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The Scent of Disease: Human Body Odor Contains an Early Chemosensory Cue of Sickness

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Abstract

Observational studies have suggested that with time, some diseases result in a characteristic odor emanating from different sources on the body of a sick individual. Evolutionarily, however, it would be more advantageous if the innate immune response were detectable by healthy individuals as a first line of defense against infection by various pathogens, to optimize avoidance of contagion. We activated the innate immune system in healthy individuals by injecting them with endotoxin (lipopolysaccharide). Within just a few hours, endotoxin-exposed individuals had a more aversive body odor relative to when they were exposed to a placebo. Moreover, this effect was statistically mediated by the individuals' level of immune activation. This chemosensory detection of the early innate immune response in humans represents the first experimental evidence that disease smells and supports the notion of a "behavioral immune response" that protects healthy individuals from sick ones by altering patterns of interpersonal contact.

Keywords

olfactory perception, human body, health

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Diagnosis of ailments based on tasting and smelling bodily fluids goes back to ancient history. More recently, several diseases have been reported to yield characteristic odors, such as *Scrofula* (which smells like stale beer), Typhoid fever (which smells like baked bread) and Yellow fever (which smells like a butcher's shop; Penn & Potts, 1998). Today, the idea of medical diagnosis of infectious diseases and other disorders through analysis of volatile organic compounds from skin, breath, feces, or urine by aid of electronic noses has refocused attention on these observations, and the results hold promise for disease-specific volatile biomarkers to be of widespread clinical use in the future (Shirasu & Touhara, 2011).

In rodents, a wide array of infections, ranging from gastrointestinal nematodes to viruses, are known to alter

body odor. This alteration results in a lowered preference for the infected individual during initial investigation (Ehman & Scott, 2001, 2002; Kiesecker, Skelly, Beard, & Preisser, 1999). Chemosensory-mediated avoidance of sick conspecifics in animals is now well established (Arakawa, Cruz, & Deak, 2011; Kavaliers & Colwell, 1995a, 1995b). To investigate whether the first line of defense to microbes entails detectable chemosensory sickness cues, researchers in animal studies have used lipopolysaccharide (LPS) to activate the innate immune

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system and an inflammatory response (Beutler, 2009; Suffredini, Fantuzzi, Badolato, Oppenheim, & O'Grady, 1999). Indeed, in the rat, it has been shown that LPS injection influences the body odor of an individual such that other rats avoid contact (Arakawa, Blandino, & Deak, 2009; Dantzer, 2009). Therefore, the innate immune response is also relevant to the investigation of olfactory markers in humans.

With this background, we set out to—for the first time—experimentally test the idea of a chemosensory sickness cue in humans. We hypothesized that humans are able to perceptually dissociate between healthy and sick individuals' body odors. Moreover, under the assumption that this capacity has evolved to reduce contamination risks, we hypothesized that it should be present at an early stage of the sickness response. We tested this hypothesis by comparing body-odor samples from individuals following LPS treatment to samples from the same individuals following saline treatment. Because inflammatory cytokines are involved in sickness behavior (Avitsur, Cohen, & Yirmiya, 1997) and are also implicated in the expression of aversive odor cues in response to a number of pathogens in animals (Dantzer, 2004), we measured proinflammatory cytokines as key mediators of these odor cues.

Method

Sampling of body odors

Eight healthy volunteers (7 men, 1 woman; mean age = 24 years, $SD = 3.71$) were recruited for donation of body odor during two sessions. To be included in the study, participants had to be between 18 and 45 years old, right-handed, and nonsmoking and to neither be taking medication (including nonbarrier contraceptives for female participants) nor have a history of drug abuse, chronic pain, or psychiatric disorders. The eight donors took part in two sessions, both conducted at 1 p.m. and separated by 28 days, in which they received either LPS or saline injections. Participants wore tight T-shirts to allow for body-odor sampling. The sampling took place in a hospital environment and lasted for a total of 4 hr. A physician supervised the donors (for details, see Body-Odor Sampling in the Supplemental Material available online). The study was approved by the regional ethical review board in Stockholm. Written informed consent was obtained from all participants.

