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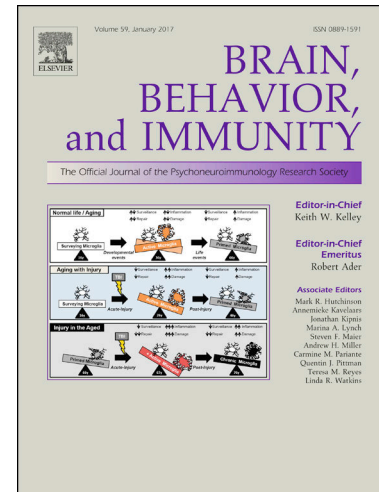
1 **Perception of unfamiliar caregivers during sickness – using the new Caregiver Perception**
2 **Task (CgPT) during experimental endotoxemia**

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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.

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

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), 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^2), 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-α (TNF-α) 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-α = 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±1.5 years, 3 women) acted as sick, and five
219 actors with healthcare professions (average age: 43±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 relatability, 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

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 (Lasselin, 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
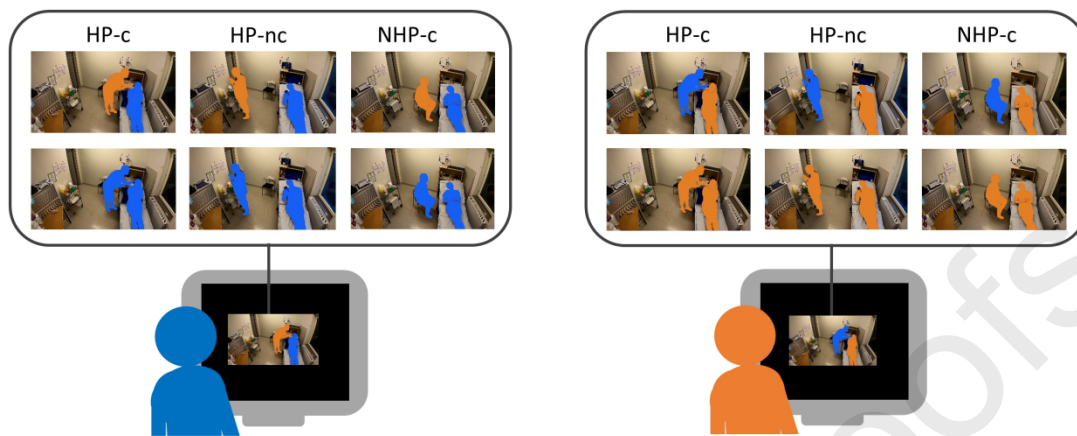
294
295 **Figure 1. Stimuli presentation during the Caregiver Perception Task (CgPT).** Participants watched six video
296 clips, two of each caregiver condition (HP-c, HP-nc, NHP-c), in a randomized order. Male (blue) and female
297 (orange) participants watched gender-matched actors playing sick individuals. All participants watched one
298 scene with a female caregiver and one scene with a male caregiver per caregiver condition. After each video
299 clip, participants rated the caregiver on different scales (i.e., likability, trust, professionalism, willingness to
300 interact, willingness to receive care). *Abbreviations:* HP-c: Healthcare professionals taking care of a sick
301 individual, HP-nc: healthcare professionals not taking care of a sick individual, NHP-c: non-healthcare
302 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*

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

2.5.3 Facial expressions while watching caregivers during experimental sickness

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

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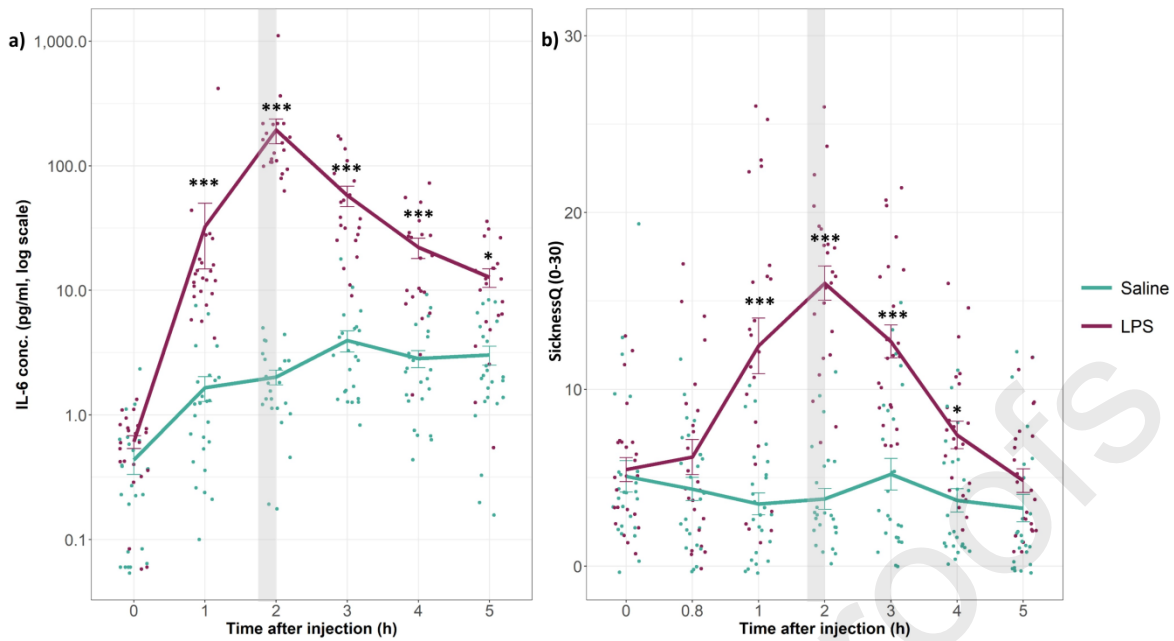
3. Results

