**-780.81**	**-42.46**
Sex	-.14	-71.96	127.96	-.56	-337.33	193.40
BMI	-.004	-.18	12.43	-.01	-25.95	25.60
Relationship type	-.31	-77.23	50.59	-1.53	-182.14	27.69

Pre-vaccine IL-6	-.52	-326.90	198.95	-1.64	-739.50	85.70
Predicting change in accuracy in withdrawal behavior away from support figure						
Change IL-6	-.29	-.08	.07	-1.14	-0.22	0.06
Sex	-.42	-.08	.05	-1.65	-0.18	0.02
BMI	-.14	-.002	.01	-.43	-0.01	0.01
Relationship type	-.26	.02	.02	-1.20	-0.06	0.02
Pre-vaccine IL-6	-.10	-.02	.08	-.28	-0.18	0.14
Predicting change in latency in withdrawal behavior away from support figure						
Change IL-6	.21	122.18	145.26	.84	-179.07	423.43
Sex	.21	84.78	104.41	.81	-131.76	301.32
BMI	.15	4.70	10.14	.46	-16.33	25.73
Relationship type	.15	29.37	41.28	.71	-56.24	114.97
Pre-vaccine IL-6	.40	196.22	162.35	1.21	-140.47	532.91

Note. BMI = Body Mass Index. $^{\dagger}p$ <.06. $^{*}p$ <.05.

Figure 2



Note. Within-subject change in latency approaching support figure from pre-vaccine to post-vaccine predicted by within-subject change in IL-6. Model adjusted for sex, BMI, relationship type, and pre-vaccine IL-6.

Change in Inflammation and Automatic Approach and Withdrawal Behavior Toward Strangers

Change in IL-6 was significantly associated with change in accuracy in approaching the strangers (B = -.47, b = -.15, p = .021). Specifically, those who demonstrated a greater change in IL-6 following the vaccine decreased in accuracy on trials in which they had to approach the strangers (see Figure 3, Panel A). Results remained significant when controlling for pre-vaccine IL-6 levels.

Change in IL-6 was also approaching a statistically significant association with change in accuracy in withdrawing from strangers (B = .41, b = .13, p = .06). Specifically, those who demonstrated a greater change in IL-6 following the vaccine marginally increased in the proportion of trials responded to accurately when withdrawing from strangers (see Figure 3, Panel B). The association was significant when controlling for pre-vaccine IL-6 levels. Change in IL-6 was not associated with changes in latency in approaching (B = .19, b = 120.69, p = .36), or withdrawing from (B = -.07, b = -41.96, p = .77), the strangers. Results for change in accuracy remained significant when controlling for pre-vaccine IL-6 levels; results for change in latency did not change when accounting for pre-vaccine IL-6 levels. See Table 5.

Conclusions for behavior toward strangers held when controlling for time between blood draws (see SM).

Table 5

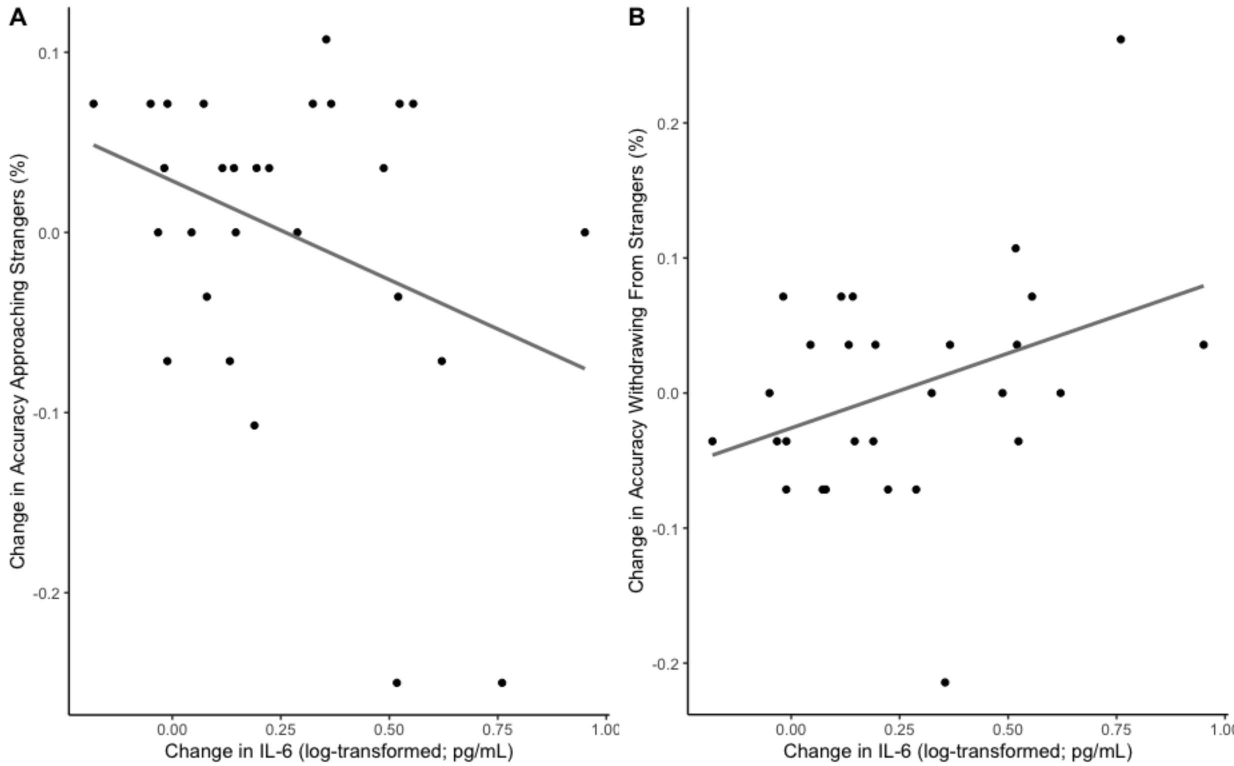
Model results predicting change in automatic approach and withdrawal behavior toward strangers from change in IL-6