Measures of sickness response

During the sampling period, tympanic temperature was measured (using a Thermoscan PRO-1; Braun, Inc., San Diego, CA) before injection and once every hour following injection. Four hours after injection with LPS, participants'

body temperature had increased by about 1 °C (Fig. 1d). Plasma samples were provided 0 hr (baseline), 1 hr, 1.5 hr, 2 hr, 3 hr, and 4 hr after injection; they were frozen at -70 °C and were later thawed for analysis with Millipore's MILLIPLEX MAP high-sensitivity human-cytokine kit (Millipore, Billerica, MA) using Luminex xMAP methodology (Luminex, Austin, TX). In response to LPS, clear rises in levels of tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and IL-8, peaking between 1.5 and 2 hr after injection, were observed, confirming an inflammatory response to LPS (see Figs. 1a–1c).

Chemical assays

We conducted chemical assays of body-odor samples to assess the relative abundance of potentially odorous (i.e., volatile) compounds with gas chromatography–mass spectrometry (GC-MS; see GC-MS Analysis in the Supplemental Material for details).

Participants

Forty participants (28 women, 12 men; mean age = 26.2 years, $SD = 6.3$) were recruited from the Karolinska Institutet university campus to take part in the body-odor-assessment portion of the study. To be included, participants had to be nonsmokers and to have self-reported good health and functional sense of smell.

Procedure

Using a double-blind, within-group experimental design, we tested participants separately with 18 unique odor stimuli (8 LPS body-odor samples, 8 placebo body-odor samples, and 2 samples from unworn T shirts, which served as controls) in squeeze bottles.

For each participant, the odor stimuli were first presented one at a time in a uniquely randomized order with an intertrial interval of 30 s. After a short break of 1.5 min, the odor stimuli were presented a second time, again in a uniquely randomized order. On each trial, the participant could squeeze the bottle and smell the headspace a maximum of two times to prevent sensory adaptation. After smelling the sample, they rated its perceived intensity (using a scale from 0 to 7), pleasantness (using a scale from -7 to 7), and health (using a scale from -4 to 4). Unique scales were used to avoid the potential confound that participants would convert ratings from one scale to another. The extremes of the scales were referred to as “maximal experiences.” The value of 0 on the pleasantness and health scales was referred to as “neither pleasant nor unpleasant” and “neither healthy nor sick,” respectively. We used a measure of perceived intensity to assess whether there was a quantitative rather than qualitative difference between sick and healthy

