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Perception of unfamiliar caregivers during sickness – using the new Caregiver Perception Task (CgPT) during experimental endotoxemia

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Abstract

Social withdrawal is a well-established part of sickness behavior, but in some contexts sick animals might gain from keeping close instead of keeping away. For instance, sick individuals are more willing to be near known individuals who can provide care and safety (close others) compared to when healthy. Yet, interactions with some strangers might also be beneficial (i.e., healthcare professionals), but it is not known how sickness interplay with social behavior towards such individuals. Here, we assessed if sickness affects perception of caregivers and developed a new task, the Caregiver Perception Task (CgPT). Twenty-six participants conducted the CgPT, once after an injection of lipopolysaccharide (LPS, 0.8 ng/kg body weight, n=24), and once after an injection of saline (n=25), one hour and forty-five minutes post-injection. During the task, participants watched short video-clips of three types of caregivers: a healthcare professional taking care of a sick individual (HP-c), a

healthcare professional not taking care of a sick individual (HP-nc), and a non-healthcare professional taking care of their sick adult child or partner (NHP-c). After each video clip, the likability, trustworthiness, professionalism, and willingness to interact with and receive care from the caregiver were rated on visual analogue scales. Results showed that participants injected with saline rated healthcare professionals who did not take care of a sick individual less positively on all aspects compared to healthcare professionals who took care of a sick individual. Moreover, compared to saline, LPS increased the participants' willingness to receive care from healthcare professionals and non-healthcare professionals providing care, but not from healthcare professionals not providing care. Thus, our results indicate that sick individuals may approach unknown individuals with potential to provide care and support.

1. Introduction

"*There are only four kinds of people in the world: Those who have been caregivers. Those who are currently caregivers. Those who will be caregivers, and those who will need a caregiver."* – Rosalyn Carter

Humans and other animals respond to intruding pathogens with the triggering of immune cascades aiming at neutralizing the invaders, but also with various behavioral changes initiated by immune-to-brain signaling (Dantzer et al., 2008). These changes include increased fatigue, decreased food intake, and an overall reduction in activity (Dantzer, 2001). Such recuperative "sickness behavior" is preserved across species (Lopes et al., 2021) and is believed to adaptively promote immune functions and recovery (Aubert, 1999). Social withdrawal was early on described as a hallmark of sickness (Dantzer and Kelley, 1989). For instance, sick rodents are less interested in exploring new social objects (Fishkin and Winslow, 1997). Sick female rodents also exhibit decreased sexual behavior (Avitsur and Yirmiya, 1999). Humans made sick experimentally by an intravenous injection of a bacterial endotoxin (lipopolysaccharide, LPS) feel more socially disconnected (Eisenberger et al., 2010) and are more willing to be alone (Hannestad et al., 2011), compared to when healthy. This inflammation-induced social withdrawal fits with the adaptive framing of sickness behavior, allowing for redirection of energy from social behaviors to immune responses (Dantzer, 2001), but also by protecting the sick individual from encountering threatful others who could cause additional harm to a body with an ongoing infection (Hart, 1988; Leschak and Eisenberger, 2019). Indeed, humans injected with LPS are more sensitive to social threats (Inagaki et al., 2012) and to social exclusion (Eisenberger et al., 2009) compared to when healthy. Crucially, other individuals do not only convey risk for harm; they can also bring care. Hence, if a social interaction results in care, it might be favorable for a sick animal to keep close rather than keeping away (Smith and Bilbo, 2021).

It has been suggested that sickness affects social behavior in an ambivalent manner (Hennessy et al., 2014; Muscatell, 2021; Smith and Bilbo, 2021). Social withdrawal is not the sole outcome in studies investigating inflammation-induced changes in social behavior, several findings suggest the potential for sickness to foster social approach under specific conditions. Apes cling to their cage mates (Willette et al., 2007) and rats increase their huddling behavior, at the same time as they show increased avoidance of social environments (Yee and Prendergast, 2012) after an injection with LPS compared to saline. Additionally, humans show an LPS-induced increase in sensitivity to positive feedback from a person evaluating them based on an interview (Muscatell et al., 2016). It is sensible that the direction of the social behavioral change during sickness is affected by the identity and function of the social interaction partner (Muscatell and Inagaki, 2021). For instance, immune challenged bats decrease social grooming of non-kin while maintaining grooming of their offspring (Stockmaier et al., 2020). In humans, sick individuals express an increased desire to be near a support figure (Inagaki et al., 2015) after an LPS injection compared to a saline injection. Furthermore, in an approach-avoidance task where participants were instructed to move a manikin towards or away from a picture of either a support figure or a

stranger, an increase in the concentration of the pro-inflammatory marker interleukin-6 after an influenza shot was associated with a faster approach towards support figures (Jolink et al., 2022). Altogether, these findings imply that the ambivalent nature of social sickness behavior lies in the relationship between the sick individual and the target of social interaction, thus being functionally flexible. Yet, some strangers might be especially prone to provide care, even for unknown sick individuals (i.e., healthcare professionals). Thus, it is possible that sickness increases positive social behavior towards unknown individuals if they are clearly in their healthcare professional roles, but this remains to be investigated. Furthermore, given the importance of care providers' behavior on health outcomes (Finset, 2014), a sickness-induced change of an individual's social approach is likely to be affected by the perceived benefit from interaction with a specific individual.

