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Olfactory Cues of Naturally Occurring Systemic Inflammation: A Pilot Study of Seasonal Allergy

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Keywords
Olfactory cues of sickness · Inflammation · Behavioural immune system · Body odours · Pollen allergy · Cytokines

Abstract

Introduction: In an attempt to avoid contact with infectious individuals, humans likely respond to generalized rather than specific markers of disease. Humans may thus perceive a noninfectious individual as socially less attractive if they look (e.g., have facial discolouration), move (e.g., have a slower walking pace), or sound (e.g., sneeze) sick. This pilot study tested whether humans are averse to the body odour of noninfectious individuals with a low-grade systemic inflammation. ***Methods:*** We collected the axillary body odour of individuals with severe seasonal allergy (N = 14) and healthy controls (N = 10) during and outside the allergy season and measured serum levels of two inflammatory cytokines (tumour necrosis factor-α and interleukin-5). Independent participants (N = 67) then sampled and rated these odours on intensity and pleasantness. ***Results:*** While individuals with seasonal allergy had nominally more unpleasant and intense body odours during the allergy season, relative to outside the allergy season and to healthy controls, these effects were not significant. When examining immune markers, the change in perceived pleasantness of an individual's body odour (from out-to-inside pollen season) was significantly related to the change in their interleukin-5 levels but not to tumour necrosis factor-α. ***Discussion:*** Our findings tentatively suggest that the human olfactory system could be sensitive to inflammation as present in a noncommunicable condition. Larger replications are required to determine the role of olfaction in the perception of infectious and noninfectious (e.g., chronic diseases) conditions.

Introduction

Infectious diseases pose a significant selection pressure on humans and animals [1–4]. In an attempt to avoid infection from strangers, humans tend to err on the side

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of caution, avoiding conspecifics who display common cues of infection, irrespective of the cue's accuracy and veracity [5, 6]. Presumably, this is because it would be safer for an organism to make a false-positive error (incorrectly assuming a conspecific is infectious) than a false-negative error (incorrectly assuming a conspecific is noninfectious). In support of this, people are averse to noninfectious individuals, who display visual (e.g., facial disfiguration [6]) and auditory cues (e.g., sneezes [7]) associated with infection. It remains unclear whether humans express a similar aversion to olfactory cues associated with noninfectious conditions such as chronic diseases or allergies.

Infectious diseases and noninfectious conditions may produce similar phenotypic changes in humans through common physiological processes, such as inflammation [8]. For example, in studies using an experimental endotoxemia model, individuals are injected with a bacterial endotoxin (lipopolysaccharide [LPS]). Akin to an infection, an LPS injection triggers an increase in body temperature and circulating pro-inflammatory cytokine levels (such as IL-6, IL-8, TNF-α) [9]. Relative to a saline injection, an LPS injection results in discernible changes to one's facial appearance [8, 10–13], gait [14, 15], and body odour [16–18]. These changes are perceived as unpleasant and unhealthy by others [11, 12, 16, 17] and may serve as a cue for avoidance [11, 17].

While experimental inductions of systemic inflammation offer valuable insights, they also have their limitations. One key concern in this regard is whether experimentally induced inflammation and naturally occurring inflammation produce similar phenotypic changes. To address this concern, at least three studies focussing on body odours have been conducted. First, Moshkin et al. [19] found that individuals with gonorrhoea had slightly but significantly more unpleasant body odours than those who had recovered or never had gonorrhoea. Second, Sarolidou et al. [20] collected body odour samples from individuals when sick with a respiratory illness and when they were healthy. While sick odours tended to be more unpleasant, intense, and disgusting, the effects were not statistically significant [20]. Third, Tognetti et al. [21] reused Sarolidou et al.'s [20] samples and found that participants could discriminate sick from healthy body odours 57% of the time (i.e., slightly above chance) when these odours were presented side by side.

Given the mixed nature of these findings, it remains unclear whether naturally occurring systemic inflammation alters affective perception (pleasantness, intensity) of an individual's body odour. Further, as past studies examined infectious individuals [19–21], it remains to be determined whether systemic inflammation resulting from noninfectious conditions alters the perception of body odours. One way to address these questions would be to compare the body odour of an individual when they have, and do not have, naturally occurring and noninfectious activation of inflammatory processes. Individuals with severe seasonal pollen allergies, who exhibit noninfectious low-grade systemic inflammation during pollen season but not outside it, represent a population well-suited for this investigation. Indeed, in pollen allergy (aka allergic rhinitis), exposure to a specific allergen results in the binding of immunoglobin E to mast cells, causing a release of several pro-inflammatory cytokines, e.g., Il-4, IL-5, IL-13 [22], and TNF-α [23–25], a process which partly overlaps with the early response phase of infectious diseases [22].