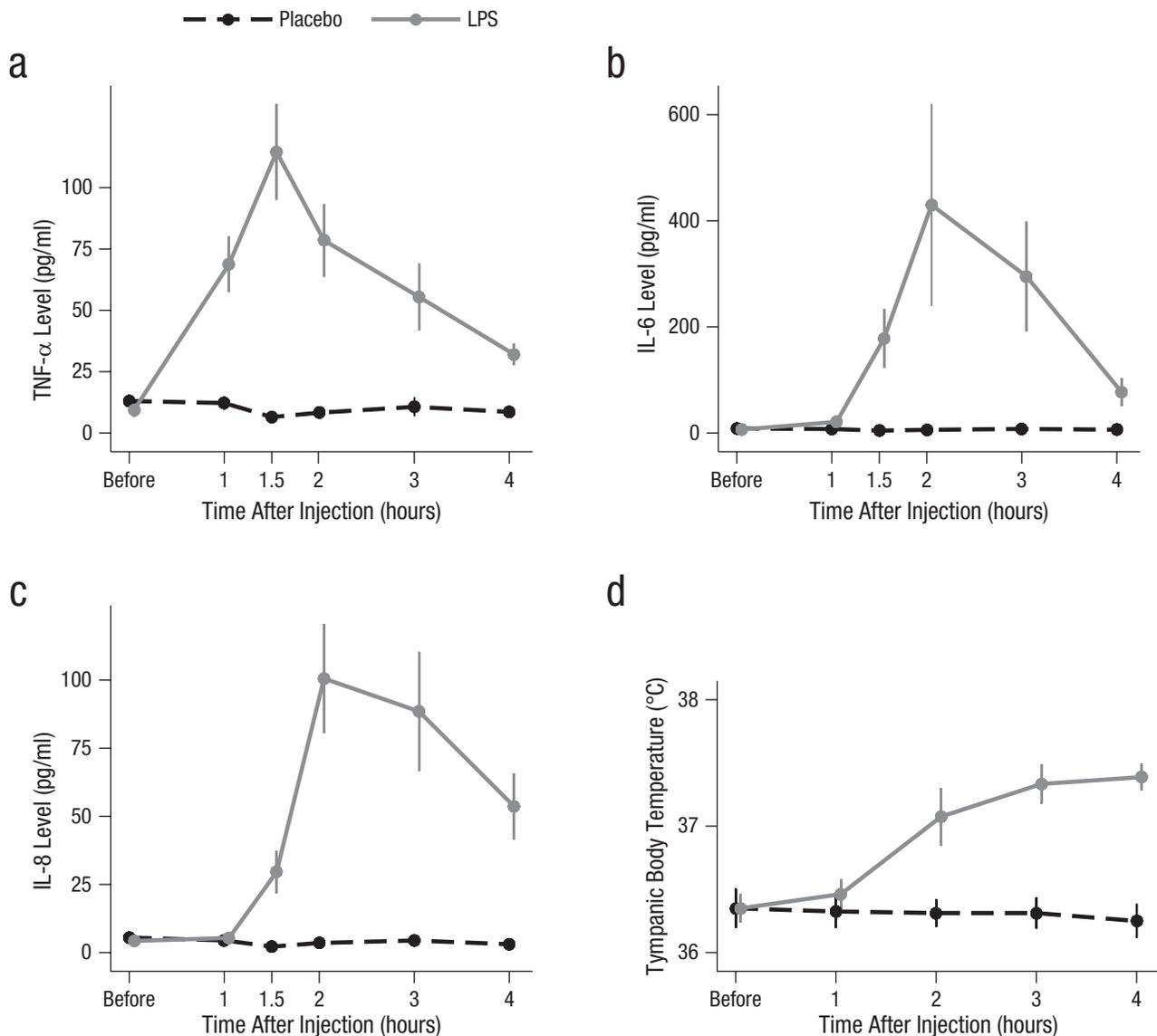


Fig. 1. Mean levels of proinflammatory cytokines (a) tumor necrosis factor- α (TNF- α), (b) interleukin-6 (IL-6), and (c) IL-8 and (d) tympanic body temperature as a function of time after injection and treatment (lipopolysaccharide, LPS, vs. placebo). Error bars represent standard errors.

body odors, and we used a measure of pleasantness because it is the primary dimension of the olfactory perceptual space and is therefore at the base of olfactory functioning (Khan et al., 2007).

Results and Discussion

Participants' ratings of the perceived intensity, pleasantness, and health of odor samples from the three experimental conditions (LPS, placebo, and control; see Fig. 2) were submitted to analyses. Control odors (unworn T-shirts) were rated as smelling significantly less intense,

more pleasant, and healthier than the LPS and placebo odors (worn T-shirts; see Additional Analyses of Ratings of Control Shirts and Table S1 in the Supplemental Material), which indicates that the body-odor-sampling technique was adequate. Further analyses, therefore, were focused on the difference between LPS and placebo body odors. Linear mixed model analyses, using both donors and raters as statistical units (see Choice of Statistical Analysis of Body-Odor Ratings in the Supplemental Material for details) with Bonferroni-Holm correction for multiple testing (Holm, 1979), showed that the LPS body odors smelled significantly more unpleasant, $d = 0.259$, $t(592) = 4.487$,

