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### ► To cite this version:

L.S. Hansson, Arnaud Tognetti, P. Sigurjónsson, E. Brück, K. Wåhlén, et al.. Perception of unfamiliar caregivers during sickness – Using the new caregiver perception task (CgPT) during experimental endotoxemia. *Brain, Behavior, and Immunity*, 2024, 10.1016/j.bbi.2024.04.031 . hal-04566863

**HAL Id: hal-04566863**

<https://hal.inrae.fr/hal-04566863v1>

Submitted on 2 May 2024

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## Journal Pre-proofs

Perception of unfamiliar caregivers during sickness – Using the new caregiver perception task (CgPT) during experimental endotoxemia

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PII: S0889-1591(24)00379-9  
DOI: <https://doi.org/10.1016/j.bbi.2024.04.031>  
Reference: YBRBI 5485

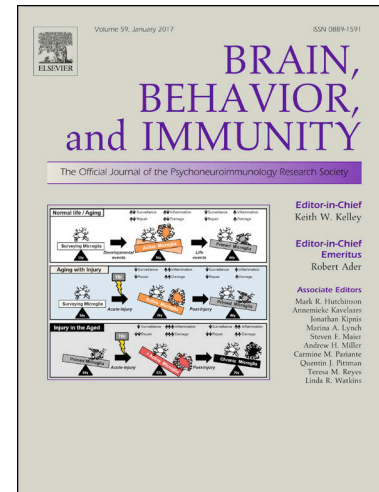
To appear in: *Brain, Behavior, and Immunity*

Received Date: 11 December 2023  
Revised Date: 25 March 2024  
Accepted Date: 22 April 2024

Please cite this article as: Hansson, L.S., Tognetti, A., Sigurjónsson, P., Brück, E., Wåhlén, K., Jensen, K., Olsson, M.J., Toll John, R., Wilhelms, D.B., Lekander, M., Lasselin, J., Perception of unfamiliar caregivers during sickness – Using the new caregiver perception task (CgPT) during experimental endotoxemia, *Brain, Behavior, and Immunity* (2024), doi: <https://doi.org/10.1016/j.bbi.2024.04.031>

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

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24 **Abstract**

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

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

## 46 1. Introduction

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

50

51 Humans and other animals respond to intruding pathogens with the triggering of immune  
52 cascades aiming at neutralizing the invaders, but also with various behavioral changes  
53 initiated by immune-to-brain signaling (Dantzer et al., 2008). These changes include  
54 increased fatigue, decreased food intake, and an overall reduction in activity (Dantzer,  
55 2001). Such recuperative "sickness behavior" is preserved across species (Lopes et al., 2021)  
56 and is believed to adaptively promote immune functions and recovery (Aubert, 1999). Social  
57 withdrawal was early on described as a hallmark of sickness (Dantzer and Kelley, 1989). For  
58 instance, sick rodents are less interested in exploring new social objects (Fishkin and  
59 Winslow, 1997). Sick female rodents also exhibit decreased sexual behavior (Avitsur and  
60 Yirmiya, 1999). Humans made sick experimentally by an intravenous injection of a bacterial  
61 endotoxin (lipopolysaccharide, LPS) feel more socially disconnected (Eisenberger et al.,  
62 2010) and are more willing to be alone (Hannestad et al., 2011), compared to when healthy.  
63 This inflammation-induced social withdrawal fits with the adaptive framing of sickness  
64 behavior, allowing for redirection of energy from social behaviors to immune responses  
65 (Dantzer, 2001), but also by protecting the sick individual from encountering threatful  
66 others who could cause additional harm to a body with an ongoing infection (Hart, 1988;  
67 Leschak and Eisenberger, 2019). Indeed, humans injected with LPS are more sensitive to  
68 social threats (Inagaki et al., 2012) and to social exclusion (Eisenberger et al., 2009)  
69 compared to when healthy. Crucially, other individuals do not only convey risk for harm;  
70 they can also bring care. Hence, if a social interaction results in care, it might be favorable  
71 for a sick animal to keep close rather than keeping away (Smith and Bilbo, 2021).

72

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

89 stranger, an increase in the concentration of the pro-inflammatory marker interleukin-6  
90 after an influenza shot was associated with a faster approach towards support figures (Jolink  
91 et al., 2022). Altogether, these findings imply that the ambivalent nature of social sickness  
92 behavior lies in the relationship between the sick individual and the target of social  
93 interaction, thus being functionally flexible. Yet, some strangers might be especially prone  
94 to provide care, even for unknown sick individuals (i.e., healthcare professionals). Thus, it is  
95 possible that sickness increases positive social behavior towards unknown individuals if they  
96 are clearly in their healthcare professional roles, but this remains to be investigated.  
97 Furthermore, given the importance of care providers' behavior on health outcomes (Finset,  
98 2014), a sickness-induced change of an individual's social approach is likely to be affected by  
99 the perceived benefit from interaction with a specific individual.