In the current study, we aimed to investigate if acute sickness modifies the explicit preferences for healthcare professionals using a newly developed task, the Caregiver Perception Task (CgPT). In a double-blind, placebo-controlled, randomized, cross-over study, twenty-six participants received an intravenous injection of LPS (0.8 ng/ kg body weight) and saline at two different occasions, and conducted the CgPT during the peak of sickness symptoms. During the CgPT, participants watched video recordings showing scenes with healthcare professionals providing care or not to sick individuals, and non-healthcare professionals providing care to sick individuals, and rated the professional and non-professional caregivers on different aspects (i.e., likability, trust, professionalism, willingness to interact, willingness to receive care). The purpose with the design of the task was to create a controlled standardized test to assess perception of unfamiliar caregivers in different sickness-relevant conditions. As described above, previous studies investigating social behavior during sickness have used pictures of close others and pictures of strangers (Inagaki et al., 2015; Jolink et al., 2022). The video clips in the CgPT provides the participant with more information about the unfamiliar individual (e.g., ability to provide care), and thus allows to assess if sick individuals exhibit positive social behavior towards some strangers with specific characteristics. Moreover, the CgPT resembles a real-life setting where sick individuals might see unfamiliar caregivers interacting with other individuals (e.g., at the emergency department). Hence, we believe that this more ecologically valid design of the task can add to the current literature on ambivalent social sickness behavior (Hennessy et al., 2014; Muscatell, 2021; Smith and Bilbo, 2021) by nuancing the view of sickness-induced avoidance of strangers. We also measured emotional expressions of the participants during the CgPT. We hypothesized that LPS would increase positive ratings and the facial expressions of happiness towards healthcare professionals taking care of sick individuals, compared to healthcare professionals who did not provide any care and compared to non-healthcare professionals providing care.

2. Method

2.1 Participants

This study was part of an investigation of individual differences in response to inflammatory stimulation and took place at the Karolinska University Hospital (Stockholm, Sweden), between October 2021 and August 2022. The study was ethically approved (2020-05177, 2021-03034, 2021-04705, and 2021-05317-02), and pre-registered (https://osf.io/mgu73) prior to the start of the data collection. The study was advertised at campuses in the Stockholm area, via Accindi (www.accindi.se), and a participant recruitment system (https://ki-behavioraltesting.sona-systems.com/) for psychological tests. Prior to inclusion, participants provided informed consent and took part in a health screening procedure. The screening included a thorough medical examination, comprehensive laboratory analyses, and an assessment of depressive symptoms using the PHQ-9 questionnaire (Kroenke et al., 2001). According to the inclusion and exclusion criteria of the study, participants had to be between 18-35 years of age, normal weight (BMI 18.5-25 kg/m^2), non-smokers and non-excessive drinkers, without somatic and psychological disease, and without medication (except from contraceptives). Participants conducted some tasks (not the CgPT) in a MR scanner, and thus had to be eligible for brain scanning (e.g., not suffer from claustrophobia nor have metallic implants). Additionally, participants had to be vaccinated against COVID-19 (two doses, last dose at least one month prior to participation), and should not have had COVID-19 or symptoms indicating a SARS-CoV-2 infection the past 6 months, or a history of severe or long-term COVID-19 (high intensity or/and more than 8 weeks of symptoms).

Twenty-six (gender: 15 women, 10 men, 1 transgender man; average age: 25.2±4.5 years; BMI range: 19.5-25.9) healthy volunteers were included in the study. The sample size calculation was based on the main hypothesis of the main study, investigating how inflammation affects brain morphology (https://osf.io/t6bjh). We conducted an *a posteriori* power calculation (with G*Power, alpha=0.05, power=80%) indicating that the sample size of 26 allows to detect a medium-to-large effect size (f=0.29). Noticeably, previous studies indicate that a sample size of 20-25 is sufficient to investigate LPS-induced behavioral changes (Dooley et al., 2018). Participants were compensated with 1750 SEK for each study day (i.e., 3500 SEK in total, which equals to about $350/€320).

2.2 Study design

The study had a double-blind, within-subject, crossover, placebo-controlled design. In order to induce an acute systemic inflammatory response, participants were injected with an intravenous injection of LPS (*Escherichia coli* endotoxin, Lot H0K354, CAT number 1235503, United States Pharmacopeia, Rockville, MD, USA) at 0.8 ng per kg body weight on one occasion, and saline (0.9% NaCl) on another occasion (placebo). The injections were given in a randomized order and were separated with a washout period of at least 4 weeks (range: 5-15 weeks). Participants and all study personnel, apart from the medical doctor who took

care of the participants and who was responsible for the participant's safety during the day, were blind to the order of the assigned treatments. Three participants took part in the first study day only (*N*=2 saline, *N*=1 LPS) due to developing COVID-19 in between the two sessions.

2.3 Inflammatory markers and sickness behavior

Blood samples were drawn in EDTA vacutainers® at baseline, and at 1 hour, 2 hours, 3 hours, 4 hours, and 5 hours post-injection. Samples were centrifuged for 15 minutes at 2000 g (4°C), and extracted plasma aliquots were stored at -80 °C prior to analysis. Concentration (pg/mL) of the cytokine interleukin (IL)-6 was measured as a part of a multiplex assay including IL-8, IL-10, and tumor necrosis factor-α (TNF-α) using a V-PLEX Custom Human Biomarkers assays (Meso Scale Discovery (MSD), Rockville, USA). The multiplex assays were prepared in accordance with the manufacturer's manual, and the plates were read on a SQ 120 instrument with the software Methodical Mind (version 1.0.38). The data was processed and extracted from the software Discovery Workbench (version 4.0.13, MSD). Samples were averaged across duplicates, and values below the detection range were replaced with the lower limit of detection value for each cytokine (IL-6 = 0.06 pg/ml, IL-8=0.07 pg/ml, IL-10 = 0.04 pg/ml, TNF-α = 0.04 pg/ml). Five values for IL-6 were below the limit of detection for the two duplicates and replaced with the lower limit of detection (0.06 pg/ml). Only the results for IL-6 are presented in the current paper to validate that the LPS injection induced a systemic inflammatory response.

Sickness behavior was measured at baseline, 50 minutes post-injection, and at 1, 2, 3, 4 and 5 hours post injection, using the Sickness Questionnaire (SicknessQ) (Andreasson et al., 2018). The questionnaire consists of ten items that measure sickness symptoms (e.g., "my body feels sore"). Each item is rated on a 4-point scale, with a higher score indicating more intense sickness behavior. Questionnaires were provided with the survey distribution program REDCap (Harris et al., 2019, 2009).