Predictor	*B*	*b*	*SE*	*t*	95% CI	
					Lower	Upper
Predicting change in accuracy in approach behavior toward strangers						
Change IL-6*	**-.47**	**-.15**	**.06**	**-2.47**	**-.28**	**-.03**
Sex	-.36	-.08	.04	-1.86	-.17	.01
BMI†	-.42	-.01	.004	-2.00	-.02	.0001
Predicting change in latency in approach behavior toward strangers						
Change IL-6	.19	120.69	129.51	.93	-146.61	387.99
Sex	.21	93.40	91.27	1.02	-94.97	281.77
BMI†	.46	15.50	7.62	2.03	-.24	31.23
Predicting change in accuracy in withdrawal behavior away from strangers						
Change IL-6†	**.41**	**.13**	**.06**	**1.98**	**-.01**	**.26**
Sex	.07	.02	.04	.35	-.08	.11
BMI	.13	.002	.004	.58	-.01	.01
Predicting change in latency in withdrawal behavior away from strangers						
Change IL-6	-.07	-41.96	133.53	-.31	-317.56	233.64
Sex	-.07	-29.85	94.10	-.32	-224.06	164.38
BMI	.05	1.53	7.86	.19	-14.70	17.75
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels						
Predicting change in accuracy in approach behavior toward strangers						
Change IL-6*	**-.48**	**-.16**	**.08**	**-2.08**	**-0.31**	**0.00**
Sex	-.35	-.08	.05	-1.66	-0.18	0.02
BMI	-.41	-.01	.01	-1.42	-0.02	0.003
Pre-vaccine IL-6	-.02	-.01	.08	-.06	-0.8	0.17
Predicting change in latency in approach behavior toward strangers						
Change IL-6	.24	149.30	155.80	.96	-173.00	471.59
Sex	.18	79.89	100.88	.79	-128.81	288.58
BMI	.39	13.10	10.41	1.26	-8.44	34.64
Pre-vaccine IL-6	.11	59.35	171.84	.35	-296.13	414.84
Predicting change in accuracy in withdrawal behavior away from strangers						
Change IL-6*	**.57**	**.17**	**.07**	**2.35**	**0.02**	**0.33**
Sex	-.03	-.01	.05	-.15	-0.11	0.09
BMI	-.12	-.002	.01	-.39	-0.01	0.01

Pre-vaccine IL-6	.40	.10	.08	1.24	-0.07	0.27
Predicting change in latency in withdrawal behavior away from strangers						
Change IL-6	-.40	-241.40	140.78	-1.72	-532.62	49.83
Sex	.15	-64.34	91.16	.71	-124.24	252.91
BMI	.56	18.22	9.41	1.94	-1.24	37.69
Pre-vaccine IL-6*	**-.83**	**-413.77**	**155.28**	**-2.67**	**-734.99**	**-92.56**

Note. BMI = Body Mass Index. †p < .06. *p <.05.

Figure 3



Note. Within-subject change in accuracy approaching strangers (a) and withdrawing from strangers (b) from pre-vaccine to post-vaccine predicted by within-subject change in IL-6 from pre-vaccine to post-vaccine. Models adjusted for sex and BMI.