100

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

127

## 128 **2. Method**

### 129 **2.1 Participants**

130 This study was part of an investigation of individual differences in response to inflammatory  
131 stimulation and took place at the Karolinska University Hospital (Stockholm, Sweden),  
132 between October 2021 and August 2022. The study was ethically approved (2020-05177,  
133 2021-03034, 2021-04705, and 2021-05317-02), and pre-registered (<https://osf.io/mgu73>)  
134 prior to the start of the data collection. The study was advertised at campuses in the  
135 Stockholm area, via Accindi ([www.accindi.se](http://www.accindi.se)), and a participant recruitment system  
136 (<https://ki-behavioraltesting.sona-systems.com/>) for psychological tests. Prior to inclusion,  
137 participants provided informed consent and took part in a health screening procedure. The  
138 screening included a thorough medical examination, comprehensive laboratory analyses,  
139 and an assessment of depressive symptoms using the PHQ-9 questionnaire (Kroenke et al.,  
140 2001). According to the inclusion and exclusion criteria of the study, participants had to be  
141 between 18-35 years of age, normal weight (BMI 18.5-25 kg/m<sup>2</sup>), non-smokers and non-  
142 excessive drinkers, without somatic and psychological disease, and without medication  
143 (except from contraceptives). Participants conducted some tasks (not the CgPT) in a MR  
144 scanner, and thus had to be eligible for brain scanning (e.g., not suffer from claustrophobia  
145 nor have metallic implants). Additionally, participants had to be vaccinated against COVID-  
146 19 (two doses, last dose at least one month prior to participation), and should not have had  
147 COVID-19 or symptoms indicating a SARS-CoV-2 infection the past 6 months, or a history of  
148 severe or long-term COVID-19 (high intensity or/and more than 8 weeks of symptoms).

149

150 Twenty-six (gender: 15 women, 10 men, 1 transgender man; average age: 25.2±4.5 years;  
151 BMI range: 19.5-25.9) healthy volunteers were included in the study. The sample size  
152 calculation was based on the main hypothesis of the main study, investigating how  
153 inflammation affects brain morphology (<https://osf.io/t6bjh>). We conducted an *a posteriori*  
154 power calculation (with G\*Power, alpha=0.05, power=80%) indicating that the sample size of  
155 26 allows to detect a medium-to-large effect size (f=0.29). Noticeably, previous studies  
156 indicate that a sample size of 20-25 is sufficient to investigate LPS-induced behavioral  
157 changes (Dooley et al., 2018). Participants were compensated with 1750 SEK for each study  
158 day (i.e., 3500 SEK in total, which equals to about \$350/€320).

159

160

161

162

## 163 **2.2 Study design**

164 The study had a double-blind, within-subject, crossover, placebo-controlled design. In order  
165 to induce an acute systemic inflammatory response, participants were injected with an  
166 intravenous injection of LPS (*Escherichia coli* endotoxin, Lot H0K354, CAT number 1235503,  
167 United States Pharmacopeia, Rockville, MD, USA) at 0.8 ng per kg body weight on one  
168 occasion, and saline (0.9% NaCl) on another occasion (placebo). The injections were given in  
169 a randomized order and were separated with a washout period of at least 4 weeks (range:  
170 5-15 weeks). Participants and all study personnel, apart from the medical doctor who took



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

175

### 176 **2.3 Inflammatory markers and sickness behavior**

177 Blood samples were drawn in EDTA vacutainers® at baseline, and at 1 hour, 2 hours, 3  
178 hours, 4 hours, and 5 hours post-injection. Samples were centrifuged for 15 minutes at 2000  
179 g (4°C), and extracted plasma aliquots were stored at -80 °C prior to analysis. Concentration  
180 (pg/mL) of the cytokine interleukin (IL)-6 was measured as a part of a multiplex assay  
181 including IL-8, IL-10, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) using a V-PLEX Custom Human  
182 Biomarkers assays (Meso Scale Discovery (MSD), Rockville, USA). The multiplex assays were  
183 prepared in accordance with the manufacturer's manual, and the plates were read on a SQ  
184 120 instrument with the software Methodical Mind (version 1.0.38). The data was  
185 processed and extracted from the software Discovery Workbench (version 4.0.13, MSD).  
186 Samples were averaged across duplicates, and values below the detection range were  
187 replaced with the lower limit of detection value for each cytokine (IL-6 = 0.06 pg/ml, IL-  
188 8=0.07 pg/ml, IL-10 = 0.04 pg/ml, TNF- $\alpha$  = 0.04 pg/ml). Five values for IL-6 were below the  
189 limit of detection for the two duplicates and replaced with the lower limit of detection (0.06  
190 pg/ml). Only the results for IL-6 are presented in the current paper to validate that the LPS  
191 injection induced a systemic inflammatory response.