Thus, the aim of this study was to assess whether individuals with seasonal allergies were perceived as having more aversive body odours during the allergy season compared to outside the allergy season. We collected body odour samples from individuals with and without seasonal allergies during two distinct periods: during the allergy season (April to June) and outside the allergy season (October to March). Independent participants were then asked to rate the intensity and pleasantness of the donors' body odours. We hypothesized that individuals with pollen allergy would exhibit more aversive (less pleasant and more intense) body odours during the pollen season compared to outside the allergy season and compared to control donors. Additionally, we expected that the difference in allergy-specific (IL-5) and pro-inflammatory (TNF-α) cytokine levels between seasons would correlate with the difference in aversion (pleasantness and intensity) between seasons.

Methods

Overview

This study formed part of a larger project examining the central and peripheral nervous system impacts of seasonal allergy [24], and was approved by Etikprövningsmyndigheten, the Regional Ethical Review Board of Stockholm (No. 2011/1846-31/1; 2012/202-31/1). All participants provided written informed consent knowing the aims of the study. The experimental procedure consisted of two stages. First, individuals with and without pollen allergy (matched for age and sex) donated body odours at two sessions, outside the pollen allergy season (October to March) and during the pollen allergy season, (April to June). Second, newly recruited participants evaluated these body odour samples on intensity and pleasantness.

Stage One: Collection of Odours and Blood Samples

Donor Participants

Eighteen individuals with severe allergic rhinitis, sensitized to birch or grass pollen (median age [interquartile range] = 34.0 [30.2–44.2] years; 8 women), were recruited from allergen immunotherapy waiting lists at allergy clinics in Stockholm, Sweden. Control donors comprised of 13 individuals (median age [interquartile range] = 34.0 [27.0–46.0] years; 5 women), without atopy or pollen allergy, and these individuals were recruited via advertisements (for more details, see [24]). A Phadiatop and/or skin prick test confirmed the allergy donors had pollen allergy, and the control donors were not sensitized to pollen [24]. All donors were further screened for factors that could influence their body odour, immune system, or procedural understanding, i.e., (1) a history of chronic diseases (except, pollen allergy for allergy donors); (2) use of regular medication (except allergy medication for allergy donors); (3) current pregnancy; (4) nonfluency in Swedish; (5) a BMI <29; and (6) use of antihistamines, steroids, or leukotriene antagonists, consuming alcohol, wearing artificial fragrances, and smoking prior to donation.

Procedure

All donors were asked to donate their body odours at two sessions (outside the allergy season [October to March] and during the allergy season [April to June]) between 2012 and 2014. The birch pollen reached extremely high levels in 2012 and 2014, while remaining at a moderate level in 2013. As for grass pollen, it reached high levels in 2012, 2013, and 2014 (for more details, see [24]). Allergy donors were asked to refrain from using steroids (topical or systemic) and leukotriene antagonists for 10 days and antihistamines for 5 days prior to their experimental session.

The two sessions were the exact same, except that one occurred outside and the other during the allergy season [24]. First, all donors were provided a t-shirt and asked to wear it for 4 h while completing different tasks (see [24]). After 4 h, the t-shirts were collected from the donors and the armpits from the shirt were cut. The shirt cut-outs were placed in smell-free freezer bags and stored in a −30°C freezer. Second, venous blood was collected from participants. After 1–1.5 h, the samples were centrifuged for 10 min at 3,200 *g* or 20 min at 1,500 *g* in room temperature and serum was aliquoted and put in −80°C until analysis. Serum samples were analysed for cytokine levels, including IL-4, IL-5, IL-13, and TNF-α, by sandwich immunoassays (see [24] for full blood collection analysis). In the current study, our primary focus was on two mediators, namely, IL-5, a cytokine contributing to the allergic inflammation, and TNF-α, a classic pro-inflammatory marker, both of which contribute to allergy-related symptoms. Indeed, our prior investigation revealed a significant increase in IL-5 and TNF-α levels among allergic patients during versus outside the allergy seasons, whereas such variations were not observed in the healthy control group [24]. Consequently, these cytokines appeared as valuable indicators of heightened systemic inflammation within the patient group population. Furthermore, previous studies have demonstrated that TNF-α influences perceptions of body odour; specifically, circulating TNF-α levels, following an LPS injection, mediated the relationship between systemic inflammation and odour pleasantness [16]. Although IL-4 and IL-13 are also associated with allergic inflammation, their levels in the previous investigation were below the required detection threshold [24] and therefore were not included in our analysis.