Discussion

Increases in inflammation often lead to the prototypical "sickness behavior" of social withdrawal, but recent work suggests that the effects of inflammation on social behavior may be more nuanced, such that whether a person approaches or withdraws in the face of an inflammatory challenge may depend on one's relationship to a given social target (Eisenberger et al., 2017; Muscatell & Inagaki, 2021). Data from the present study contribute to this growing literature, as we found that greater increases in inflammation (i.e., levels of IL-6) following the influenza vaccine were associated with greater withdrawal behavior from strangers, but not close others. Specifically, using a standard computerized task of social approach and withdrawal behavior, greater IL-6 increases from pre- to post-vaccine were associated with decreased accuracy in approaching strangers and increased accuracy in withdrawing from strangers. Change in IL-6 was not associated with changes in the speed at which participants approached or withdrew from strangers, or any automatic withdrawal behavior away from close others. These data suggest that relatively small changes in inflammation such as those elicited by the influenza vaccine are related to automatic social avoidance/withdrawal behavior specifically away from strangers, with no associations between change in inflammation and avoidance/withdrawal behavior away from close others. This is the first known study to demonstrate differences in withdrawal behavior based on target following an inflammatory challenge in humans.

The finding that greater increases in inflammation are associated with greater withdrawal from strangers aligns with theoretical and empirical work showing links between inflammation and social withdrawal (Dantzer et al., 2008; Hart, 1998), such as reduced social exploration in animals (Bluthe et al., 1994; 1996; Marvel et al., 2004), increased feelings of depressed mood and social disconnection in humans (Eisenberger et al., 2009; 2010; Moieni et al., 2015) and decreased contact with peripheral or less familiar social others (Lindsay et al., 2021). Critically, the present study builds on the prior literature in two key ways. First, all prior work found effects using a relatively extreme inflammatory challenge (i.e., LPS/endotoxin) to induce increases in inflammation; the current findings extend this to include the low-grade inflammatory challenge of the influenza vaccine. Second, prior human work used self-reports and brain-based measures to quantify social connection/disconnection (Eisenberger et al., 2009; Inagaki et al., 2012; Muscatell et al., 2016), but no work has studied *actual* social behavioral responses (and not simply self-reports) following an inflammatory challenge. Thus, the present study provides the first test of the association between changes in inflammation and objective social behavioral responses in humans, specifically increased accuracy in withdrawing from strangers and decreased accuracy in approaching strangers.

We also found that changes in inflammation following the influenza vaccine were *not* associated with changes in self-reported motivation to engage in affiliative social behaviors with new or existing relationships. At the low levels of inflammation induced by the influenza vaccine, people's self-reported desire to withdraw from unfamiliar others (i.e., new relationships) or connect with familiar others (i.e., existing relationships) might have been outside their conscious awareness, and thus not detectable in explicit self-report measures. Because greater changes in IL-6 were associated with the more "implicit" measure of automatic withdrawal behavior from unfamiliar others (i.e., strangers) but not with deliberate self-reported motivation to withdraw, these findings suggest that the low levels of inflammation induced here may have been sufficient to correlate with automatic but not conscious, self-reported social behavior. In addition, given that the self-report measure asked participants *generally* about their new and existing relationships but not about motivation to engage with specific social targets (e.g., a romantic partner or parent), it may not have captured associations between inflammation and motivation to engage with specific individuals in one's social network. Future research should explore how changes in inflammation in response to the influenza vaccine are associated with self-reported affiliative (or withdrawal) social behavior toward a specific close other. Despite the null effects with the self-report measures, their inclusion still advances the literature by demonstrating the importance of distinguishing between implicit, automatic social behavior and explicit, conscious, self-reports of social behavior following an inflammatory challenge.

Although we found a consistent association between inflammation and withdrawal behavior from strangers, contrary to our hypotheses, we did not find strong evidence that greater inflammation following the influenza vaccine was associated with approach behavior toward close others. The one exception was that participants who demonstrated greater increases in IL-6 decreased in the speed at which they approached their close other (but did not change in accuracy), suggesting that participants with a larger inflammatory response to the vaccine demonstrated behavior consistent with wanting to approach their close other. However, this result emerged only when controlling for pre-vaccine levels of IL-6 and there is ongoing debate about the most appropriate way to account for baseline levels when using change scores in analyses (Sorjoonen et al., 2019). These (mostly) null findings are in contrast with other experimental animal and human work, which has shown that exposure to an inflammatory challenge that elicits bigger increases in inflammation (e.g., LPS) predicts approach behavior toward close others or mates (Inagaki et al., 2015; Willette et al., 2007; Yee & Prendergast, 2010). One interpretation of these findings in light of the existing literature is that people may be more motivated to approach close others when they are acutely ill and experiencing high levels of inflammation (e.g., after endotoxin or after LPS-injection); on the contrary, in the present study, participants demonstrated a small increase in inflammation and their self-reported symptoms indicated they were not acutely sick, and thus they may not have been highly motivated to approach their close others. Additionally, from an evolutionary lens, avoiding strangers may be the most critical for survival and recovery during an acute illness – and therefore the primary focus of the brain when the body is inflamed – with approaching close others being a more secondary goal (Dantzer, 2001; Eisenberger, et al 2017). Future research could examine this hypothesis directly by comparing approach and withdrawal behavior following LPS-injection vs. the influenza vaccine, to examine if the magnitude of inflammatory response does indeed lead to differences in social approach behaviors toward close others and social withdrawal behaviors away from strangers.