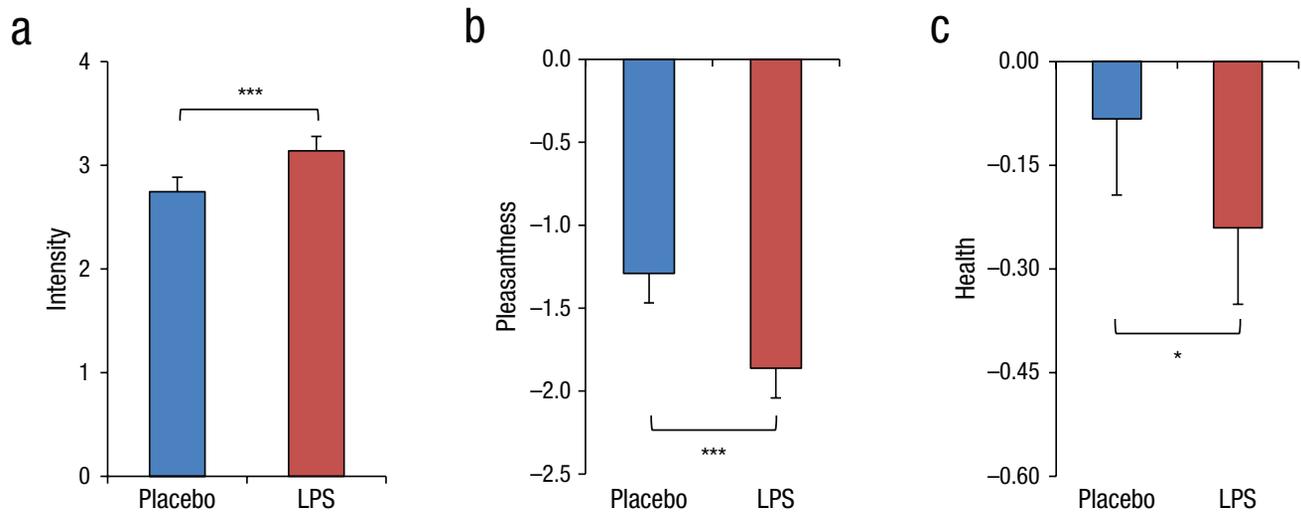


Fig. 2. Mean ratings of the perceived (a) intensity, (b) pleasantness, and (c) health of odors of T-shirts worn by individuals exposed to lipopolysaccharide (LPS) and a placebo. Error bars show standard errors. Asterisks indicate significant differences between conditions (* $p < .05$; *** $p < .001$).

$p < .001$, more intense, $d = 0.212$, $t(592) = 4.423$, $p < .001$, and more unhealthy, $d = 0.133$, $t(592) = 2.025$, $p = .043$.

These results indicate that humans can indeed dissociate between the odors of sick and healthy individuals within 4 hr of innate immune-system activation; there are at least two possible reasons for this effect. The body odors of sick and healthy people may differ in perceived intensity, reflecting that the sick body emits more of the same types of volatile and odorous substances as the healthy body. The higher perceived intensity of the sick body-odor samples supports such a “more-of-the-same” model. The other possible, and more intriguing, explanation for the LPS-induced changes in body odor is that the pattern of substance concentrations emitted from the body has changed and forms a cue of sickness, reflecting the activation of the innate immune system. Such a qualitative shift, independent of overall odorant concentration, would be a more ecologically viable candidate to modulate behavioral adaptations. The observation that a sick individual’s body odor smells more unpleasant and unhealthy supports such a “sickness-cue” model.

However, it is well established that odor pleasantness—in addition to odor intensity—changes as a function of odorant concentration (Doty, 1975). Whereas intensity increases with odor concentration, pleasantness follows a more complicated model: Pleasant odors tend to have an optimum along the stimulus-concentration range, and unpleasant odors simply get more unpleasant as the concentration increases (Lawless, 1977). Given that body odors are on the unpleasant end of the olfactory continuum (Fig. 2), we expect that an increase in body-odor intensity would be accompanied by an increase in unpleasantness. Hence, a more-of-the-same model could also predict a shift in odor pleasantness.