Across the two experimental sessions, body odours could not be collected for logistic reasons from 4 out of 18 allergic donors and from 3 out of 10 control donors. As a result, we used the 48 samples obtained from the 14 remaining allergic donors (5 women) and the 10 remaining controls (2 women) who provided samples in both seasons as stimuli for stage two, detailed below.

Stage 2: Judge Ratings of the Odours

Participants

The judges were 76 participants who were recruited through an online advertisement posted on Karolinska Institutet's recruitment system and flyers posted around Karolinska Institutet's campus. All judges were screened for factors that could influence their olfactory function or procedural understanding, i.e., (1) reported weakness or impairment of smell; (2) current pregnancy; (3) smoking; (4) noncorrectable visual impairments, and (5) lacking fluency in Swedish. Accordingly, nine judges were excluded as they were either not fluent in Swedish or reported having an impaired sense of smell during their participation. This resulted in a final sample of 67 participants (38 females, 28 men, 1 other; age: M = 28.8 years, SD = 7.3), who proceeded to judge the odour samples on intensity and pleasantness.

Procedure

The experiment was run between May to June 2019, prior to the COVID-19 pandemic. It consisted of three parts and was conducted in a double-blind procedure (i.e., the experimenter was not aware of the nature [allergic individuals vs. controls] of the body odours). In the first part, participants were asked to smell half of the body odour samples (i.e., 24 glass jars, each containing a donor's cut-out t-shirt). The experimenter wore fragrance-free gloves and presented one jar under the participants' nose. Participants were instructed to smell each sample for 4–5 s, and after smelling, to rate how intense and pleasant they found it, using 100-point line scales. The intensity scale was unipolar (anchors not at all "0" and very "100"), and the pleasantness scale was bipolar (anchors very unpleasant "0", neither pleasant nor unpleasant "50", and very pleasant "100"). To avoid sensory adaptation, there was a 12-s break between the end of a trial and the onset of the next one. The second part was a 10-min break, where participants were asked basic demographic questions (age, sex) and to report their level of olfactory functioning (impaired, normal). The third part was the same as the first part, however, used the remaining 24 body odour samples from the donors. At the end of the experiment, participants received their reimbursement (i.e., two cinema vouchers) and this concluded the experimental session.

Analyses

Because some of the judges (participants rating the body odours) indicated they could smell perfume from a few samples, a post-hoc investigation was conducted to exclude the samples containing artificial fragrance (online suppl. Materials; for all online suppl. material, see https://doi.org/10.1159/000535047). Hence, prior to the analyses, we removed data associated with 7 odour samples (from 5 allergic and 2 control donors). This led to 41 remaining samples from 14 allergy donors (9 samples during and 14 samples outside the allergy season) and 10 controls (9 during and 9 outside the allergy season).

To examine whether inflammation (pollen allergy) influenced the body odour's perceived aversiveness, we used linear mixed

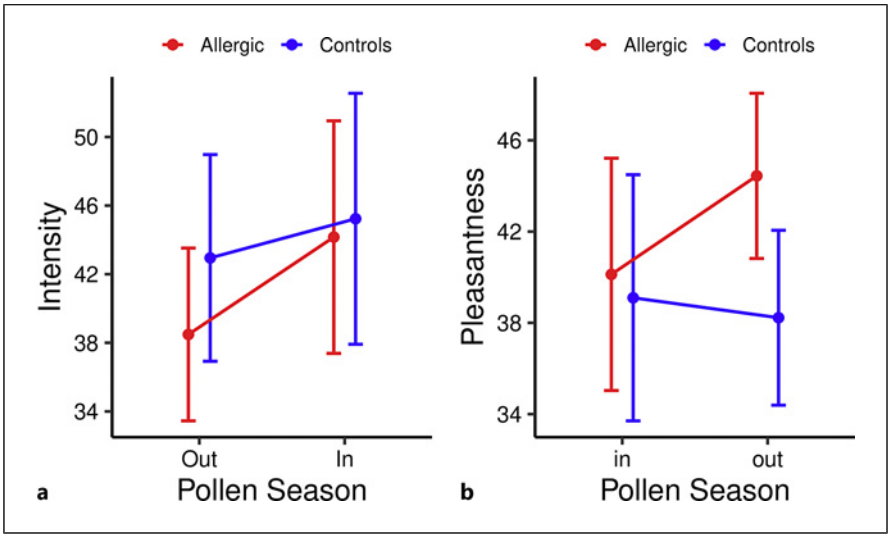

Fig. 1. Body odour intensity (**a**) and pleasantness (**b**) ratings from allergic (red) and control (blue) donors collected during the pollen and nonpollen seasons. Mean and standard errors (predicted values from the LMMs) are represented.