It is worth noting some idiosyncrasies of the Approach-Avoid task used here that should be considered when interpreting the present results. First, this task is not particularly difficult (De Houwer et al., 2001), and therefore people do not make many errors on it. Thus, changes in accuracy from pre-vaccine to post-vaccine were quite small, given that across the board accuracy was very high. Despite these small changes in accuracy, we still found that the magnitude of the change in IL-6 predicted changes in accuracy approaching and withdrawing from strangers. Further, while performance on the computer-based task of approach/withdraw behavior used here is not the most ecologically-valid measure of social behavior, other work has shown that responses to this automatic task are related to real-world behavior. For example, drinkers who demonstrated greater approach motivation toward alcohol trials on the task reported higher alcohol cravings (Field et al., 2005) and smokers who approached smoking-related images faster reported higher nicotine cravings (Mogg et al., 2005). Beyond this specific task, some prior work in social cognition has shown that behavior on automatic/implicit tasks is related to behavior in the real world (e.g., Greenwald et al., 2003; McConnell & Leibold, 2001); however, other work has shown the opposite, or simply no association, between behavior on implicit tasks and real-world behavior (Blair, 2001; Dovidio et al., 2001; Karpinski & Hilton, 2001). As such, future work should examine if small changes in approach/avoid behavior on this task following an inflammatory challenge predict changes in social behavior “in the wild”, and/or utilize more ecologically-valid social behavior measures.

Finally, the present study contributes to a growing body of work documenting the utility of using the influenza vaccine as a low-grade inflammatory challenge (Boyle et al., 2019; Kuhlman et al., 2018; 2020; Radin et al., 2021). Overall, the sample demonstrated a significant increase in circulating IL-6 levels from before the vaccine to 24-hours after receiving it (with 80% of participants demonstrating an increase in IL-6). While the increase in IL-6 was small (i.e., 1.16 pg/mL on average) and not associated with changes in self-reported physical symptoms, these findings add support to the literature that the influenza vaccine is a viable way to manipulate low-grade levels of inflammation in humans. Future work should expand on these initial findings to examine how social approach and withdrawal behavior converges or differs following other inflammatory challenge paradigms (e.g., endotoxin or typhoid).

It is important to note limitations. No causal conclusions can be drawn from this work because of the lack of a control or placebo condition. Like other existing work using the influenza vaccine to induce an inflammatory response (Carty et al., 2006; Christian et al., 2011; Kuhlman et al., 2018; Tsai et al., 2005), the present study tests within-subject hypotheses. Specifics of our sample demographics also limit generalizability. Our sample was predominantly female, but we did not have a large enough sample size to meaningfully test for interactions with assigned sex at birth. Given that prior work has found sex differences in perceptions following an inflammatory challenge (Moieni et al., 2015; 2019), future work should consider the potential moderating role of sex assigned at birth. Further, future work should also replicate these findings in a sample with a bigger age range or different age groups. In addition, because of the small sample size used here, findings should be considered preliminary and will need to be replicated in future work.

Some methodological limitations should also be considered. The correlation between change in IL-6 and time between the two blood draws, as well as the correlation between change in IL-6 and time between when the vaccine was administered and when the post-vaccine blood draw was taken, were approaching statistical significance (p = .10; p = .09, respectively). These correlations suggest the possibility that levels of IL-6 were somewhat sensitive to time of day the blood was drawn and the delay between when the vaccine was given and when the post-vaccine blood draw occurred. Given that the influenza vaccine as inflammatory challenge paradigm is still fairly new, these data suggest that more research is needed to fully map the kinetics of the inflammatory response. Regarding the Approach-Avoid (Manikin) task used to measure automatic social behavior, we note that the photos of strangers were not matched to the demographic characteristics (e.g., gender presentation; racial phenotypically) of the close other, and we did not collect ratings of familiarity or closeness to strangers. As such, we cannot be certain that differences between findings for the strangers vs. close others are not due to demographic, familiarity, or closeness differences. While most work, including the present study, examining within-person changes in inflammation following the influenza vaccine in humans has focused on IL-6 as a marker of inflammation, we do not mean to argue that the effects seen here are unique or specific to IL-6, and future research should explore other markers of inflammation (e.g., IL-1ß). Because the time course of IL-6 reactivity to the influenza vaccine has been most widely-studied (Radin et al., 2021), we did not measure other cytokines here as doing so may have risked missing their peak response. Finally, data were collected during the 2020-2021 coronavirus pandemic, which may have influenced results in unforeseen ways.

