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Functional Neuronal Processing of Human Body Odors

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Abstract

Body odors carry informational cues of great importance for individuals across a wide range of species, and signals hidden within the body odor cocktail are known to regulate several key behaviors in animals. For a long time, the notion that humans may be among these species has been dismissed. We now know, however, that each human has a unique odor signature that carries information related to his or her genetic makeup, as well as information about personal environmental variables, such as diet and hygiene. Although a substantial number of studies have investigated the behavioral effects of body odors, only a handful have studied central processing. Recent studies have, however, demonstrated that the human brain responds to fear signals hidden within the body odor cocktail, is able to extract kin specific signals, and processes body odors differently than other perceptually similar odors. In this chapter, we provide an overview of the current knowledge of how the human brain processes body odors and the potential importance these signals have for us in everyday life.

I. The Microsmatic Fallacy

Body odors carry information of great importance for individuals across a wide variety of species. That humans may be among these species has been, for a long time, dismissed outright. We now know, however, that each human has a unique odor signature that carries information related to his or her genetic makeup (Kwak *et al.*, 2010), as well as information about personal environmental variables, such as diet and hygiene (Havlicek and Lenochova, 2006; Penn and Potts, 1998b). Moreover, much like our fellow animals, humans seem to have the ability to extract biological and social cues from conspecific body odors (i.e., originating from the same species), and respond to those cues. Although the available literature on the central processing of human body odors (endogenous odors) has grown greatly of late, our understanding of this phenomenon is still dispersed and incomplete in many ways, and we recognize that, as a result of these knowledge gaps, some of the arguments we make in this overview are speculative. Nonetheless, it is our hope that this review identifies the important aspects of how the human brain processes body odors, and that this chapter will stimulate future discussions and research.

One long-standing view propagated in scientific and popular scientific literature and accepted by scientists and laymen alike is that the olfactory system plays a subordinate or unimportant role in human social lives. In reality, the US market alone spent more than $25 billion in 2001 on scented products in an effort to eliminate, hide, or enhance natural human body odors (Gilbert and Firestein, 2002). This directly contradicts the general view that the olfactory sense is in any way “residual” or subordinate to the other human sensory systems. The notion that humans do not use their sense of smell in everyday life can, arguably, be traced back (Schaal and Porter, 1991) to the writings of the French anatomist Pierre Paul Broca (1824–1880). Broca, best known for his discovery of the speech processing area

subsequently named after him, labeled mammals as either microsmatic or macrosmatic entirely on the basis of the relative sizes of their olfactory systems and how important a role the olfactory system plays in their daily lives (Broca, 1888). Microsmatic animals, according to Broca's description, pay little attention to odors in their daily lives and possess an olfactory apparatus with little-to-no functional capacity. Humans were grouped with the microsmatic species on the basis of the small size of their olfactory system relative to those of other species. How Broca went about characterizing the size of the human olfactory system is not known, but we can likely assume that guessing played at least some part in his estimations. More recently, modern genetic techniques have demonstrated that mankind has more pseudo-olfactory genes than other comparative species, often taken as supportive evidence for Broca's notion (Glusman *et al.*, 2001; Rouquier *et al.*, 2000; Young *et al.*, 2002). However, comparative psychophysical studies of the olfactory function of humans and other species have demonstrated that olfactory performance is not directly correlated with the anatomical size of olfactory structures and the percentage of expressed olfactory genes (Laska and Freyer, 1997; Laska and Teubner, 1998; Laska *et al.*, 1999, 2005). Rather, olfactory performance appears to be dependent on the relevance of the message conveyed by a given odorant to an individual perceiving that odorant (Laska *et al.*, 2005). Together with recent advances in the scientific field of olfaction, these findings directly contradict Broca's influential but flawed notion of microsmatic humans and support the much different conclusion that odors exert a significant impact on a range of human behaviors.

II. Human Body Odor Perception and Production

The conscious percept, or mental impression, of a body odor often contains an emotional component that evokes polarized responses of strong like or dislike. For many of us, the two words “body odor” are sufficient to trigger an unpleasant percept related to heavy perspiration. Simple though that seems, the perception of body odor is multifaceted and more complex than a straightforward aversion to gym odor. Consider, for example, that the body odor of your lover may be a very pleasant percept, whereas the body odor of the person sitting next to you on the bus may be highly negative. Moreover, as we discuss in detail below, there is a clear distinction between the conscious and the nonconscious perception of body odors.