effects models (LMMs). Our dependent variables were a judge's intensity and pleasantness ratings for each of the 41 odour samples. We included "season" (i.e., pollen vs. nonpollen allergy seasons) and "donors" category" (i.e., allergic vs. control donors) as fixed effects. Our variable of interest was the interaction between "season" and "donors" category". We included a random intercept for each judge and donor (ID and ID_Donor, respectively). Random slopes were specified maximally, but the final models only converged when controlling for random slopes for season by ID_Donor. Thus, the model was:

Intensity or Pleasantness ~ Season × Donors' Category + (1 | ID) + (1 + Season | ID_Donor).

Next, we used similar LMMs to examine if differences in odour perception (pleasantness and intensity) between seasons were related to differences in cytokine levels (TNF-α and log-transformed IL-5). Following [24], IL-5 was log-transformed for statistical analyses to better approximate a normal distribution. To calculate these difference scores, only 17 donors could be used as 7 donors had to be excluded because of perfume contained in one of their samples (see above). The dependent variable was either the difference of perceived intensity "Δ_Intensity" or pleasantness "Δ_Pleasantness" between the pollen and nonpollen allergy season. We used two separate models for each of these two dependent variables, one for each studied cytokine. Hence, the exploratory variable was either the difference of IL-5 "Δ_IL-5" or TNF-α levels "Δ_TNF-α" between the pollen and nonpollen allergy season of each donor. Donors' category was included as the controlling variable. We included a random intercept for each judge and donor (the models did not converge while controlling for random slopes for the change in cytokine by judge). Thus, the models were:

Δ_Intensity or Δ_Pleasantness ~ Δ_IL-5 + Donors' Category + (1 | ID) + (1 | ID_Donor)

and

Δ_Intensity or Δ_Pleasantness ~ Δ_TNF-α + Donors' Category + (1 | ID) + (1 | ID_Donor).

Analyses were run on R version 4.1.3 [26] using the *lmer* function in the lme4 package. The significance of each variable of interest was tested with likelihood ratio tests comparing the full model to those without the term of interest. Descriptive statistics on ratings and cytokines levels can be found in the online supplementary material.

Results

Effect of Season on Body Odour Aversiveness

The LMMs revealed that the interaction between season and donors' category, our variable of interest, was neither significantly associated with perceived intensity ($\beta = -3.39$, SE = 7.24, $X^2 = 0.22$, df = 1, $p = 0.64$) nor with perceived pleasantness ($\beta = 5.75$, SE = 4.53, $X^2 = 1.61$, df = 1, $p = 0.20$). Thus, relative to controls, the body odour of individuals with pollen allergy only tended to be more intense and unpleasant in the allergy season compared to the nonallergy season (Fig. 1).

Effect of Cytokines on Body Odour Aversiveness

The LMMs revealed that the difference in IL-5 levels between the pollen and nonpollen seasons significantly related to the difference in perceived pleasantness ($\beta = -6.85$, SE = 2.60, $X^2 = 6.92$, df = 1, $p = 0.008$), but not with perceived intensity ($\beta = 7.44$, SE = 4.56, $X^2 = 2.67$, df = 1, $p = 0.10$), of the body odours. In other words, as the amount of circulating IL-5 increased, odour pleasantness significantly decreased (as expected), with no significant changes in odour intensity (Fig. 2a, b). The difference in TNF-α levels between the pollen and nonpollen seasons (Fig. 2c, d) did neither significantly relate with perceived pleasantness ($\beta = -8.43$, SE = 4.61, $X^2 = 3.34$, df = 1, $p = 0.07$) nor with perceived intensity ($\beta = 7.07$, SE = 7.83, $X^2 = 0.82$, df = 1, $p = 0.37$).