To answer the question of whether or not there was a treatment-related shift in body-odor pleasantness independent of the changes in odor intensity, we performed an analysis similar to that used to assess the effect of body-odor type (LPS, placebo) on pleasantness ratings, but we added odor intensity as a covariate. The results showed a significant and separate effect of LPS treatment on body-odor pleasantness, $d = -0.118$, $t(597) = 2.424$, $p = .016$, and this effect could not be explained by differences in intensity. The same test of perceived health using intensity as a covariate did not reveal a significant separate effect of treatment, $d = -0.046$, $t(598) = -0.730$, $p = .465$.

Moreover, to directly test the more-of-the-same model, we analyzed the body-odor samples (using GC-MS) to assess the concentration of odorous compounds. Because the samples had been used in the behavioral test and were therefore potentially depleted and contaminated, the analysis was restricted to determining the overall abundance of volatile compounds in the LPS and placebo samples. The results indicated that the concentrations of the LPS samples were, on average, lower than those in placebo samples across all compounds identified, but insignificantly so, $d = 0.134$, $t(16) = 0.715$, n.s. In other words, LPS-treated participants did not seem to sweat more, but rather less, than those who were placebo treated. Thus, these results fail to support a more-of-the-same model as the explanation of LPS-induced changes in body odor and are consistent with the notion that during a generalized sickness response, humans emit a chemical cue. Dedicated studies should target these chemicals in the future.

In order to link the change in body-odor composition not only to the LPS treatment but also to the actual

treatment-induced inflammatory response, we performed mediation analyses of cytokines. Cytokines IL-6 and TNF- α , but not IL-8, significantly mediated the effect of treatment on body-odor pleasantness and intensity (Table 1). Taken together, these results strongly support that humans emit a chemical cue during a generalized sickness response that can be perceived by others.

According to participants' verbal reports, rating body-odor intensity and pleasantness was an easier task than rating the perceived health of body-odor samples. Moreover, the effect size of LPS treatment on health ratings, albeit significant, was relatively small. In fact, there was no significant effect of treatment on health ratings when either pleasantness or intensity was controlled for; thus, these results do not support a direct perception of health status. Instead, health ratings may have been based on inferences from the other aspects of the odor, such as its pleasantness. It has also been suggested that the emotion of disgust has evolved as a disease-avoidance mechanism (Oaten, Stevenson, & Case, 2009). The current results may be relevant to this hypothesis, in that a disgust-driven, negative response promotes withdrawal from and avoidance of a sick individual by healthy ones. In concert with the social withdrawal exhibited by infected individuals, such mechanisms are modeled to be highly effective in containing an epidemic—particularly if instigated soon after infection (Cole, 2006). In this study, when participants rated body odors of “sick” individuals, they found them significantly more unpleasant than “healthy” body odors; future studies should focus on the role of disgust in such responses to “sick” body odor.

The exact nature of the cue or signal has yet to be determined. For instance, the volatile substances in the skin mediating the effect from an inflammatory response to body odor need careful investigation. Moreover, with

regard to theory, there are two assumptions one can make about a sickness odor: It could be viewed as either a cue or a signal. As a cue, it would be inadvertent on behalf of the sender and beneficial to the receiver. In line with that notion, most animal studies have revealed avoidance behavior in response to a sick body odor. However, the avoidance behavior is typically seen in response to body odors of unfamiliar conspecifics; in contrast, increased maternal licking of LPS-treated rat pups has also been reported (Breivik et al., 2002). This pattern of results supports the idea that the sickness odor can also be a signal beneficial to the sender. Some evidence even suggests that, rather than being aversive, the odor of infected males simply loses its attractiveness, which suggests a reduced signal of health rather than an increased signal of sickness (Kavaliers & Colwell, 1995a; Penn, Schneider, White, Slev, & Potts, 1998). It is not yet clear whether these changes are best characterized as a cue of illness beneficial to recipients or simply as a reduced signal of health from a sender whose resources necessary for health-signal maintenance have been reallocated (Penn & Potts, 1998). It should also be noted that the specificity of the type of olfactory cue indicated here and in animal models remains to be determined.