192

193 Sickness behavior was measured at baseline, 50 minutes post-injection, and at 1, 2, 3, 4 and  
194 5 hours post injection, using the Sickness Questionnaire (SicknessQ) (Andreasson et al.,  
195 2018). The questionnaire consists of ten items that measure sickness symptoms (e.g., "my  
196 body feels sore"). Each item is rated on a 4-point scale, with a higher score indicating more  
197 intense sickness behavior. Questionnaires were provided with the survey distribution  
198 program REDCap (Harris et al., 2019, 2009).

199

### 200 **2.4 The Caregiver Perception Task (CgPT)**

#### 201 **2.4.1 Description of the CgPT**

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



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

215

#### 216 **2.4.2 Recording and processing of video stimuli**

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

229

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

241

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

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

255

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

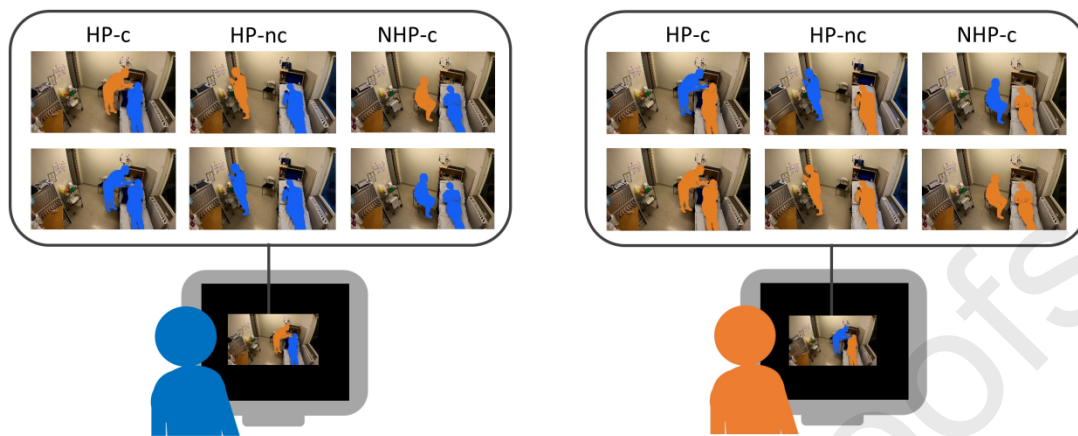
266

#### 267 **2.4.3. Experimental task**

268 Participants conducted the task 1h and 45 minutes after each injection. This time point  
269 occurs during the peak of sickness symptoms (Lasselín, 2021). Participants were seated in  
270 front of a curved monitor (1920 × 1080, 27", Dell SE2722H) adjusted to a comfortable height.  
271 Before starting the task, participants were instructed that they were going to watch video  
272 clips, and answer questions about the person outside of the bed in each video clip.  
273 Participants did not receive any other information about the context or individuals  
274 presented in the video clips (see full instructions in supplementary text 3). Each participant  
275 was assigned a stimuli list (see above) and watched and rated six video clips (see **Figure 1**).  
276 To prepare the participant for a new trial, a small square was presented for 1.5 seconds. A  
277 beep sounded before and after each video clip to indicate the stimuli length and enable  
278 matching of the stimuli with the facial expression data (see below). Each caregiver was  
279 rated on four visual analogue scales: How much do you like this person? (Not at all – Very  
280 much), How much do you trust this person? (Not at all – Very much), How much would you  
281 like to interact with this person right now? (Not at all – Very much), and How much would  
282 you like to be taken care of by this person right now? (Not at all – Very much). Additionally,  
283 healthcare professionals (HP-c, HP-nc) were rated on professionalism: How good is this  
284 person at their job? (Not at all – Very good). Each rating was saved as a value between 0 and  
285 100 (a high value indicating a positive rating). Participants had an unlimited time for each  
286 rating (average response time after LPS: 3.8 sec ± 3.4 sec, average response time after saline:  
287 4.2 sec ± 2.6 sec, response time data are missing for the first study day of two participants  
288 due to logistic reasons). The order of the video clips and scales was randomized. To avoid  
289 fatigue, the task included a one minute break after the third video clip. The task lasted for  
290 approximately 15 minutes. The software OpenSesame (Mathôt et al., 2012) was used to  
291 prepare and run the task.

292

293



294

295

296 **Figure 1. Stimuli presentation during the Caregiver Perception Task (CgPT).** Participants watched six video  
 297 clips, two of each caregiver condition (HP-c, HP-nc, NHP-c), in a randomized order. Male (blue) and female  
 298 (orange) participants watched gender-matched actors playing sick individuals. All participants watched one  
 299 scene with a female caregiver and one scene with a male caregiver per caregiver condition. After each video  
 300 clip, participants rated the caregiver on different scales (i.e., likability, trust, professionalism, willingness to  
 301 interact, willingness to receive care). *Abbreviations:* HP-c: Healthcare professionals taking care of a sick  
 302 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.