2.4 The Caregiver Perception Task (CgPT)

2.4.1 Description of the CgPT

To investigate if LPS-induced systemic inflammation affects perception of caregivers, we developed a computerized task in which participants watch and rate short video clips of caregivers. The task compares three different caregiver conditions: a healthcare professional in scrubs taking care of a sick individual (HP-c), a healthcare professional in scrubs not providing care (HP-nc), and a non-healthcare professional (parent or partner) taking care of their sick adult child or partner (NHP-c). This design focuses thus on the perception of healthcare professionals and enables assessments of the effect of type of caregiver (healthcare professional vs. non-healthcare professional) as well as the effect of caregiving per se (healthcare professional providing care vs. healthcare professional not

providing care), and how these effects interact with systemic inflammation. We chose not to include a condition with a non-healthcare professional not providing care for two main reasons: 1) to limit the duration of the task; 2) because a person in civil clothes who is not interacting with the sick individual might not be perceived as a caregiver.

2.4.2 Recording and processing of video stimuli

Eleven volunteering non-professional "actors" took part in video recordings after providing informed consent. Six actors (average age 29±1.5 years, 3 women) acted as sick, and five actors with healthcare professions (average age: 43±19.4 years, 3 women, two medical doctors, two psychologists, and one medical student) acted as caregivers (healthcare professionals and non-healthcare professionals). All actors were native Swedish speakers. The actors were divided into three teams that recorded three unique scenes each (one per condition). Two actor teams recorded the scenes with all possible gender combinations (sick female + female caregiver, sick male + female caregiver, sick female + male caregiver, sick male + male caregiver), while one group recorded the scenes only with a female caregiver due to shortage of male actors (sick female + female caregiver, sick male + female caregiver). Given that six scenes had four versions, and three scenes had two versions, the final sample constituted of 30 video clips.

The video clips were recorded at the MR centrum in the same study room and in a matching context and set-up as the present study, prior to the start of the data collection. Actors playing sick wore similar clothing as the study participants (white t-shirts and sweatpants), and were instructed to remove makeup prior to the recordings. Caregivers were provided with scrubs when acting as healthcare professionals, and kept their regular clothes when acting as non-healthcare professionals. To mimic the setting of the study day and to reduce risk for contagion, all caregivers wore facemasks. The videos were recorded with a GoPro® Hero 8 camera that was placed 1.9 m above the floor. The camera recorded continuously, and each scene was repeated as many times as possible during the recording session (1.5 hours). Actors were compensated with three movie ticket vouchers or one movie ticket voucher together with a gift card of 300 SEK (about $27/€25).

The scenes in the video clips resembled common interactions between participants injected with LPS and medical study personnel (see examples of scripts in supplementary text 1). In the HP-c condition, a medical doctor takes care of a sick individual (e.g., measuring temperature, helping the sick individual to the bathroom). In the NHP-c condition, a parent/partner takes care of their sick adult child or partner (e.g., providing tea or a magazine). The relationship between the sick individual and the caregiver was conveyed by the greeting (e.g., "Hi dad", "Hi sweetie") as well as with the behaviors of the caregiver (e.g. soothing touches). All scenes with caretaking (HP-c and NHP-c) includes both elements of instrumental support (e.g., providing a blanket or a glass of water) and emotional support (e.g., reassuring touch and empathic communication). In the HP-nc condition, a medical

doctor is present in the same room as a sick individual but without providing care (e.g., a medical doctor wearing scrubs checks blood samples while a sick individual looks at their phone). See information about the processing of the video clips in supplementary text 2.

For each participant, six video clips of caregivers were needed (see **Figure 1**). Thus, we created stimuli lists according to the following criteria: six unique scenes, two scenes per condition (2 HP-c, 2 HP-nc, 2 NHP-c), and one female and male caregiver per condition. The same caregiver did not participate as both a healthcare professional and a non-healthcare professional in the same list. These criteria resulted in four separate lists that were randomized across participants. To avoid confusion (e.g., watching the same scene with different actors), the participants watched the same list on both study days. To increase relatability, participants only watched videos with gender-matched sick individuals. Lists with a mix of sick women and males were prepared for non-binary participants, but only participants identifying as either male or female took part in the study.

2.4.3. Experimental task

Participants conducted the task 1h and 45 minutes after each injection. This time point occurs during the peak of sickness symptoms (Lasselin, 2021). Participants were seated in front of a curved monitor (1920 × 1080, 27', Dell SE2722H) adjusted to a comfortable height. Before starting the task, participants were instructed that they were going to watch video clips, and answer questions about the person outside of the bed in each video clip. Participants did not receive any other information about the context or individuals presented in the video clips (see full instructions in supplementary text 3). Each participant was assigned a stimuli list (see above) and watched and rated six video clips (see **Figure 1**). To prepare the participant for a new trial, a small square was presented for 1.5 seconds. A beep sounded before and after each video clip to indicate the stimuli length and enable matching of the stimuli with the facial expression data (see below). Each caregiver was rated on four visual analogue scales: How much do you like this person? (Not at all – Very much), How much do you trust this person? (Not at all – Very much), How much would you like to interact with this person right now? (Not at all – Very much), and How much would you like to be taken care of by this person right now? (Not at all – Very much). Additionally, healthcare professionals (HP-c, HP-nc) were rated on professionalism: How good is this person at their job? (Not at all – Very good). Each rating was saved as a value between 0 and 100 (a high value indicating a positive rating). Participants had an unlimited time for each rating (average response time after LPS: 3.8 sec±3.4 sec, average response time after saline: 4.2 sec ±2.6 sec, response time data are missing for the first study day of two participants due to logistic reasons). The order of the video clips and scales was randomized. To avoid fatigue, the task included a one minute break after the third video clip. The task lasted for approximately 15 minutes. The software OpenSesame (Mathôt et al., 2012) was used to prepare and run the task.

