



# Detection of sickness in conspecifics using olfactory and visual cues

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## Social Communication in Humans

Social communication in humans, although largely based on sophisticated language skills, is also substantially mediated by nonverbal cues that the receiver perceives through his/her senses. It is largely acknowledged that humans are highly visual organisms and that their perception of the social and physical environment is dominated by vision. In the field of person perception (i.e., how we process information about people), an enormous research effort has been dedicated in particular to the understanding of face perception (1) and how information, such as the individual's emotional state or quality as a mate, can be conveyed through facial features (color, shape, expression, etc.). However, other sensory channels have more recently been revealed as highly pertinent: the auditory channel [through the voice (2)] and the olfactory channel. Although olfaction has long been a neglected sense in humans (3), there is now convincing evidence that humans are efficient in using it (4) and able to extract relevant cues conveyed by smells, and respond to them in an adaptive manner. For example, several experiments using "fear sweat" (body odor produced by donors experiencing fear) revealed emotional contagion in the receiver (5). Alarm is one of the major functions of olfaction (6), with obvious survival relevance. In the food domain, olfactory cues allow us to avoid the deadly threat of ingesting spoiled food. In the social context, threat detection through smell can, for example, materialize in the recognition of infected status. The medical community has been using olfactory cues in diagnoses for centuries (7), and dogs have the ability to recognize sick individuals by smell (8, 9). However, the mechanisms of disease avoidance through smell in humans remain at present poorly explored or understood, in terms of both the nature of the chemicals produced by the healthy or sick individual and the expression and cerebral representation of the perception of such highly relevant olfactory cues. The article in PNAS by Regenbogen et al. (10), by tackling the latter issue, is therefore a pioneer in this area.

## Sickness Communicated Through Olfaction and Vision

The first question asked in this study was how humans perceive early sickness cues of conspecifics sampled just hours after the induction of immune system activation. The second question concerned the neural mechanisms involved in the detection of these sickness cues. To address these questions, the authors conducted a double-blind, placebo-controlled study in which the immune system was transiently activated in 22 individuals (referred to as "donors") with an injection of lipopolysaccharide (LPS; an endotoxin). Facial photographs and body odor samples were taken from the same donors when "sick" (after LPS injection) and when "healthy" (after saline injection). These visual and olfactory stimuli were then presented to a new sample of 30 naive participants in a functional magnetic resonance imaging (fMRI) study in which their neural responses to faces and body odors were measured. Here, sick and healthy facial stimuli, displayed on a computer screen, were presented paired with either sick or healthy body odors, or with a control olfactory condition; olfactory stimuli were diffused by an olfactometer. During fMRI scanning, participants rated their liking of the person depicted in the facial visual stimulus. After the fMRI session, they were also asked to rate stimuli along various dimensions: intensity, pleasantness, and healthiness (for odors) as well as attractiveness, healthiness, and desired social interaction (for faces).

Regenbogen et al. (10) show that liking behavior toward another person was modulated by activation of the immune system, in that sick faces were less liked, and were judged less attractive, healthy, or socially desirable than healthy faces. Moreover, faces associated with sick body odors were less liked than faces paired with the control olfactory condition. Such perceptual changes were associated with neural modulation: "Visual sickness" (perception of sick faces in comparison to healthy faces) induced activations mainly in secondary brain areas: middle and superior frontal gyrus, posterior insula, and middle cingulate cortex. Note that when visual and olfactory cues of sickness were combined, significant functional connectivity was shown between a set of brain

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regions (inferior parietal sulcus and temporal cortices, inferior parietal lobe, cingulate cortices, precuneus, primary visual cortex, and fusiform cortex), indicating the existence of an amodal neural network extracting sickness cues.