303

#### 304 2.4.4 Collection of facial expressions

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

321

#### 322 2.5 Statistical analysis

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

327

### 328 **2.5.1 Validation of the effect of LPS on sickness responses**

329 Two linear mixed models were conducted to validate the effect of LPS on systemic  
330 inflammation (IL-6 concentration in plasma) and sickness behavior (scores on the  
331 SicknessQ). Both models included treatment (LPS vs. saline), time, and treatment  $\times$  time as  
332 fixed factors, and study day (1-2) as a covariate. The models did not converge when  
333 including the intercepts for participants and all random slopes: treatment  $\times$  caregiver  
334 condition, treatment, and caregiver condition in participants. Hence, intercepts for  
335 participants and slopes for treatment in participants were included as random factors in  
336 both models. IL-6 concentrations were log<sub>10</sub>-transformed to meet model assumptions  
337 (normality and homoscedasticity of residuals). Linear mixed models were conducted using  
338 the *lmer* function from the *lme4* package (Bates et al., 2015). Fifteen blood samples out of a  
339 total of 294 (5%) were missing due to difficulties in taking blood (LPS=12, saline=3). No  
340 SicknessQ data was missing.

341

### 342 **2.5.2 Perception of caregivers during experimental sickness**

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

358

359 In accordance with the Bonferroni method, the alpha level was set to 0.013 for the scales  
360 that tested the same research question: likability, trustworthiness, willingness to receive  
361 care from caregivers, and willingness to interact with caregivers. The scale professionalism  
362 tested a different research question, thus, the alpha level was set to 0.05. See the analysis  
363 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