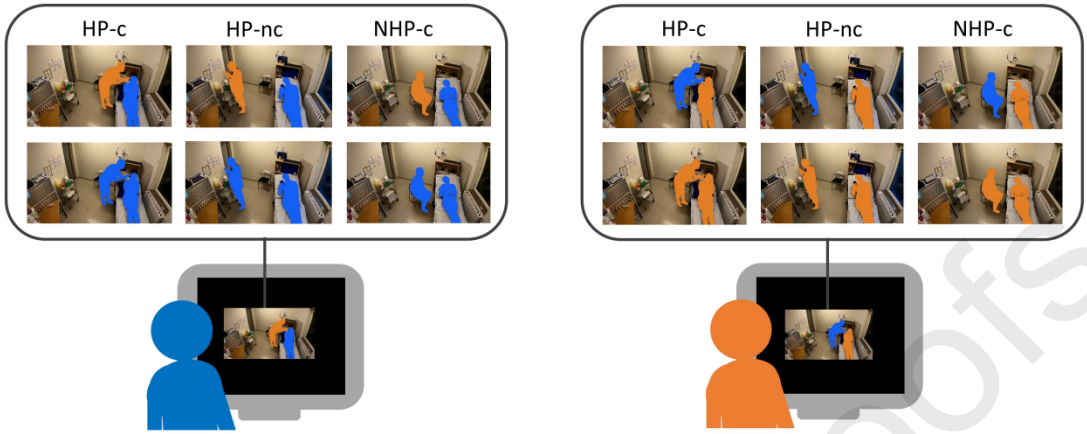

Figure 1. Stimuli presentation during the Caregiver Perception Task (CgPT). Participants watched six video clips, two of each caregiver condition (HP-c, HP-nc, NHP-c), in a randomized order. Male (blue) and female (orange) participants watched gender-matched actors playing sick individuals. All participants watched one scene with a female caregiver and one scene with a male caregiver per caregiver condition. After each video clip, participants rated the caregiver on different scales (i.e., likability, trust, professionalism, willingness to interact, willingness to receive care). *Abbrevations:* HP-c: Healthcare professionals taking care of a sick individual, HP-nc: healthcare professionals not taking care of a sick individual, NHP-c: non-healthcare professionals (i.e., parent/partner) taking care of their adult sick child or partner.

2.4.4 Collection of facial expressions

To investigate the emotional response to the caregiving scenes, participants' faces were recorded with a web camera (Logitech C925e) and the local recording option in ZOOM®. The Noldus FaceReader 9 (Noldus, 2021) was used to analyze facial expressions. The FaceReader is a well-used tool that can record facial expressions (neutral, happiness, sadness, anger, surprise, fear, disgust) from both photos and videos. A validation test showed that the software had an average accuracy of 99% when classifying emotions from a standardized stimuli set with photos of faces (Noldus, 2021; van der Schalk et al., 2011). Nevertheless, it is possible that the FaceReader will have less accuracy for more complex stimuli. The software calculates the intensity of each emotional expression (neutral, happiness, sadness, anger, surprise, fear, disgust), at each time frame, on a scale from 0 to 1.0. In the present study, the proportion of frames with an intensity above 0.5 was calculated for each emotion in each video stimulus. The analysis was conducted without calibration and with the default analysis settings. The calibration allows the software to correct for the baseline and neutral facial expression of the specific participant in order to calculate changes from baseline during the stimulus presentation. Nevertheless, we decided to use uncalibrated data due to the within-subject design, which allows for a control condition.

2.5 Statistical analysis

The analysis plan was preregistered on OSF (https://doi.org/10.17605/OSF.IO/WSGQD) prior to data analyses. Data files and scripts can be found via the same link. All analyses followed the preregistered analysis plan unless otherwise specified. All analyses were conducted in R, version 4.2.0 (R Core Team, 2017).

2.5.1 Validation of the effect of LPS on sickness responses

Two linear mixed models were conducted to validate the effect of LPS on systemic inflammation (IL-6 concentration in plasma) and sickness behavior (scores on the SicknessQ). Both models included treatment (LPS vs. saline), time, and treatment × time as fixed factors, and study day (1-2) as a covariate. The models did not converge when including the intercepts for participants and all random slopes: treatment × caregiver condition, treatment, and caregiver condition in participants. Hence, intercepts for participants and slopes for treatment in participants were included as random factors in both models. IL-6 concentrations were log10-transformed to meet model assumptions (normality and homoscedasticity of residuals). Linear mixed models were conducted using the *lmer* function from the *lme4* package (Bates et al., 2015). Fifteen blood samples out of a total of 294 (5%) were missing due to difficulties in taking blood (LPS=12, saline=3). No SicknessQ data was missing.

2.5.2 Perception of caregivers during experimental sickness

Five linear mixed models were conducted to assess the interaction effect of LPS and caregiver condition on ratings of caregivers (likability, trustworthiness, professionalism, willingness to interact, willingness to receive care). All models included treatment (LPS vs. saline), caregiver condition (HP-c vs. NHP-c and HP-nc), and treatment × caregiver condition (LPS × NHP-c and LPS × HP-nc) as fixed factors, and controlled for the study day (1-2) and the version of the stimuli list (1-4). In the preregistered analysis plan, we planned to include the stimuli list as a random effect, but we later choose to include it as a covariate instead, to simplify the models. Moreover, all models included random intercepts for participants as well as slopes for treatment × caregiver condition, treatment, and caregiver condition in participants. The model for willingness to interact with the caregiver was conducted with the *lmer* function from the *lme4* package (Bates et al., 2015), while the rest of the models were conducted with the function *blmer* from the package *blme* (Bates et al., 2015; Chung et al., 2013) due to convergence difficulties. The package *parameters* was used to retrieve p-values (Lüdecke et al., 2020). The models for likability and professionalism were rerun without an outlier in mean rating and showed similar results (see **Table S1**).

In accordance with the Bonferroni method, the alpha level was set to 0.013 for the scales that tested the same research question: likability, trustworthiness, willingness to receive care from caregivers, and willingness to interact with caregivers. The scale professionalism tested a different research question, thus, the alpha level was set to 0.05. See the analysis plan for details regarding the model selection (https://doi.org/10.17605/OSF.IO/WSGQD).