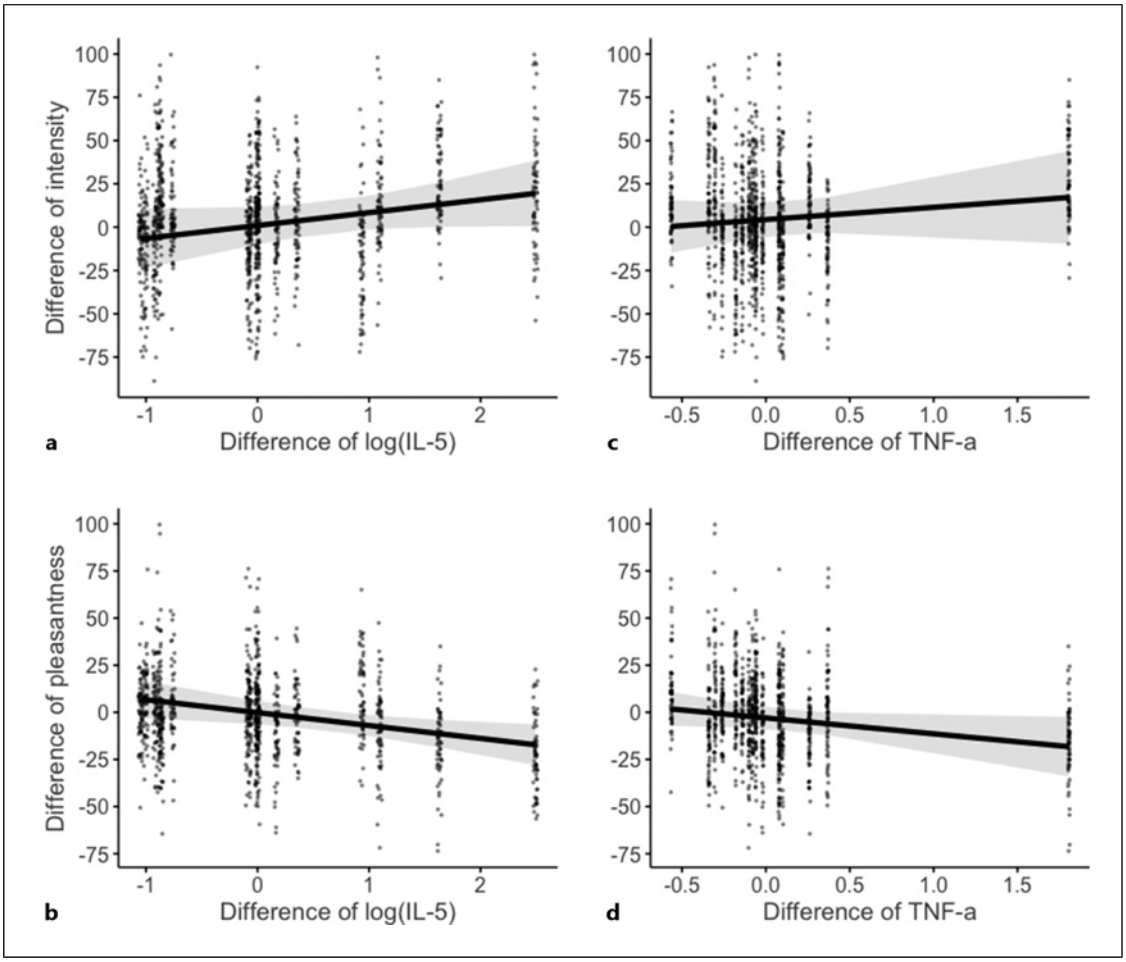

Fig. 2. Predicted linear relationship between the difference of odour intensity (top) and pleasantness (bottom) and the difference of both circulating (log-transformed) IL-5 (left) and TNF-α (right) between the pollen and nonpollen seasons. Each dot represents a difference of perception between the two seasons (in minus out of pollen season) for each judge and each odour donor.

Discussion

There were two predictions this experiment set out to test: (1) if individuals with noninfectious and naturally occurring low-grade inflammation, in the form of pollen allergy, had a more aversive (less pleasant, more intense) body odour when they were in the allergy season, compared to the nonallergy season and relative to controls; and (2) if seasonal change in body odour pleasantness and intensity was related to the change in circulating inflammatory cytokines (IL-5 and TNF-α). In terms of our first prediction, while relative to controls, individuals with pollen allergy tended to have more intense and less pleasant odours in the allergy season than the nonallergy season, these effects were not significant. There was some support for our second prediction as the seasonal change in body odour pleasantness between seasons was significantly related to the change in circulating levels of IL-5, an allergy-specific inflammatory marker, whereas no effect was observed for TNF-α. Before turning to the implications of the current findings, it is important to discuss any limitations of the following study which may have impacted their interpretability.