Among the physiological adaptations that occur after immune challenge is an activation of the hypothalamic-pituitary-adrenal (HPA) axis (Maier, Watkins, & Nance, 2001), and consequently, increased cortisol can be seen after LPS administration in humans (Grigoleit et al., 2011). This overlap between sickness and the fight-flight response is expected, given that mobilization and redirection of energy is central to handling threats from both within and without (Segerstrom & Miller, 2004). Future studies should therefore investigate the extent to which internal and external challenges result in similar olfactory changes.

Table 1. Crude and Mediated Effects on Ratings of Body-Odor Pleasantness, Intensity, and Health

Effect and mediator	Pleasantness	Intensity	Health
Crude effect			
LPS	-0.259 (0.058)***	0.212 (0.048)***	-0.133 (0.066)*
Temperature	-0.120 (0.034)***	0.091 (0.029)**	-0.041 (0.039)
IL-6	-0.181 (0.034)***	0.145 (0.029)***	-0.080 (0.039)*
IL-8	-0.144 (0.033)***	0.107 (0.027)***	-0.059 (0.037)
TNF- α	-0.153 (0.031)***	0.126 (0.026)***	-0.075 (0.035)*
Mediator of effects of LPS			
IL-6	-0.149 (0.051)**	0.113 (0.043)*	-0.049 (0.057)
IL-8	-0.070 (0.061)	0.017 (0.051)	0.013 (0.068)
TNF- α	-0.154 (0.077)* ^a	0.127 (0.064)* ^a	-0.058 (0.085)

Note: Tests of the significance of mediation effects were conducted using Sobel tests and were based on MacKinnon and Fritz (2007). Standard deviations are shown in parentheses. LPS = lipopolysaccharide; IL-6 = interleukin-6; IL-8 = interleukin-8; TNF- α = tumor necrosis factor-alpha.

^aSignificance does not withstand a Bonferroni-Holm correction for multiple testing.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Altogether, the results of this experimental study suggest that, akin to rodents, humans are able to detect a social cue of sickness from body odor alone, which can be used for avoidance of infected conspecifics. Moreover, this social information can be triggered by the innate immune response, which is observable just a few hours after innate immune-system activation and is a general response to a variety of pathogens. Human olfaction may thus prove to be a signaling route to a “behavioral immune response” (Breivik et al., 2002) that protects healthy individuals by altering patterns of interpersonal contact and, possibly, by heightening the immune-system response to infection in the receiver, as has been shown for other disease-related stimuli (Schaller & Park, 2011; Stevenson et al., 2012).

Author Contributions

M. J. Olsson, J. N. Lundström, B. Karshikoff, N. Hosseini, C. Olgart Höglund, A. Soop, J. Axelsson, and M. Lekander designed the method for data collection; data collection was carried out by A. R. Gordon, B. Karshikoff, C. Solares, N. Hosseini, and B. A. Kimball under the supervision of M. J. Olsson. A. Soop administered lipopolysaccharide. M. J. Olsson and K. Sorjonen wrote the statistical-analysis plan and carried out the statistical analyses. Data analyses were conducted by A. R. Gordon, C. Solares, and B. A. Kimball, and J. Axelsson conducted GC-MS analyses. M. J. Olsson, C. Olgart Höglund, and M. Lekander obtained funding with help from J. Axelsson. The manuscript was drafted by M. J. Olsson, N. Hosseini, and K. Sorjonen and revised by J. N. Lundström, A. R. Gordon, B. Karshikoff, C. Solares, N. Hosseini, K. Sorjonen, B. A. Kimball, J. Axelsson, and M. Lekander. M. J. Olsson served as the study's guarantor. All authors approved the final version of the manuscript for submission.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

Additional supporting information may be found at <http://pss.sagepub.com/content/by/supplemental-data>

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