Despite these limitations, the current study advances knowledge regarding the association between inflammation and social behavior, finding greater circulating IL-6 following the influenza vaccine associated with more withdrawal behavior from strangers. In addition, one intriguing finding suggests that when accounting for pre-vaccine IL-6, greater increases in inflammation were associated with faster approach behavior toward a close other. These data triangulate on the possibility that a low-grade inflammatory stimulus may not induce the uniform "sickness behavior" of social withdrawal, but rather withdrawal behavior that is specific to strangers and not close others. This work thus adds to the growing literature suggesting that we need to move beyond a singular focus on the effects of inflammation on social withdrawal to instead appreciate the nuanced ways in which inflammation may shape social behavior differently depending upon the magnitude of the inflammatory response, and the target of social behavior.

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Supplemental Material- Table of Contents

Total Number of Participants Screened Out or Excluded

In total, 68 interested individuals screened out of participating in the study. Fifty-four individuals expressed interest but were ineligible based on the screening questionnaire, which assessed inclusion/exclusion criteria. Fourteen additional individuals were determined to be ineligible during the consent process (e.g., had recently had the flu, were taking a beta blocker, had a needle phobia, etc.).

Table of Raw and Winsorized Values From Approach-Avoid Task

Supplementary Table 1 provides information about the five outlying values from the Approach-Avoid task, and the new, transformed values after outliers were winsorized.

Supplementary Table 1

Raw and Winsorized Values of Outlying Data from Approach and Withdrawal Behavioral Task

Variable	Raw Value (n)	Winsorized Value
Accuracy in Approach Behavior Toward Support Figure	.25 (1)	.186
Latency in Approach Behavior Toward Support Figure	-968.88 (1)	-760.51
Latency in Withdrawal Behavior Away From Support Figure	-521.00 (1)	-516.52
Accuracy in Withdrawal Behavior Away From Strangers	.29 (1)	.261
Latency in Withdrawal Behavior Away From Strangers	597.55 (1)	500.35

Correlation Table with Main Study Variables

All zero-order bivariate correlations for main study variables – pre-vaccine (baseline) measurements, post-vaccine measurements and change scores – can be found at this OSF page: https://osf.io/5e3uc/.

Correlations between Pre-Vaccine IL-6 and Social Behavior Task Performance at Baseline

Because there was variability in participants' baseline levels of IL-6, we examined bivariate correlations (without covariates) of pre-vaccine IL-6 and pre-vaccine social behavior scores. Results are in Supplementary Table 2.

Supplementary Table 2

Correlations between Pre-vaccine IL-6 and Social Behavior Task Performance at Baseline

Social Behavior Measures	*r* (*p*)
Accuracy in approach toward support figure	-.12 (.55)
Latency in approach toward support figure	.16 (.42)
Accuracy in withdrawal from support figure	-.06 (.75)
Latency in withdrawal from support figure	-.07 (.71)
Accuracy in approach toward strangers	-.06 (.76)
Latency in approach toward strangers	.07 (.72)
Accuracy in withdrawal from strangers	.06 (.78)
Latency in withdrawal from strangers	.17 (.38)

Results of Changes in IL-6 Predicting Change in Approach and Withdrawal Behavior Including Non-Transformed Raw Data (i.e., including outliers)

Supplementary Tables 3 and 4 show results of change in IL-6 predicting approach and withdrawal behavior using the original raw, not winsorized, values. Model results do not change.

Supplementary Table 3

Model results predicting change in automatic approach and withdraw behavior toward the support figure from change in IL-6

Predictor	*b*	*SE*	*t*	95% CI	
				Lower	Upper
Predicting change in accuracy in approach behavior toward support figure					
Change IL-6	.04	.05	.74	-.07	.14
Sex	.04	.04	.96	-.04	.12
BMI	.003	.003	.87	-.004	.01
Relationship type	.03	.02	1.58	-.01	.06
Predicting change in latency in approach behavior toward support figure					
Change IL-6	-309.96	177.78	-1.74	-677.74	57.81
Sex	-194.97	134.85	-1.45	-473.92	83.98
BMI	-16.41	10.61	-1.55	-38.35	5.53
Relationship type	-113.07	57.83	-1.96	-232.70	6.56
Predicting change in accuracy in withdrawal behavior away from support figure					
Change IL-6	-.07	.06	-1.18	-.19	.05
Sex	-.09	.04	-1.99	-.18	.003
BMI	-.003	.003	-.87	-.01	.004
Relationship type	.02	.02	-1.29	-.06	.01
Predicting change in latency in withdrawal behavior away from support figure					
Change IL-6	32.95	126.63	.26	-229.00	294.91
Sex	137.76	96.05	1.43	-60.93	336.45
BMI	13.02	7.55	1.72	-2.60	28.65
Relationship type	13.30	41.19	.93	-46.91	123.51
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels					
Predicting change in accuracy in approach behavior toward support figure					
Change IL-6	.05	.06	.77	-0.08	0.17
Sex	.03	.04	.73	-0.06	0.12