364

365 **2.5.3 Facial expressions while watching caregivers during experimental sickness**

366 One participant injected with saline missed facial expression data due to technical problems.
367 Additionally, three participants missed facial expression data for several video clips due to
368 problems with the camera (2 participants injected with LPS = missing data for two video
369 clips, 1 participant injected with saline = missing data for five video clips). Data from one
370 participant was excluded due to poor data quality (the participant hides their face with their
371 hand while watching the video clips). Moreover, data from one video clip presentation was
372 excluded for one participant injected with LPS due to poor data quality (face not visible
373 during 20% of the video presentation because the participant was sitting too close to the
374 screen).

375

376 Due to missing and excluded data, data for 266 video clip presentations (LPS=133,
377 saline=133) was available for analysis. The presentation of only 17% of these video clips
378 resulted in an expression of happiness. This amount of data was judged too small for
379 analyses of interactions between the treatment (LPS, saline) and caregiver condition (HP-c,
380 HP-nc, NHP-c) on emotional expressions to address our hypothesis. In order to explore if
381 experimental sickness by itself might modify the expression of emotions in general, as
382 indicated earlier (Sarolidou et al., 2019), we conducted exploratory analyses to assess the
383 effect of treatment (LPS vs. saline) on emotional expressions during the task. We did not
384 analyze the expression of fear and surprise, given that no video presentations resulted in an
385 expression of fear and only 2 video presentations resulted in an expression of surprise. For
386 remaining emotional expressions (neutral, happiness, sadness, anger, disgust) we conducted
387 paired samples Wilcoxon tests to assess if there was any difference in the mean expression
388 of each emotion after a LPS injection compared to a saline injection.

389

390 **3. Results**

391 ***3.1 Validation of the effect of LPS on sickness responses***

392 During the Caregiver Perception Task (CgPT), participants injected with LPS had significantly
393 higher concentrations of IL-6 (B=1.72(0.14), $p<0.001$), and higher SicknessQ scores
394 (B=11.82(1.31), $p<0.001$), compared to when injected with saline (**Table S2**, **Figure 2**).

395

396

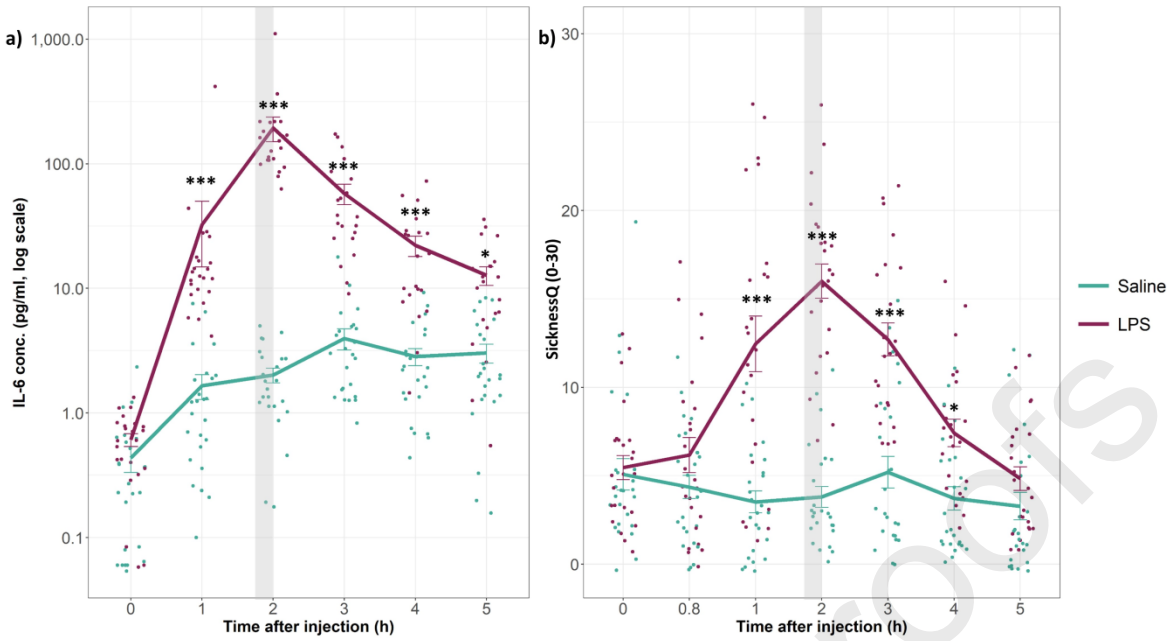

Figure 2. Effect of lipopolysaccharide (LPS) on interleukin-6 concentrations and sickness behavior. The injection of LPS (purple) significantly increased interleukin-6 concentrations (a) and SicknessQ scores (b), compared to saline (cyan). The Caregiver Perception Task (CgPT) was conducted 1h and 45min after each injection (grey area). Significance levels represent the interaction between LPS and time and were derived from linear mixed models. Log10 transformed interleukin-6 concentrations were used in the analysis while the figure shows raw data. The data points have been jittered to increase the readability of the figure. See **S2** for statistics. ***p<0.001, *p <0.05. Error bars: SEM. Abbrevations: IL-6: Interleukin-6, SicknessQ: Sickness Questionnaire, LPS: Lipopolysaccharide.

3.2 Perception of caregivers when healthy

Participants injected with saline rated healthcare professionals not taking care of sick individuals as less likable, less trustworthy, and less good at their job compared to healthcare professionals who took care of sick individuals (see **Table 1** and **Figure 3a-3c**). Participants injected with saline were also more willing to interact with and receive care from healthcare professionals taking care of sick individuals compared to healthcare professionals not taking care of sick individuals (see **Table 1** and **Figure 3d-3e**).