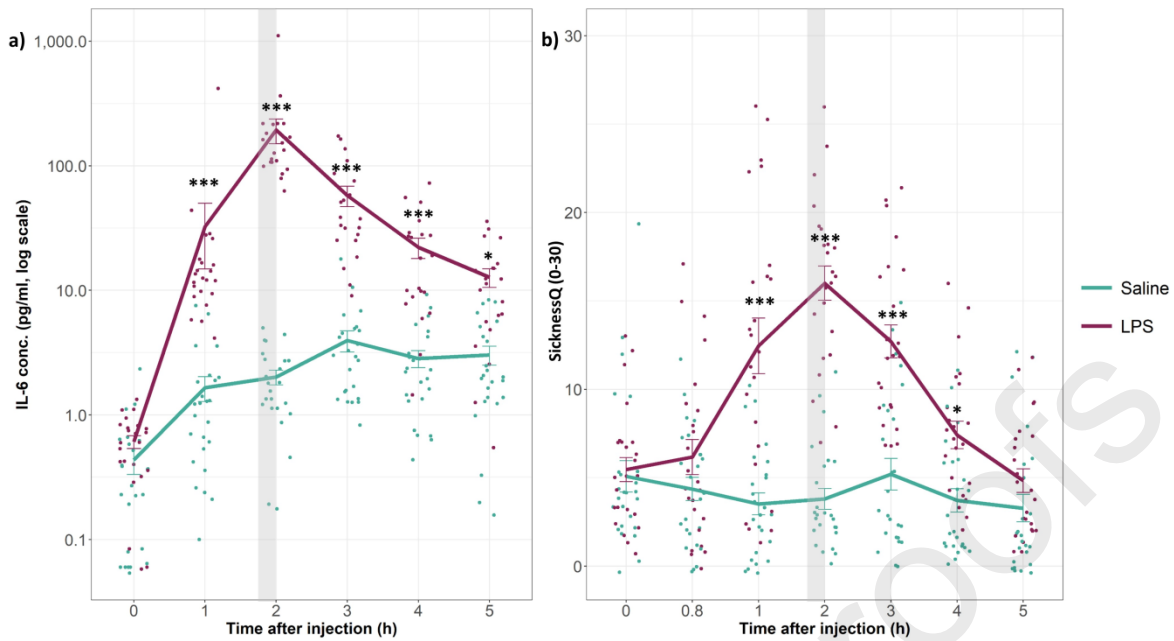
## 390 **3. Results**

### 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



397

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

406

### 407 **3.2 Perception of caregivers when healthy**

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

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

419

### 420 **3.3. Perception of caregivers during experimental sickness**

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



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

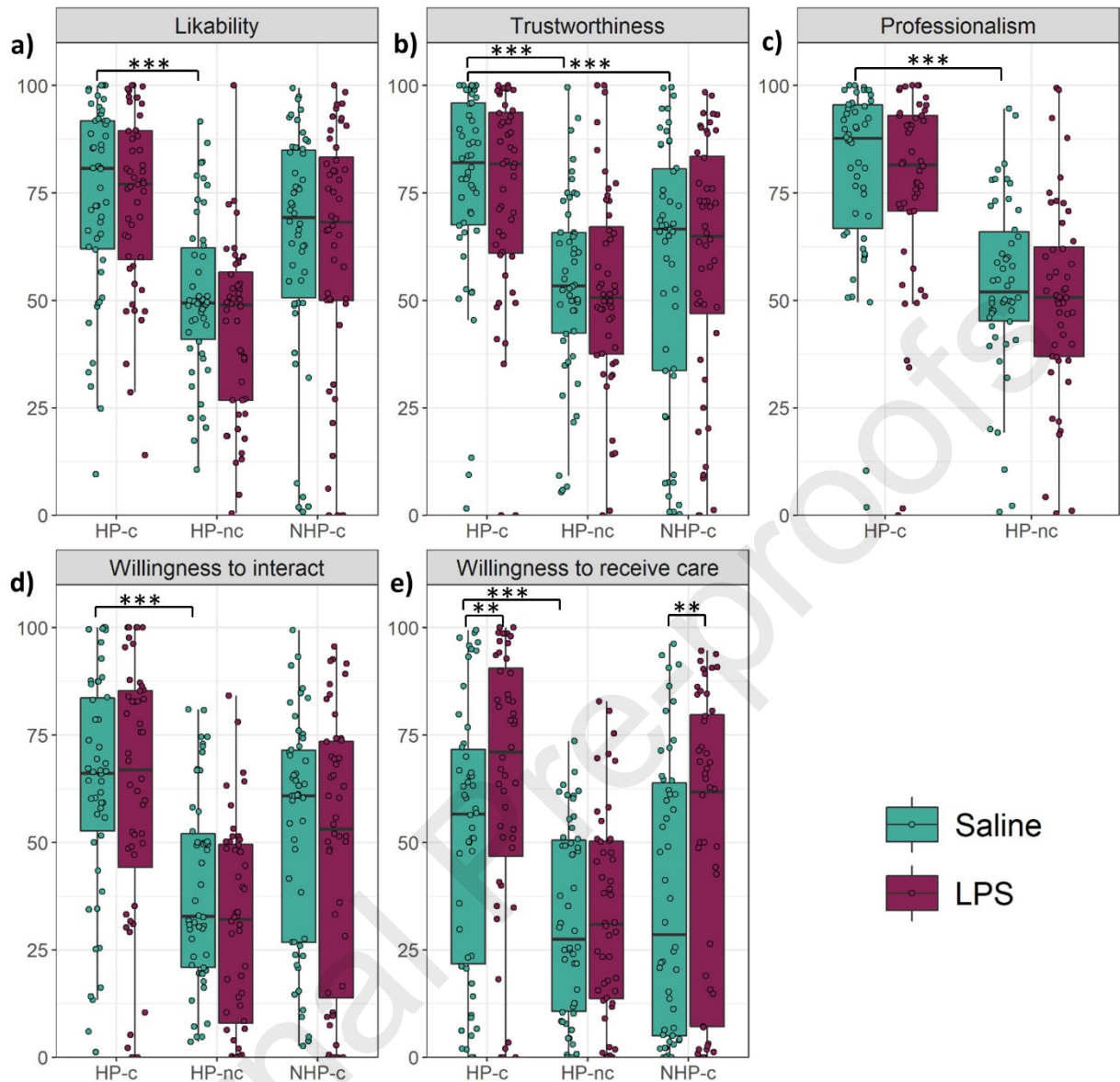
435



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

	B	SE	NOBS	NIND	p
<b><i>Likability</i></b>					
<b>Intercept</b>	<b>71.1</b>	<b>6.0</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>
<b>Caregiver condition (HP-nc)</b>	<b>-22.4</b>	<b>4.1</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>
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
<b><i>Trustworthiness</i></b>					
<b>Intercept</b>	<b>72.2</b>	<b>6.4</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>
<b>Caregiver condition (HP-nc)</b>	<b>-22.9</b>	<b>4.4</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>
<b>Caregiver condition (NHP-c)</b>	<b>-19.3</b>	<b>5.7</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>
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
<b><i>Professionalism</i></b>					
<b>Intercept</b>	<b>78.7</b>	<b>6.2</b>	<b>196</b>	<b>26</b>	<b>&lt;0.001</b>
<b>Caregiver condition (HP-nc)</b>	<b>-25.8</b>	<b>4.1</b>	<b>196</b>	<b>26</b>	<b>&lt;0.001</b>

437							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. <i>Abbreviations:</i> 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).
438	LPS (in HP-c)	-2.3	3.7	196	26	0.53	
439							
440							
441	LPS × HP-nc	-0.2	5.7	196	26	0.97	
442							
443							
444	<b><i>Willingness to interact</i></b>						
445							
446							
447	<b>Intercept</b>	<b>59.1</b>	<b>6.5</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>	
448							
449							
450	<b>Caregiver condition (HP-nc)</b>	<b>-23.2</b>	<b>4.8</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>	
451							
452							
453	Caregiver condition (NHP-c)	-9.9	6.0	294	26	0.10	
454							
455							
456	LPS (in HP-c)	-1.2	7.0	294	26	0.86	
457							
458							
459	LPS × HP-nc	-8.2	5.8	294	26	0.16	
460							
461							
462	LPS × NHP-c	-4.0	5.4	294	26	0.46	
463							
464							
465	<b><i>Willingness to receive care</i></b>						
466							
467							
468	<b>Intercept</b>	<b>43.5</b>	<b>8.1</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>	
469							
470							
471	<b>Caregiver condition (HP-nc)</b>	<b>-18.2</b>	<b>4.9</b>	<b>294</b>	<b>26</b>	<b>&lt;0.001</b>	
472							
473							
	Caregiver condition (NHP-c)	-12.4	5.8	294	26	0.03(#)	
	<b>LPS (in HP-c)</b>	<b>15.2</b>	<b>5.1</b>	<b>294</b>	<b>26</b>	<b>&lt;0.01</b>	
	<b>LPS × HP-nc</b>	<b>-14.1</b>	<b>5.4</b>	<b>294</b>	<b>26</b>	<b>&lt;0.01</b>	
	LPS × NHP-c	-2.6	5.9	294	26	0.66	