BMI	.002	.004	.43	-0.01	0.01
Relationship type	.03	.02	1.48	-0.01	0.06
Pre-vaccine IL-6	.02	.07	.29	-0.12	0.16
Predicting change in latency in approach behavior toward support figure					
Change IL-6*	**-465.19**	**201.14**	**-2.31**	**-882.33**	**-48.06**
Sex	-103.13	144.58	-.71	-402.97	196.70
BMI	-2.01	14.04	-.14	-31.13	27.11
Relationship type	-97.93	57.16	-1.71	-216.47	20.60
Pre-vaccine IL-6	-340.12	224.79	-1.51	-806.31	126.08
Predicting change in accuracy in withdrawal behavior away from support figure					
Change IL-6	-.08	.07	-1.14	-0.22	0.06
Sex	-.08	.05	-1.65	-0.18	0.02
BMI	-.002	.01	-.43	-0.01	0.01
Relationship type	.02	.02	-1.20	-0.06	0.02
Pre-vaccine IL-6	-.02	.08	-.28	-0.18	0.14
Predicting change in latency in withdrawal behavior away from support figure					
Change IL-6	123.22	145.73	.85	-179.00	425.45
Sex	84.36	104.75	.81	-132.88	301.60
BMI	24.65	10.17	.46	-16.45	25.74
Relationship type	29.50	41.41	.71	-56.38	115.38
Pre-vaccine IL-6	197.78	162.87	1.21	-139.99	535.55

Note. BMI = Body Mass Index. $^{\dagger}p$ =.05. $^{*}p$ <.05.

Supplementary Table 4

Model results predicting change in automatic approach and withdrawal behavior toward stranger from change in IL-6

Predictor	*b*	*SE*	*t*	95% CI	
				Lower	Upper
Predicting change in accuracy in approach behavior toward strangers					
Change IL-6*	**-.15**	**.06**	**-2.47**	**-.28**	**-.03**
Sex	-.08	.04	-1.86	-.17	.01
BMI	-.01	.004	-2.00	-.02	.0001
Predicting change in latency in approach behavior toward strangers					
Change IL-6	120.69	129.51	.93	-146.61	387.99
Sex	93.40	91.27	1.02	-94.97	281.77
BMI	15.50	7.62	2.03†	-.24	31.23
Predicting change in accuracy in withdrawal behavior away from strangers					
Change IL-6†	**.13**	**.07**	**2.03**	**-.002**	**.27**
Sex	.02	.05	.38	-.08	.11
BMI	.002	.004	.62	-.01	.01
Predicting change in latency in withdrawal behavior away from strangers					
Change IL-6	-46.56	143.70	-.32	-343.15	250.03
Sex	-25.75	101.27	-.25	-234.76	183.26
BMI	1.45	8.46	.17	-16.01	18.91
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels					
Predicting change in accuracy in approach behavior toward strangers					
Change IL-6*	**-.16**	**.08**	**-2.08**	**-0.31**	**0.00**
Sex	-.08	.05	-1.66	-0.18	0.02
BMI	-.01	.01	-1.42	-0.02	0.003
Pre-vaccine IL-6	-.01	.08	-.06	-0.18	0.17
Predicting change in latency in approach behavior toward strangers					
Change IL-6	149.30	155.80	.96	-173.00	471.59
Sex	79.89	100.88	.79	-128.81	288.58
BMI	13.10	10.41	1.26	-8.44	34.64
Pre-vaccine IL-6	59.35	171.84	.35	-296.13	414.84
Predicting change in accuracy in withdrawal behavior away from strangers					
Change IL-6*	**.18**	**.08**	**2.42**	**0.03**	**0.34**
Sex	-.01	.05	-.14	-0.11	0.10
BMI	-.002	.01	-.38	-0.01	0.01

Pre-vaccine IL-6	.11	.08	1.27	-0.07	0.28
Predicting change in latency in withdrawal behavior away from strangers					
Change IL-6	-263.25	151.05	-1.74	-575.72	49.21
Sex	76.58	97.81	.78	-125.75	278.91
BMI	19.59	10.10	1.94	-1.30	40.47
Pre-vaccine IL-6*	**-499.57**	**166.61**	**-2.70**	**-794.22**	**-104.93**

Note. BMI = Body Mass Index. $^{\dagger}p = .05$. $*p < .05$.