Non-healthcare professionals providing care were rated as less trustworthy compared to healthcare professionals taking care of sick individuals (see **Table 1** and **Figure 3b**). Additionally, there was a trend of a decreased willingness to receive care from non-healthcare professionals providing care compared to healthcare professionals providing care (see **Table 1** and **Figure 3d**).

3.3. *Perception of caregivers during experimental sickness*

Participants injected with LPS did not rate caregivers' likability, trustworthiness, professionalism, and willingness to interact differently, compared to when injected with saline (see **Table 1** and **Figure 3a-3d**). However, participants injected with LPS were more

willing to receive care from healthcare professionals providing care compared to when injected with saline (see **Table 1** and **Figure 3e**). The effect of LPS was similar in non-healthcare professionals providing care and in healthcare professional providing care, as indicated by the fact that the interaction effect of LPS and non-healthcare professionals on the willingness to receive care was not significant. In other words, participants injected with LPS were more willing to receive care also from non-healthcare professionals compared to when healthy. However, there was a negative interaction effect of LPS and healthcare professionals not providing care. Post-hoc analysis of the effect of LPS vs saline in the HP-nc condition only indicated that there was no significant difference in the willingness to receive care from healthcare professionals not providing care in the LPS condition compared to saline (B=1.4(5.7), p=0.8).

436 **Table 1. Perception of caregivers during experimental sickness.**

	B	SE	NOBS	NIND	p
Likability					
Intercept	**71.1**	**6.0**	**294**	**26**	**<0.001**
Caregiver condition (HP-nc)	**-22.4**	**4.1**	**294**	**26**	**<0.001**
Caregiver condition (NHP-c)	-9.2	6.0	294	26	0.13
LPS (in HP-c)	0.7	4.1	294	26	0.86
LPS × HP-nc	-7.9	5.0	294	26	0.12
LPS × NHP-c	-1.4	5.0	294	26	0.78
Trustworthiness					
Intercept	**72.2**	**6.4**	**294**	**26**	**<0.001**
Caregiver condition (HP-nc)	**-22.9**	**4.4**	**294**	**26**	**<0.001**
Caregiver condition (NHP-c)	**-19.3**	**5.7**	**294**	**26**	**<0.001**
LPS (in HP-c)	-0.8	3.6	294	26	0.82
LPS × HP-nc	-0.1	5.9	294	26	0.99
LPS × NHP-c	3.8	5.2	294	26	0.46
Professionalism					
Intercept	**78.7**	**6.2**	**196**	**26**	**<0.001**
Caregiver condition (HP-nc)	**-25.8**	**4.1**	**196**	**26**	**<0.001**

LPS (in HP-c)	-2.3	3.7	196	26	0.53
LPS × HP-nc	-0.2	5.7	196	26	0.97
Willingness to interact					
Intercept	**59.1**	**6.5**	**294**	**26**	**<0.001**
Caregiver condition (HP-nc)	**-23.2**	**4.8**	**294**	**26**	**<0.001**
Caregiver condition (NHP-c)	-9.9	6.0	294	26	0.10
LPS (in HP-c)	-1.2	7.0	294	26	0.86
LPS × HP-nc	-8.2	5.8	294	26	0.16
LPS × NHP-c	-4.0	5.4	294	26	0.46
Willingness to receive care					
Intercept	**43.5**	**8.1**	294	26	**<0.001**
Caregiver condition (HP-nc)	**-18.2**	**4.9**	**294**	**26**	**<0.001**
Caregiver condition (NHP-c)	-12.4	5.8	294	26	0.03(#)
LPS (in HP-c)	**15.2**	**5.1**	**294**	**26**	**<0.01**
LPS × HP-nc	**-14.1**	**5.4**	**294**	**26**	**<0.01**
LPS × NHP-c	-2.6	5.9	294	26	0.66

Results from linear mixed models that assessed the effects of treatment (LPS vs. saline), caregiver condition (HP-c vs. HP-nc and NHP-c), and the interaction effects of treatment and caregiver condition (LPS × HP-nc, LPS × NHP-c) on caregiver ratings. All models controlled for study day and stimuli list. All models included random intercept for participants as well as random slopes for treatment × caregiver condition, treatment and caregiver condition in participants. The alpha level was set to 0.013 for models assessing likability, trustworthiness, willingness to interact, and willingness to receive care due to multiple testing. The alpha level for professionalism was set to 0.05. *Abbreviations:* LPS: lipopolysaccharide, HP-c: Healthcare professionals taking care of a sick individual, HP-nc: healthcare professionals not taking care of a sick individual, NHP-c: non-healthcare professionals (i.e., parent/partner) taking care of their adult sick child or partner, NOBS: number of observations, NIND: number of individuals, #: Did not reach statistical significance (<0.013) but is here listed as a trend (<0.05).