474

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

489

### 490 **3.3. Facial expressions during experimental sickness.**

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

495

## 496 **4. Discussion**

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

514

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

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

538

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

554

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

565

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

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

576

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

594

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

611

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



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

621

622

### 623 **Declaration of competing interests**

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

626

### 627 **Acknowledgment**

628 We want to thank PhD H. Engler for his help and advice regarding the preparation of LPS,  
629 PhD P. Olofsson and PhD L. Tarnawski for helping us to prepare the LPS, and PhD MD P.  
630 Naucler for his advice about usage of the LPS-model during an ongoing pandemic. In  
631 addition, we wish to thank the department Biobank and Study Support at Karolinska  
632 University Hospital for their contribution including professional service and support. We are  
633 grateful for a number of people directly involved in the development of CgPT: PhD MD S.  
634 Tamm and L. Strøm for providing feedback on the scripts for the video clips, PhD MD G.  
635 Nilsonne and PhD A. Andreasson for their advice on statistical analyses, and the “actors” for  
636 their excellent performances. We also want to thank E. Trachtenberg for reading and  
637 providing feedback on the manuscript. Lastly, we are highly grateful to the MR Centrum  
638 team, Rouslan Sitnikov, Amir Hossein Montazeri Najafabadi, and Jonathan Berrebi, for  
639 bearing with us during data collection and provided support anytime we needed it.

640

### 641 **Funding**

642 This work was supported by the Swedish Research Council [grant numbers: 2017-02629 to  
643 M.L., 2020-01606 to JL, 2020-02567 to MJO, 2021-03184 to AT], Region Stockholm [ALF  
644 grant: 20200474 to JL], Karolinska Institutet [KID-funding: 2019-01026 to ML], as well as  
645 Heumanska stiftelsen and the Swedish Brain Foundation.

646

647

### 648 **5. References**

649 Andreasson, A., Wicksell, R.K., Lodin, K., Karshikoff, B., Axelsson, J., Lekander, M., 2018. A global  
650 measure of sickness behaviour: Development of the Sickness Questionnaire. *J Health Psychol*  
651 23, 1452–1463. <https://doi.org/10.1177/1359105316659917>



- 652 Aubert, A., 1999. Sickness and behaviour in animals: a motivational perspective. *Neurosci Biobehav*  
653 *Rev* 23, 1029–1036. [https://doi.org/10.1016/s0149-7634\(99\)00034-2](https://doi.org/10.1016/s0149-7634(99)00034-2)
- 654 Avitsur, R., Yirmiya, R., 1999. Cytokines inhibit sexual behavior in female rats: I. Synergistic effects of  
655 tumor necrosis factor alpha and interleukin-1. *Brain Behav Immun* 13, 14–32.  
656 <https://doi.org/10.1006/brbi.1999.0555>
- 657 Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting Linear Mixed-Effects Models Using lme4.  
658 *Journal of Statistical Software* 67, 1–48. <https://doi.org/10.18637/jss.v067.i01>
- 659 Chung, Y., Rabe-Hesketh, S., Dorie, V., Gelman, A., Liu, J., 2013. A Nondegenerate Penalized  
660 Likelihood Estimator for Variance Parameters in Multilevel Models. *Psychometrika* 78, 685–  
661 709. <https://doi.org/10.1007/s11336-013-9328-2>
- 662 Dantzer, R., 2001. Cytokine-induced sickness behavior: where do we stand? *Brain Behav Immun* 15,  
663 7–24. <https://doi.org/10.1006/brbi.2000.0613>
- 664 Dantzer, R., Kelley, K.W., 1989. Stress and immunity: An integrated view of relationships between  
665 the brain and the immune system. *Life Sciences* 44, 1995–2008.  
666 [https://doi.org/10.1016/0024-3205\(89\)90345-7](https://doi.org/10.1016/0024-3205(89)90345-7)
- 667 Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to  
668 sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9,  
669 46–56. <https://doi.org/10.1038/nrn2297>
- 670 Dooley, L.N., Kuhlman, K.R., Robles, T.F., Eisenberger, N.I., Craske, M.G., Bower, J.E., 2018. The role  
671 of inflammation in core features of depression: Insights from paradigms using exogenously-  
672 induced inflammation. *Neurosci Biobehav Rev* 94, 219–237.  
673 <https://doi.org/10.1016/j.neubiorev.2018.09.006>
- 674 Eisenberger, N.I., Inagaki, T.K., Mashal, N.M., Irwin, M.R., 2010. Inflammation and social experience:  
675 an inflammatory challenge induces feelings of social disconnection in addition to depressed  
676 mood. *Brain Behav. Immun.* 24, 558–563. <https://doi.org/10.1016/j.bbi.2009.12.009>
- 677 Eisenberger, N.I., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2009. An fMRI study of  
678 cytokine-induced depressed mood and social pain: the role of sex differences. *Neuroimage*  
679 47, 881–890. <https://doi.org/10.1016/j.neuroimage.2009.04.040>
- 680 Finset, A., 2014. 50 years of research on the effect of physician communication behavior on health  
681 outcomes. *Patient Education and Counseling* 96, 1–2.  
682 <https://doi.org/10.1016/j.pec.2014.05.018>
- 683 Fishkin, R.J., Winslow, J.T., 1997. Endotoxin-induced reduction of social investigation by mice:  
684 interaction with amphetamine and anti-inflammatory drugs. *Psychopharmacology* 132, 335–  
685 341. <https://doi.org/10.1007/s002130050353>
- 686 Hannestad, J., DellaGioia, N., Ortiz, N., Pittman, B., Bhagwagar, Z., 2011. Citalopram reduces  
687 endotoxin-induced fatigue. *Brain, Behavior, and Immunity* 25, 256–259.  
688 <https://doi.org/10.1016/j.bbi.2010.10.013>
- 689 Harris, P.A., Taylor, R., Minor, B.L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G.,  
690 Delacqua, F., Kirby, J., Duda, S.N., REDCap Consortium, 2019. The REDCap consortium:

- 691 Building an international community of software platform partners. *J Biomed Inform* 95,  
692 103208. <https://doi.org/10.1016/j.jbi.2019.103208>
- 693 Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data  
694 capture (REDCap)—a metadata-driven methodology and workflow process for providing  
695 translational research informatics support. *J Biomed Inform* 42, 377–381.  
696 <https://doi.org/10.1016/j.jbi.2008.08.010>
- 697 Hart, B.L., 1988. Biological basis of the behavior of sick animals. *Neuroscience & Biobehavioral*  
698 *Reviews* 12, 123–137. [https://doi.org/10.1016/S0149-7634\(88\)80004-6](https://doi.org/10.1016/S0149-7634(88)80004-6)
- 699 Hennessy, M.B., Deak, T., Schiml, P.A., 2014. Sociality and sickness: have cytokines evolved to serve  
700 social functions beyond times of pathogen exposure? *Brain Behav Immun* 37, 15–20.  
701 <https://doi.org/10.1016/j.bbi.2013.10.021>
- 702 Howe, L.C., Goyer, J.P., Crum, A.J., 2017. Harnessing the placebo effect: Exploring the influence of  
703 physician characteristics on placebo response. *Health Psychol* 36, 1074–1082.  
704 <https://doi.org/10.1037/hea0000499>
- 705 Inagaki, T.K., Muscatell, K.A., Irwin, M.R., Cole, S.W., Eisenberger, N.I., 2012. Inflammation selectively  
706 enhances amygdala activity to socially threatening images. *NeuroImage* 59, 3222–3226.  
707 <https://doi.org/10.1016/j.neuroimage.2011.10.090>
- 708 Inagaki, T.K., Muscatell, K.A., Irwin, M.R., Moieni, M., Dutcher, J.M., Jevtic, I., Breen, E.C.,  
709 Eisenberger, N.I., 2015. The role of the ventral striatum in inflammatory-induced approach  
710 toward support figures. *Brain Behav Immun* 44, 247–252.  
711 <https://doi.org/10.1016/j.bbi.2014.10.006>
- 712 Jolink, T.A., Fendinger, N.J., Alvarez, G.M., Feldman, M.J., Gaudier-Diaz, M.M., Muscatell, K.A., 2022.  
713 Inflammatory reactivity to the influenza vaccine is associated with changes in automatic  
714 social behavior. *Brain, Behavior, and Immunity* 99, 339–349.  
715 <https://doi.org/10.1016/j.bbi.2021.10.019>
- 716 Kroenke, K., Spitzer, R.L., Williams, J.B.W., 2001. The PHQ-9. *J Gen Intern Med* 16, 606–613.  
717 <https://doi.org/10.1046/j.1525-1497.2001.016009606.x>
- 718 Lasselin, J., 2021. Back to the future of psychoneuroimmunology: Studying inflammation-induced  
719 sickness behavior. *Brain Behav Immun Health* 18, 100379.  
720 <https://doi.org/10.1016/j.bbih.2021.100379>
- 721 Leschak, C.J., Eisenberger, N.I., 2019. Two Distinct Immune Pathways Linking Social Relationships  
722 With Health: Inflammatory and Antiviral Processes. *Psychosom Med* 81, 711–719.  
723 <https://doi.org/10.1097/PSY.0000000000000685>
- 724 Lopes, P.C., French, S.S., Woodhams, D.C., Binning, S.A., 2021. Sickness behaviors across vertebrate  
725 taxa: proximate and ultimate mechanisms. *Journal of Experimental Biology* 224, jeb225847.  
726 <https://doi.org/10.1242/jeb.225847>
- 727 Lüdecke, D., Ben-Shachar, M.S., Patil, I., Makowski, D., 2020. Extracting, Computing and Exploring  
728 the Parameters of Statistical Models using R. *Journal of Open Source Software* 5, 2445.  
729 <https://doi.org/10.21105/joss.02445>