Results of Changes in IL-6 Predicting Change in Motivation to Foster Connection with New and Existing Relationships, Controlling for Time Between Blood Draws

Supplementary Table 5 shows change in IL-6 predicting change in self-reported motivation to foster connection with new and existing relationships, while controlling for time between blood draws. Model results are the same as in the main text.

Supplementary Table 5

Model results predicting change in motivation to foster connection with new and existing relationships from change in IL-6

Predictor	*b*	*SE*	*t*	95% CI	
				Lower	Upper
Predicting change in motivation to foster connection with new relationships					
Change IL-6	.01	.65	.02	-1.32	1.34
Sex	-.01	.40	-.03	-0.84	0.82
BMI	-.02	.03	-.68	-0.09	0.05
Time between blood draws	<.001	<.001	1.90	0.000	0.000
Predicting change in motivation to foster connection with existing relationships					
Change IL-6	.43	.65	.67	-0.91	1.77
Sex	.20	.41	.50	-0.63	1.04
BMI	.05	.03	1.44	-0.02	0.12
Time between blood draws	<.001	<.001	1.70	0.000	0.000
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels					
Predicting change in motivation to foster connection with new relationships					
Change IL-6	-.14	.77	-.18	-1.73	1.45
Sex	.05	.44	.11	-0.86	0.96
BMI	-.01	.05	-.25	-0.11	0.09
Pre-vaccine IL-6	-.31	.82	-.37	-2.01	1.40
Time between blood draws	<.001	<.001	1.89	0.000	0.000
Predicting change in motivation to foster connection with existing relationships					
Change IL-6	.67	.77	.86	-0.93	2.26
Sex	.11	.44	.24	-0.81	1.02
BMI	.03	.05	.66	-0.07	0.13
Pre-vaccine IL-6	.48	.83	.58	-1.23	2.18

Time between blood draws	<.001	<.001	1.64	0.000	0.000

Note. BMI = Body Mass Index. $^{\dagger}p$ <.06. *p <.05.

Results of Changes in IL-6 Predicting Change in Approach and Withdrawal Behavior, Controlling for Time Between Blood Draws

Supplementary Tables 6 and 7 show results of change in IL-6 predicting change in approach and withdrawal behavior, controlling for time between blood draws. Model results do not change.

Supplementary Table 6

Model results predicting change in automatic approach and withdraw behavior toward the support figure from change in IL-6

Predictor	*b*	*SE*	*t*	95% CI	
				Lower	Upper
Predicting change in accuracy in approach behavior toward support figure					
Change IL-6	.02	.05	.33	-0.08	0.11
Sex	.03	.04	.89	-0.04	0.11
BMI	.002	.003	.71	-0.004	0.01
Relationship type	.02	.02	1.40	-0.01	0.05
Time between blood draws	<-.001	<.001	-.56	0.000	0.000
Predicting change in latency in approach behavior toward support figure					
Change IL-6	-298.58	167.48	-1.78	-645.92	48.75
Sex	-134.38	126.43	-1.06	-396.59	127.82
BMI	-14.02	9.56	-1.47	-33.85	5.80
Relationship type	-86.27	52.65	-1.64	-195.46	22.92
Time between blood draws	-.01	.01	-.74	-0.02	0.01
Predicting change in accuracy in withdrawal behavior away from support figure					
Change IL-6	-.07	.06	-1.20	-0.20	0.05
Sex	-.08	.05	-1.79	-0.18	0.01
BMI	-.003	.003	-.85	-0.01	0.004
Relationship type	-.02	.02	-1.21	-0.06	0.02
Time between blood draws	<-.001	<.001	-.32	0.000	0.000
Predicting change in latency in withdrawal behavior away from support figure					
Change IL-6	53.29	134.00	.40	-224.61	331.18
Sex	122.98	101.16	1.22	-86.80	332.77
BMI	13.01	7.65	1.70	-2.85	28.87