Some considerations of the current pilot study may, in part, account for the lack of effects of donor-category (allergy vs. healthy control) on perceived pleasantness and intensity of the body odours. The low sample size of odour donors (N = 24) may have led to insufficient powering. Low sample sizes are unfortunately not uncommon in body odour studies as they require significant preparation before the experiment (i.e., strictures on

eating, use of perfumes, washing, etc.) and time-commitment during participation (i.e., participants are often asked to wear a clean shirt for several hours [as in this study] to overnight). Our reliance of a non-convenience sample (i.e., patients with acute seasonal allergy) further reduced the pool of available participants. It should also be noted that the patients with allergy had considerably less systemic inflammatory activation (i.e., TNF-α level) when compared to past studies using LPS injections [16, 27]. In addition, there was a long interval between the collection of body odours (stage 1, 2012–2014) and the sampling of them by the judges (stage 2, 2019). Although there is evidence suggesting that freezing preserves body odour samples over time [28], we cannot ensure that this extended freezing duration did not result in comparatively weaker odours and possible effects. Taken together, these limitations generally tend to work against demonstrating an influence of allergy on body odour perception. Future replications of the current study using a larger sample size are warranted, given our findings were in expected directions while employing conservative statistical analyses (LMMs, controlling for random intercepts and slopes), a small donor sample size, and low-grade inflammation.

Turning to findings pertaining to the immune markers, while between seasonal difference in perceived pleasantness was related to differences in IL-5 levels, they were not related to differences in TNF-α. We expected seasonal difference in TNF-α to relate to the difference in odour pleasantness because circulating levels of TNF-α (following an LPS injection) were previously shown to mediate the relationship found between systemic inflammation and odour pleasantness [16]. Why, then, did IL-5, but not TNF-α, relate to seasonal change in pleasantness? One reason may be that the seasonal variation in TNF-α was too restricted in our study, relative to the levels of IL-5 and, again, substantially smaller than past LPS studies ([16–18]; see online suppl. File). IL-5 may have had greater seasonal variation as it is a more allergy-specific immune marker [24]. The finding that the difference in an inflammation-related cytokine (between the pollen and nonpollen season) was associated with differences in odour pleasantness is conceptually in line with findings from the animal literature, e.g., rats avoid the body odour (urine) of an LPS-injected conspecific [29, 30], and from human studies, e.g., an individual's body is perceived as more aversive (more unpleasant, more intense) following an LPS injection [16–18]. Taken together, the findings from this and past studies suggest that activation of systemic inflammatory processes, perhaps even at relatively lower- but longer-term states such as during pollen allergy, result in a discernible change in an individual's body odour, and this change is perceived negatively (and possibly avoided) by conspecifics.

The next question to consider, then, is why naturally occurring inflammation might increase the aversiveness (i.e., a proxy of behavioural avoidance) of a noninfectious individual's body odour? It may be because infections are a common cause of systemic inflammation, i.e., the majority of infectious diseases result in an increase in circulating pro-inflammatory cytokines [23]. Thus, detection of cues of inflammation, while less accurate than recognition of markers specific to each disease, would reduce the likelihood of incorrectly perceiving an infectious individual as healthy [5]. Nonetheless, the degree of avoidance response from conspecifics might vary depending on various characteristics, such as whether the disease is infectious or not, type of symptoms induced, its virulence, fatality rate, and transmission routes. Cues associated with noninfectious conditions and/or low-grade inflammation, like pollen allergies, may thus trigger a milder response from conspecifics. Future, larger scale studies are now required, which directly compare sickness cues from individuals who are infectious to those who suffer from noninfectious conditions with a similar degree of inflammation, to better understand if cues of inflammation can generalize to individuals who are infectious.

Alternatively, as inflammation occurs in non-communicable conditions, it may serve as a cue for sub-optimal health. As such, aversion to individuals with inflammation may serve a direct (infection to self) or indirect (mating) fitness goal. In the case of allergic inflammation, it should be noted that a type-2 allergic cytokine response (like IL-5) has been considered to represent a dysregulated activation of an evolutionary old defence to helminth/parasite infections [31, 32]. This speaks further for a perspective in which inflammatory processes could be viewed as perceptible signs of bodily perturbations beyond acute infectious states of a broader value in social interaction. If alarm responses to perceived threats outside or in the body are (more or less) generalized, it is likely that social threat perception related to others' internal bodily states are similarly generalized and not restricted to specific infectious states only. For example, if symptoms are perceived in peers, this might be signs of a broader and diverse range of environmental such as irritants or toxins [31] that may lead to place or host aversion to reduce future threat.