- 730 Mathôt, S., Schreij, D., Theeuwes, J., 2012. OpenSesame: an open-source, graphical experiment  
731 builder for the social sciences. *Behav Res Methods* 44, 314–324.  
732 <https://doi.org/10.3758/s13428-011-0168-7>
- 733 Muscatell, K.A., 2021. Social psychoneuroimmunology: Understanding bidirectional links between  
734 social experiences and the immune system. *Brain, Behavior, and Immunity* 93, 1–3.  
735 <https://doi.org/10.1016/j.bbi.2020.12.023>
- 736 Muscatell, K.A., Inagaki, T.K., 2021. Beyond social withdrawal: New perspectives on the effects of  
737 inflammation on social behavior. *Brain Behav Immun Health* 16, 100302.  
738 <https://doi.org/10.1016/j.bbih.2021.100302>
- 739 Muscatell, K.A., Moieni, M., Inagaki, T.K., Dutcher, J.M., Jevtic, I., Breen, E.C., Irwin, M.R.,  
740 Eisenberger, N.I., 2016. Exposure to an inflammatory challenge enhances neural sensitivity  
741 to negative and positive social feedback. *Brain Behav Immun* 57, 21–29.  
742 <https://doi.org/10.1016/j.bbi.2016.03.022>
- 743 Noldus, 2021. FaceReader: Tool for automatic analysis of facial expressions: Version 9 [Software].  
744 Wageningen, The Netherlands: Noldus Information Technology B.V.
- 745 R Core Team, 2017. R: A language and environment for statistical computing. R Foundation for  
746 Statistical Computing, Vienna, Austria. <https://www.R-project.org/>
- 747 Sarolidou, G., Axelsson, J., Sundelin, T., Lasselín, J., Regenbogen, C., Sorjonen, K., Lundström, J.N.,  
748 Lekander, M., Olsson, M.J., 2019. Emotional expressions of the sick face. *Brain Behav Immun*  
749 80, 286–291. <https://doi.org/10.1016/j.bbi.2019.04.003>
- 750 Shakhar, K., Shakhar, G., 2015. Why Do We Feel Sick When Infected—Can Altruism Play a Role? *PLOS*  
751 *Biology* 13, e1002276. <https://doi.org/10.1371/journal.pbio.1002276>
- 752 Smith, C.J., Bilbo, S.D., 2021. Sickness and the Social Brain: Love in the Time of COVID. *Front*  
753 *Psychiatry* 12, 633664. <https://doi.org/10.3389/fpsy.2021.633664>
- 754 Stockmaier, S., Bolnick, D.I., Page, R.A., Carter, G.G., 2020. Sickness effects on social interactions  
755 depend on the type of behaviour and relationship. *J Anim Ecol* 89, 1387–1394.  
756 <https://doi.org/10.1111/1365-2656.13193>
- 757 van der Schalk, J., Hawk, S.T., Fischer, A.H., Doosje, B., 2011. Moving faces, looking places: Validation  
758 of the Amsterdam Dynamic Facial Expression Set (ADFES). *Emotion* 11, 907–920.  
759 <https://doi.org/10.1037/a0023853>
- 760 Willette, A.A., Lubach, G.R., Coe, C.L., 2007. Environmental context differentially affects behavioral,  
761 leukocyte, cortisol, and interleukin-6 responses to low doses of endotoxin in the rhesus  
762 monkey. *Brain Behav Immun* 21, 807–815. <https://doi.org/10.1016/j.bbi.2007.01.007>
- 763 Yee, J.R., Prendergast, B.J., 2012. Endotoxin elicits ambivalent social behaviors.  
764 *Psychoneuroendocrinology* 37, 1101–1105. <https://doi.org/10.1016/j.psyneuen.2011.11.008>
- 765 **Perception of unfamiliar caregivers during experimental sickness – using the new Caregiver Perception Task**  
766 **(CgPT)**
- 767 Hansson et al.

768 **Highlights**

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- We assessed if experimental sickness affected perception of unknown caregivers.

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- We developed the Caregiver Perception task (CgPT), in which participants watch and rate caregivers.

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- Twenty-six participants were injected with lipopolysaccharide (0.8 ng/kg body weight) and placebo.

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- Healthcare professionals providing care were rated more positively than those not providing care.

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- Experimental sickness led to increased willingness to receive care from caregivers who provided care.

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