Relationship type	34.95	42.12	.83	-52.41	122.31
Time between blood draws	.003	.01	.53	-0.01	0.02
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels					
Predicting change in accuracy in approach behavior toward support figure					
Change IL-6	.02	.06	.41	-0.09	0.14
Sex	.03	.04	.69	-0.06	0.11
BMI	.001	.004	.33	-0.01	0.01
Relationship type	.02	.02	1.31	-0.01	0.05
Pre-vaccine IL-6	.02	.06	.27	-0.11	0.14
Time between blood draws	<-.001	<.001	-.55	0.000	0.000
Predicting change in latency in approach behavior toward support figure					
Change IL-6*	**-443.95**	**185.41**	**-2.39**	**-829.52**	**-58.37**
Sex	-48.64	133.30	-.37	-325.86	228.58
BMI	-.34	12.57	-.03	-26.48	25.79
Relationship type	-72.21	51.61	-1.40	-179.53	35.12
Pre-vaccine IL-6	-322.96	201.21	-1.61	-741.39	95.47
Time between blood draws	-.01	.01	-.73	-0.02	0.01
Predicting change in accuracy in withdrawal behavior away from support figure					
Change IL-6	-.08	.07	-1.16	-0.23	0.07
Sex	-.08	.05	-1.49	-0.18	0.02
BMI	-.002	.01	-.43	-0.01	0.01
Relationship type	-.02	.02	-1.12	-0.06	0.02
Pre-vaccine IL-6	-.02	.08	-.27	-0.18	0.14
Time between blood draws	<-.001	<.001	-.31	0.000	0.000
Predicting change in latency in withdrawal behavior away from support figure					
Change IL-6	140.59	152.26	.92	-176.05	457.24
Sex	71.48	109.47	.65	-156.18	299.14
BMI	4.79	10.32	.47	-16.67	26.25
Relationship type	26.51	42.38	.63	-61.63	114.64
Pre-vaccine IL-6	193.98	165.24	1.17	-149.65	537.60
Time between blood draws	.003	.01	.50	-0.01	0.02

Note. BMI = Body Mass Index. $^{\dagger}p$ =.05. $^{*}p$ <.05.

Supplementary Table 7

Model results predicting change in automatic approach and withdrawal behavior toward stranger from change in IL-6

Predictor	*b*	*SE*	*t*	95% CI	
				Lower	Upper
Predicting change in accuracy in approach behavior toward strangers					
Change IL-6*	**-.16**	**.07**	**-2.38**	**-0.30**	**-0.02**
Sex	-.08	.05	-1.70	-0.17	0.02
BMI	-.01	.004	-1.97	-0.02	0.0001
Time between blood draws	<-.001	<.001	-.29	0.000	0.000
Predicting change in latency in approach behavior toward strangers					
Change IL-6	127.83	139.37	.92	-160.47	416.13
Sex	89.65	96.00	.93	-108.93	288.24
BMI	15.54	7.79	2.00	-0.57	31.66
Time between blood draws	.001	.01	.16	-0.01	0.01
Predicting change in accuracy in withdrawal behavior away from strangers					
Change IL-6*	**.15**	**.07**	**2.29**	**0.02**	**0.29**
Sex	.002	.05	.04	-0.09	0.10
BMI	.002	.004	.63	-0.01	0.01
Time between blood draws	<.001	<.001	1.25	0.000	0.000
Predicting change in latency in withdrawal behavior away from strangers					
Change IL-6	-80.22	141.54	-.57	-373.02	212.58
Sex	-9.80	97.50	-.10	-211.48	191.89
BMI	1.29	7.91	.16	-15.08	17.65
Time between blood draws	-.01	.01	-.86	-0.02	0.01
Ancillary Analyses Adjusting for Pre-Vaccine IL-6 Levels					
Predicting change in accuracy in approach behavior toward strangers					
Change IL-6*	**-.16**	**.08**	**-2.04**	**-0.33**	**0.003**
Sex	-.08	.05	-1.53	-0.18	0.03
BMI	-.01	.01	-1.41	-0.02	0.003
Pre-vaccine IL-6	-.004	.09	-.04	-0.18	0.17
Time between blood draws	<-.001	<.001	-.28	0.000	0.000

Predicting change in latency in approach behavior toward strangers					
Change IL-6	155.07	164.34	.94	-185.74	495.88
Sex	76.07	105.33	.73	-141.61	295.27
BMI	13.20	10.66	1.24	-8.92	35.31
Pre-vaccine IL-6	58.08	175.85	.33	-306.62	422.78
Time between blood draws	.001	.01	.14	-0.01	0.01
Predicting change in accuracy in withdrawal behavior away from strangers					
Change IL-6*	**.20**	**.08**	**2.60**	**0.04**	**0.35**
Sex	-.02	.05	-.40	-0.12	0.08
BMI	-.002	.01	-.32	-0.01	0.01
Pre-vaccine IL-6	.10	.08	1.19	-0.07	0.26
Time between blood draws	<.001	<.001	1.20	0.000	0.000
Predicting change in latency in withdrawal behavior away from strangers					
Change IL-6	-271.18	146.33	-1.85	-574.65	32.29
Sex	80.11	93.79	.85	-114.40	274.61
BMI	17.75	9.49	1.87	-1.94	37.44
Pre-vaccine IL-6*	**-407.21**	**156.59**	**-2.60**	**-731.94**	**-82.47**
Time between blood draws	-.004	.01	-.82	-0.02	0.01

Note. BMI = Body Mass Index. $^{\dagger}p = .05$. $^{*}p < .05$.