In the present pilot study, we focused on olfactory cues of inflammation only. Nevertheless, it is likely that detection of sickness through smell occurs in tandem with the other sensory modalities. Findings from past studies show that LPS-injected individuals show discernible facial (skin colouration, emotional expression, etc.) and

physical movement (e.g., slower gait) changes [10, 12–15]. Similarly, Regenbogen et al. [11] found some evidence that presentation of visual (faces) and olfactory (body odour) cues of sickness together may result in increased activations in the intraparietal sulcus. Thus, future multisensory-oriented research is required to determine the relative contribution and additivity of modality specific cues in facilitating aversion and avoidance to individuals displaying cues of inflammation.

The current study represents a preliminary attempt to explore the relationship between naturally occurring inflammation in a noninfectious condition and the perception of body odour. We provide some preliminary support that low-grade activation of inflammatory processes may reduce the pleasantness of body odour in noncommunicable conditions. If our findings are replicated, it would be important to determine whether other noninfectious conditions, such as chronic diseases, also lead to perceivable changes in phenotypic traits, such as facial, olfactory, movement, and vocal cues, potentially offering a tool for early detection of inflammation and disease.

Statement of Ethics

This study formed part of a larger project examining the central and peripheral nervous system impacts of seasonal allergy [24]. The study protocol was reviewed and approved by Etikprövningsmyndigheten (the Regional Ethical Review Board of Stockholm), approval numbers 2011/1846-31/1 and 2012/202-31/1. All participants provided written informed consent knowing the aims of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

For the collection of body odours and blood samples (stage 1): S.T., B.K., S.C., M.L., and C.L. (for more details, see [24]). For the behavioural experiment (stage 2 – ratings): M.J.O. and M.L. designed the study. A.T. and M.J.O. designed the methodology. A.T. and N.L. created the computer-based experiment, recruited the participants, and collected data. A.T. performed statistical analyses with feedbacks from J.L., S.T., M.L., and M.J.O. S.S. drafted the manuscript with support from A.T. All other authors (N.L., J.L., S.T., C.L., B.K., S.C., M.L., and M.J.O.) provided critical revisions. All authors (A.T., S.S., N.L., J.L., S.T., C.L., B.K., S.C., M.L., and M.J.O.) read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study is openly available in figshare at https://doi.org/10.6084/m9.figshare.24659052. Further enquiries can be directed to the corresponding author.

References

1 Curtis V, Aunger R, Rabie T. Evidence that disgust evolved to protect from risk of disease. Proc Biol Sci. 2004;271(Suppl 4):S131–3.
2 Curtis V, de Barra M, Aunger R. Disgust as an adaptive system for disease avoidance behaviour. Philos Trans R Soc B Biol Sci. 2011;366(1563):389–401.
3 Hart BL. Behavioral adaptations to pathogens and parasites: five strategies. Neurosci Biobehav Rev. 1990;14(3):273–94.
4 Oaten M, Stevenson RJ, Case TI. Disgust as a disease-avoidance mechanism. Psychol Bull. 2009;135(2):303–21.
5 Kurzban R, Leary MR. Evolutionary origins of stigmatization: the functions of social exclusion. Psychol Bull. 2001;127(2):187–208.
6 Ryan S, Oaten M, Stevenson RJ, Case TI. Facial disfigurement is treated like an infectious disease. Evol Hum Behav. 2012;33(6):639–46.
7 Michalak NM, Sng O, Wang IM, Ackerman J. Sounds of sickness: can people identify infectious disease using sounds of coughs and sneezes? Proc Biol Sci. 2020;287(1928):20200944.
8 Tognetti A, Thunell E, Zakrzewska M, Olofsson JK, Lekander M, Axelsson J, et al. Discriminating between sick and healthy faces based on early sickness cues: an exploratory analysis of sex differences. Evol Med Public Health. 2023;11(1):386–96.
9 Lasselin J, Lekander M, Benson S, Schedlowski M, Engler H. Sick for science: experimental endotoxemia as a translational tool to develop and test new therapies for inflammation-associated depression. Mol Psychiatry. 2021;26(8):3672–83.
10 Axelsson J, Sundelin T, Olsson MJ, Sorjonen K, Axelsson C, Lasselin J, et al. Identification of acutely sick people and facial cues of sickness. Proc Biol Sci. 2018;285(1870):20172430.
11 Regenbogen C, Axelsson J, Lasselin J, Porada DK, Sundelin T, Peter MG, et al. Behavioral and neural correlates to multisensory detection of sick humans. Proc Natl Acad Sci. 2017;114(24):6400–5.
12 Sarolidou G, Axelsson J, Sundelin T, Lasselin J, Regenbogen C, Sorjonen K, et al. Emotional expressions of the sick face. Brain Behav Immun. 2019;80:286–91.
13 Henderson AJ, Lasselin J, Lekander M, Olsson MJ, Powis SJ, Axelsson J, et al. Skin colour changes during experimentally-induced sickness. Brain Behav Immun. 2017;60:312–8.
14 Hansson LS, Lasselin J, Tognetti A, Axelsson J, Olsson MJ, Sundelin T, et al. The walking sick: perception of experimental sickness from biological motion. Brain Behav Immun. 2023;113:319–27.
15 Lasselin J, Sundelin T, Wayne PM, Olsson MJ, Paues Göranson S, Axelsson J, et al. Biological motion during inflammation in humans. Brain Behav Immun. 2020;84:147–53.