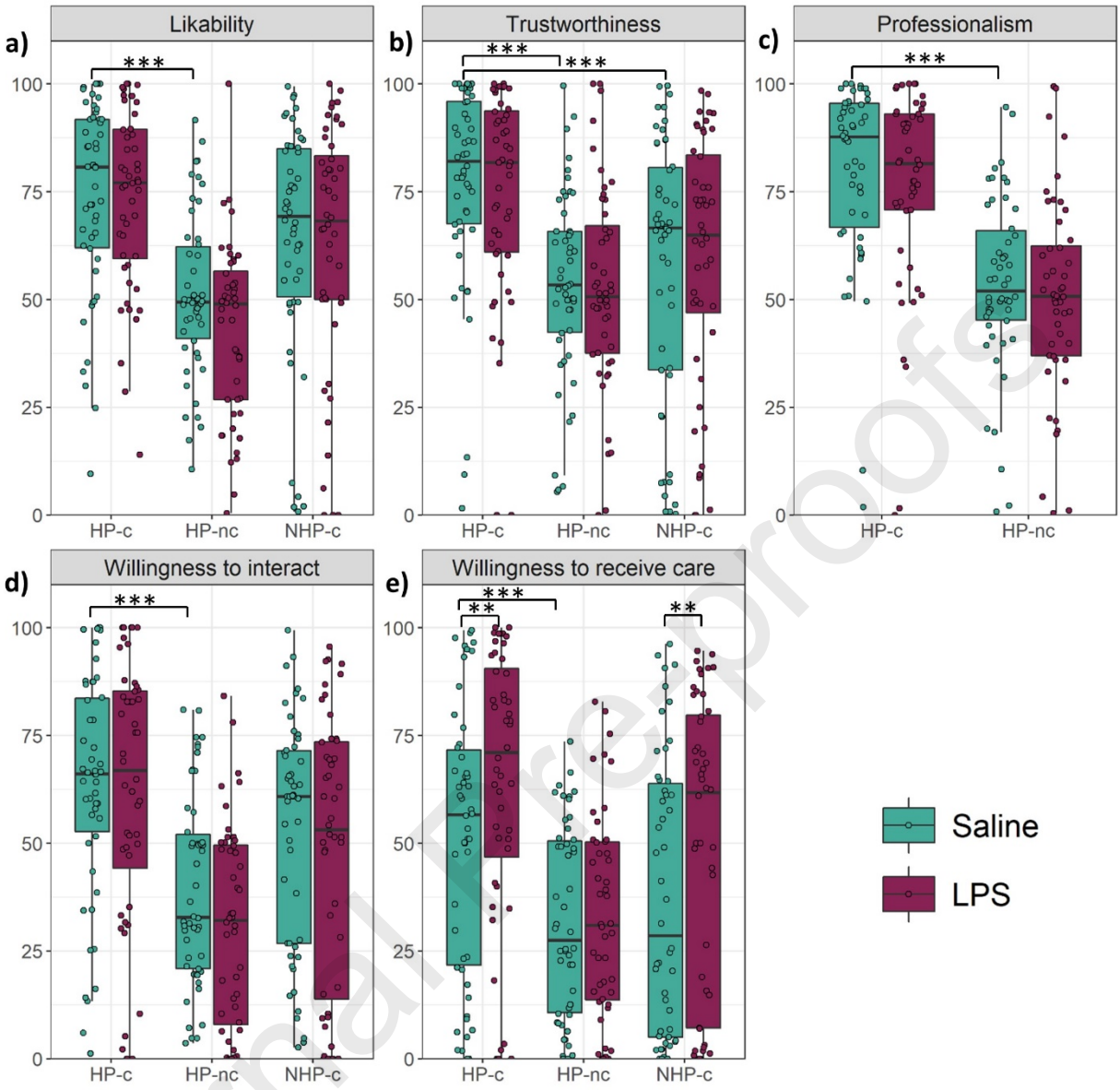

Figure 3. Perception of caregivers during experimental sickness. Participants watched video clips of healthcare professionals taking care of a sick individual (HP-c), healthcare professionals not taking care of a sick individual (HP-nc), and non-healthcare professionals (e.g., parent/partner) taking care of their adult sick child/partner after a LPS injection and a saline injection. The likability (a), trustworthiness (b), and professionalism of each caregiver (c), as well as the participant's willingness to interact with (d) and receive care from the caregiver (e), were rated on visual analogue scales (0-100). A high score indicating a positive rating. Linear mixed models were used to assess the effect of LPS (lipopolysaccharide), caregiver condition (HP-nc, NHP-c) and the interaction effects (LPS*HP-nc, LPS*NHP-c) on perception of caregivers. Professionalism was only rated for healthcare professionals (HP-c and HP-nc). The alpha level was set to 0.013 for assessments of likability, trustworthiness, willingness to receive care from caregivers, and willingness to interact with caregivers in accordance with the Bonferroni method, and 0.05 for the model assessing perceived professionalism of caregivers. The line in each box plot represents the median, the box represents upper and lower quartile, and the whiskers represent maximum and minimum values (max 1.5 * inter-quality range from the hinge). The data points have been jittered to increase the readability of the figure. **p<.01,***p<.001.

3.3. *Facial expressions during experimental sickness.*

Results from our exploratory analyses indicated that participants injected with LPS did not express a different amount of neutrality, happiness, sadness, anger, or disgust during the task, compared to when injected with saline, as detected by FaceReader. See **Table S3** for statistics.

4. Discussion

In this randomized placebo-controlled study we assessed how experimentally sick participants (injected with LPS) perceive caregivers, compared to when healthy. For this purpose, we developed the caregiver perception task (CgPT), in which participants watch video clips of caregivers and care receivers, and rate their perception of these caregivers according to different scales (i.e., likability, trust, professionalism, willingness to interact, willingness to receive care). The stimuli consist of three different types of video clips: healthcare professionals taking care of a sick individual (HP-c), healthcare professionals not taking care of a sick individual (HP-nc), and non-healthcare professionals taking care of their sick adult child or partner (NHP-c). The results show that healthy participants clearly rated the healthcare professionals taking care of sick individuals more positively than healthcare professionals not taking care of sick individuals, and also trusted healthcare professionals taking care of sick individuals more compared to non-healthcare professionals. These findings support the face validity of this task to assess explicit preferences for (health)care providers. When sick, participants reported being more willing to receive care from any care provider seen in the video clips compared to when healthy. The finding highlights the flexibility of the social response during sickness beyond the previously prevailing idea of social withdrawal.

Previous studies investigating social behavior during sickness have used the relatedness of the social interaction partner as a switch point between social withdrawal and social approach (Inagaki et al., 2015; Jolink et al., 2022). An increased approach towards close others during sickness would be sensible, given the idea that kinship selection would facilitate caregiving towards close others. However, unknown others (i.e., healthcare professionals) may also provide care for a sick individual. Clearly, in some situations, approaching strangers represents adaptive behavior during sickness. Our results support this notion by showing that sick individuals report higher willingness to approach unknown healthcare professionals, as well as non-healthcare professionals, for care compared to when they were healthy. Importantly, this effect was not observed for healthcare professionals who was not taking care of a sick individual, indicating that the sole presence of a healthcare professional is not enough. Instead, more information about the caregiver's skills might be needed to increase the willingness to receive care. A future direction may be to investigate the relationship between activation of immune processes and skilled vs non-skilled healthcare professionals, such as previously investigated in the placebo literature (Howe et al., 2017). The fact that sick individuals would be willing to receive care from a *non*-healthcare professional was unexpected, given that these individuals are strangers

who would probably not be prone to provide care for unknown individuals. Given the previously observed inflammation-induced increased willingness to be close to a support figure (Inagaki et al., 2012), we could speculate that participants injected with LPS might have projected their own close other onto the non-healthcare provider in the video (i.e., imagined being taken care of by their own parent or partner). Future studies using the CgPT task could gain from asking the participants follow-up questions regarding their ratings.