When olfactory stimuli were considered alone, because body odors were relatively weak in intensity, no clear perceptual differences were observed between sick and healthy body odors. Despite this absence of perceptual difference, neural activations by "olfactory sickness" were seen: In contrast to visual sickness, olfactory sickness enhanced activity in both primary and secondary areas (entorhinal/piriform cortex, orbitofrontal cortex, inferior frontopolar gyrus, middle frontal gyrus, and thalamus). The fact that such a neural network was activated for smells perceived as weak in intensity and difficult to discriminate raised the question of whether neural extraction of olfactory sickness is mediated by nonconscious processes. In line with this hypothesis, a series of previous reports indicated that olfactory stimuli can influence nervous system activity and behavior without being consciously detected (11, 12). The activation observed in the thalamus in particular could be explored in greater depth in future studies, because previous work suggests its involvement in attention to olfactory stimuli (13).

In all, Regenbogen et al.'s work (10) shows that the odor of a sick versus healthy body triggers differentiated cerebral responses in the recipient: This finding clearly raises the question of the nature of human body odor, its variations, and its signaling function. The chemical composition of skin odors is not yet fully known, and methods of sampling (14) and of chemical analysis are subject to debate (15). Research on the role of body odor in social interaction, not only in disease avoidance but also in human attractiveness and mate choice, suffers from these shortcomings. For example, more or less only a single family of compounds (androstenes) has been the focus (16) of attempts to identify human (sex-related) pheromones, whereas body odor is made up of hundreds of other possibly relevant compounds that clearly deserve our attention but are neglected because of lack of knowledge. With currently developing techniques in analytical chemistry, the challenge of developing our knowledge of the nature of human body odor, and thus of its signaling function, may possibly be met in the near future.

### Future Directions

In this perspective, future neuroscientific studies could benefit from experience gained in the field of food science. Humans use multiple sensory channels to detect and avoid potential threats present in food by being able to distinguish even small changes in organoleptic properties. For instance, changes in meat color from pink to brown or in fruit texture from moist to dry may indicate that the food is no longer edible or that it could represent a threat if eaten. Likewise, the

olfactory channel enables detection of small changes in the concentration of certain volatile compounds. For example, the presence of some aldehydes (specifically hexanal) suggests fat oxidation in meat and oil (17), and the presence of trimethylamine is an indicator of decay in fish (18). In all, the study of human chemical communication has everything to gain from drawing methodological inspiration from studies in food sciences, where a large number of olfactory compounds have already been isolated.

**The contribution by Regenbogen et al. is an important one in the field of nonverbal social communication. It especially highlights, for the first time, that olfactory and visual sickness cues activate specific and interacting neural networks and influence behavior toward conspecifics.**

Finally, another stimulating perspective raised by Regenbogen et al.'s article (10) is to explore further the concept of relevance of olfactory (or visual) information. The notion of relevance to the receiving subject's current needs and goals is central to the formation of his/her emotional response, as postulated by the appraisal theory of emotion (19), with the amygdala being a key cerebral substrate in relevance detection processes (20). Surprisingly, despite a functional connection between the amygdala and the intraparietal sulcus during multisensory integration, no difference in amygdala activation was found on direct comparison between sick versus healthy olfactory (or visual) stimuli in Regenbogen et al.'s study (10). Given the adaptive function of the process investigated (disease avoidance) and its underlying neural mechanism, it could be worth testing samples varying in the relevance level of their sickness cues, such as patients with or without immunodeficiency (pathology- or medication-induced) or cultural groups from geographic areas differing in average pathogen level (21). Such approaches could provide a more comprehensive framework to elucidate the cerebral and behavioral processes involved in sensory-based disease avoidance.

In conclusion, the contribution by Regenbogen et al. (10) is an important one in the field of nonverbal social communication. It especially highlights, for the first time, that olfactory and visual sickness cues activate specific and interacting neural networks and influence behavior toward conspecifics. This study opens up new avenues of research in the field of sensory and cognitive influences on behavior without clear awareness, and it deserves interdisciplinary effort with other fields, such as chemistry.

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