16 Olsson MJ, Lundström JN, Kimball BA, Gordon AR, Karshikoff B, Hosseini N, et al. The scent of disease: human body odor contains an early chemosensory cue of sickness. Psychol Sci. 2014;25(3):817–23.
17 Sarolidou G, Axelsson J, Kimball BA, Sundelin T, Regenbogen C, Lundström JN, et al. People expressing olfactory and visual cues of disease are less liked. Philos Trans R Soc B Biol Sci. 2020;375(1800):20190272.
18 Gordon AR, Kimball BA, Sorjonen K, Karshikoff B, Axelsson J, Lekander M, et al. Detection of inflammation via volatile cues in human urine. Chem Senses. 2018;43(9):711–9.
19 Moshkin M, Litvinova N, Litvinova EA, Bedareva A, Lutsyuk A, Gerlinskaya L. Scent recognition of infected status in humans. J Sex Med. 2012;9(12):3211–8.
20 Sarolidou G, Tognetti A, Lasselin J, Regenbogen C, Lundström JN, Kimball BA, et al. Olfactory communication of sickness cues in respiratory infection. Front Psychol. 2020;11:1004.
21 Tognetti A, Williams MN, Lybert N, Lekander M, Axelsson J, Olsson MJ. Humans can detect axillary odor cues of an acute respiratory infection in others. Evol Med Public Health. 2023;11(1):219–228.
22 Poon DCH, Ho YS, Chiu K, Chang RCC. Cytokines: how important are they in mediating sickness? Neurosci Biobehav Rev. 2013;37(1):1–10.
23 Borish L. Allergic rhinitis: systemic inflammation and implications for management. J Allergy Clin Immunol. 2003;112(6):1021–31.
24 Tamm S, Cervenka S, Forsberg A, Estelius J, Grunewald J, Gyllfors P, et al. Evidence of fatigue, disordered sleep and peripheral inflammation, but not increased brain TSPO expression, in seasonal allergy: a (11C)PBR28 PET study. Brain Behav Immun. 2018;68:146–57.
25 Trikojat K, Luksch H, Rösen-Wolff A, Plessow F, Schmitt J, Buske-Kirschbaum A. "Allergic mood" – depressive and anxiety symptoms in patients with seasonal allergic rhinitis (SAR) and their association to inflammatory, endocrine, and allergic markers. Brain Behav Immun. 2017;65:202–9.
26 R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R foundation for Statistical Computing; 2022. Available from: https://www.R-project.org/.
27 Tognetti A, Sarolidou G, Lasselin J, Lekander M, Olsson MJ, Lundström JN. Acute systemic experimental inflammation does not reduce human odor identification performance. Chem Senses. 2021;46:bjab004.
28 Lenochova P, Roberts SC, Havlicek J. Methods of human body odor sampling: the effect of freezing. Chem Senses. 2009;34(2):127–38.
29 Arakawa H, Arakawa K, Deak T. Acute illness induces the release of aversive odor cues from adult, but not prepubertal, male rats and suppresses social investigation by conspecifics. Behav Neurosci. 2009;123(5):964–78.
30 Arakawa H, Arakawa K, Deak T. Sickness-related odor communication signals as determinants of social behavior in rat: a role for inflammatory processes. Horm Behav. 2010;57(3):330–41.
31 Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. J Allergy Clin Immunol. 2013;131(1):23–30.
32 Henry EK, Inclan-Rico JM, Siracusa MC. Type 2 cytokine responses: regulating immunity to helminth parasites and allergic inflammation. Curr Pharmacol Rep. 2017;3(6):346–59.