The perception of caregivers and changes in this perception when one is sick is highly relevant for many clinical settings. Healthcare professionals who did not take care of a sick individual were rated as less likable, less trustworthy and less good at their job, and participants reported being less willing to interact with them, compared to healthcare professionals who took care of a sick individual. Participants were also less willing to receive care from healthcare professionals not taking care of a sick individual compared to those who took care of a sick individuals, and this effect was even stronger when the participants were sick. Thus, only observing the way the needs of other patients are attended to might affect the perception of healthcare professionals. Hence, the fact that healthcare professionals are often busy with administrative and other tasks diverting them away from actively caring for patients might lead patients to more *n*egative appraisal of their healthcare provider. Ultimately, this could affect the patient-provider relationship, which is a central component of treatment and health outcomes (Finset, 2014). Further studies should thus investigate how the type of caregiving affect perception of caregivers in different health settings.

Even though the results show an increase in willingness to receive care from care providers in the LPS condition compared to in the saline condition, a considerable amount of variance in the ratings was observed (see **Figure 3**). The inflammatory response and the sickness behavior did not predict the LPS-associated changes in willingness to receive care from care providers, although these analyses were clearly too underpowered to interpret anything from a non-significant effect (see **supplementary text 4**). It is possible that other psychosocial factors, such as psychological traits of the participants could explain the variance. Additionally, participants' previous experiences with healthcare professionals might have affected their willingness to receive care while sick. Thus, assessment of predictors for caregiver perception is an important direction for future studies.

In the present study, we also aimed to investigate if experimental sickness would affect expressions of happiness in response to caregivers. However, expressions of happiness while watching the video clips were almost absent. A previous study has shown that sick individuals with a neutral expression are perceived as expressing more negative emotions, compared to when healthy (Sarolidou et al., 2019). Yet, our exploratory analyses with the FaceReader showed that there was no difference in expression of neutrality, happiness, sadness, anger, and disgust after a LPS injection compared to a saline injection. It is possible that the FaceReader was less efficient in detecting emotions compared to the human eye.

Stimuli with stronger emotional content would most likely be needed to analyze expressions of emotions during experimental sickness with the FaceReader.

There are several limitations to consider for the present study. First of all, the task took part during the peak of sickness symptoms (Lasselin, 2021), hence, most of the participants injected with LPS noticed the often clear symptoms, and could guess they had been injected with LPS at this point. It is possible that the knowledge about the treatment would bias participants injected with LPS to give more positive ratings of the caregivers. However, given the difference in ratings between different caregiver conditions (i.e., no LPS effect in willingness to receive care for HP-nc), we do not believe that this was a problem for the present study. Another limitation is the usage of non-professional "actors" for the video clips, possibly affecting the perception of the video clips. Importantly, all the "actors" playing caregivers in the video clips were healthcare professionals (medical doctors, medical students, or clinical psychologists), and it was thus natural for them to act as a caregiver. Moreover, the likability and trustworthiness of the caregivers in the caregiver conditions with more challenging acting (HP-c, NHP-c) were high (see **Figure 3**), indicating that the participants perceived the caregiving scenes as authentic. Lastly, we did not collect any follow-up information on the perception of the task. Given the novelty of the task, it would have been favorable to ask the participants about their beliefs about the origin of the video clips and the purpose of task.

One important aspect is that it is not clear to which extent the current results can be generalized to other states of sickness and hospital settings. The injection of LPS involves a specific context in which participants have a caregiver at their bedside ready to assist them, and knowledge about that their symptoms are transient and non-harmful. Also, the experiment used video clips and participant estimations of how they believe they would act in response to a certain healthcare provider, which might limit the generalizability. Future studies need to investigate how caregivers are perceived in other settings, e.g., in settings involving sick individuals who are more vulnerable and in acute need of care. Furthermore, although the age span of the included participants was quite limited (18-33), age and lifetime experience might affect perception of caregivers as well as the effect of sickness on this perception, something that the current sample size did not allow to investigate. Moreover, participants injected with LPS are not contagious, and are most likely aware of this aspect. Approaching caregivers can be beneficial, but if the sick individual is contagious, it also comes with the risk of infecting others. Thus, it is possible that contagious sick individuals would be less willing to receive care from others due to the risk of disease spreading (Shakhar and Shakhar, 2015).

In conclusion, our study demonstrates the possibility to use the newly developed Caregiver Perception Task (CgPT) to assess explicit preferences for caregivers. Our results indicate that participants who were made sick with an injection of LPS were more willing to receive care from unknown caregivers, either healthcare professionals or non-healthcare professionals

taking care of a sick individual, compared to when healthy. Sick individuals were not more willing to receive care from healthcare professionals who did not take care of a sick individual, highlighting the specific preferences for individuals who are known to have the ability to provide care, support, and possibly a relief of symptoms, during the state of sickness.

Declaration of competing interests

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

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Highlights

- We assessed if experimental sickness affected perception of unknown caregivers.
- We developed the Caregiver Perception task (CgPT), in which participants watch and rate caregivers.
- Twenty-six participants were injected with lipopolysaccharide (0.8 ng/kg body weight) and placebo.
- Healthcare professionals providing care were rated more positively than those not providing care.
- Experimental sickness led to increased willingness to receive care from caregivers who provided care.