3.1 Validation of the effect of LPS on sickness responses

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

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
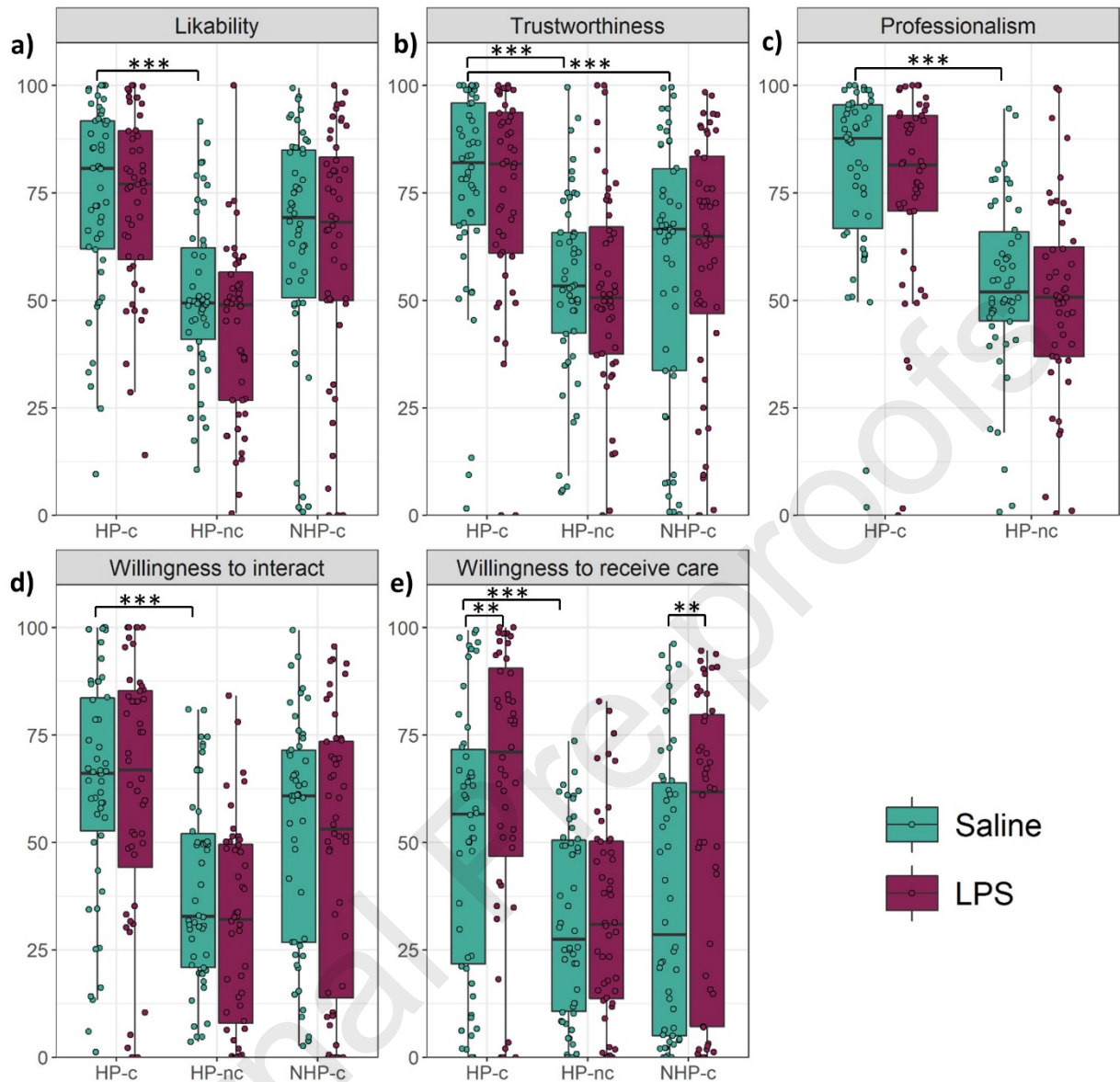
424 willing to receive care from healthcare professionals providing care compared to when
425 injected with saline (see **Table 1** and **Figure 3e**). The effect of LPS was similar in non-
426 healthcare professionals providing care and in healthcare professional providing care, as
427 indicated by 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
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).

474

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.

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

Declaration of competing interests

626

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640

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646

647

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

767 Hansson et al.

768   **<u>Highlights</u>**

769
770   • We assessed if experimental sickness affected perception of unknown caregivers.
771
772   • We developed the Caregiver Perception task (CgPT), in which participants watch and rate caregivers.
773
774   • Twenty-six participants were injected with lipopolysaccharide (0.8 ng/kg body weight) and placebo.
775
776   • Healthcare professionals providing care were rated more positively than those not providing care.
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778   • Experimental sickness led to increased willingness to receive care from caregivers who provided care.

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