The importance of body odors has been demonstrated in the conscious selection of a potential partner in that the mere percept of body odors has a negative implication for women, but not for men (Herz and Cahill, 1997; Herz and Inzlicht, 2002). In addition, the impact that biological factors have on our percept of body odors has recently been indirectly demonstrated by several experiments. Our percept of body odors is dependent on the sexual orientations of both the donor and the perceiver (Martins *et al.*, 2005), and heterosexual women's percept of men's body odor varies over their menstrual cycle (Roberts *et al.*, 2004). Body odor is consciously perceived and its perception reflects a response to a small subset of the numerous chemical compounds (approximately 120) that comprise our body odor (Labows *et al.*, 1999). In contrast, we are typically not consciously aware of perceiving the specific compounds within our body odor that may serve as social signals.

Our body odors are primarily due to the elements from skin gland excretions and bacterial activity. The human skin contains three types of exocrine glands: eccrine, sebaceous, and apocrine glands. Eccrine glands populate the entire human body and represent the dominant type of sweat gland. The principal function of eccrine glands is to cool the body, and they respond mainly to thermal stimulation. The eccrine glands produce a clear and mostly nonodorous secretion comprised of more than 90% water (Sato, 1977). The sebaceous glands are found over much of the skin surface, with regional patches of higher density, and excrete sebum, a complex lipid mixture. What type of stimulation the sebaceous glands react

to has not been well defined. The apocrine glands, nicknamed the “scent glands,” differ from eccrine and sebaceous glands in structure and location. The ducts of apocrine glands exit through the shafts of hair follicles and are concentrated in areas of hair growth, such as the axillary area, the aureole of nipples, and the genitalia (Wysocki and Preti, 2000). Apocrine secretions contain most of the odorless precursors for the odorants that we commonly call “body odor.” These secretions are small amounts of a milky lipid- and protein-rich fluid, the release of which is regulated mainly by psychological stimuli (Schaal and Porter, 1991). At the skin surface, bacteria metabolize this mixture of excretions and produce a plethora of volatile and nonvolatile substances (Gower and Ruparelia, 1993). The fact that body odors are formed by skin glands with distinct functions that respond to distinct exogenous stimuli is an important factor in our understanding of human body odors and the behavioral reactions they elicit. In short, not all body odors are created equal.

III. Central Processing of Body Odors

The mixture of chemical compounds causing our axillary body odor carries with it information that we are able to extract and utilize. Recent studies have demonstrated that humans produce individually unique body odors (Kwak *et al.*, 2010), which enable us to identify individuals (Lundstrom and Jones-Gotman, 2009; Olsson *et al.*, 2006; Russell, 1976; Wallace, 1977) and make accurate judgments about kinship based solely on body odor composition (Lundstrom *et al.*, 2009a; Porter, 1998; Porter and Moore, 1981; Weisfeld *et al.*, 2003).

Although a substantial number of studies have investigated the behavioral effects of body odors, only a handful have studied central processing. Bettina Pause was the first to explore how the human brain processes body odors. Using EEG, a method with very good temporal, but poor spatial resolution, Dr. Pause elegantly demonstrated that the human brain is able to discriminate between body odors despite an unawareness of this ability (Pause *et al.*, 1999, 2006). Interestingly, the human brain appears to make a distinction between body odors originating from oneself and body odors originating from someone else, in this case, a stranger. Not only does the brain seem to process one's own body odors faster (Pause *et al.*, 1999), but it also allocates more neuronal processing to the resulting neuronal computations of one's own body odors than to the processing of body odors from an unrelated individual (Pause *et al.*, 2006). It has been repeatedly demonstrated that visual signals with high ecological importance are processed in a privileged way, often by neuronal networks residing outside of the main visual system (Dimberg and Ohman, 1983; Morris *et al.*, 1999; Schupp *et al.*, 2004). The complex mixtures we refer to as body odors, like the high-priority visual stimuli, convey large amounts of ecologically important information. The richness of information conveyed and the commonality among animal species indicate that the complex chemical mixture we refer to as body odors is a stimulus of ecological importance and as such, would receive preferential treatment by the brain. Indeed, a recent study from our lab seems to corroborate this notion (Lundstrom *et al.*, 2008).

In an effort to elucidate whether body odors are processed as common odors or whether they recruit a separate network, we measured how the brain responds to human body odors of varying origin as well as a mixture of common odors perceptually indistinguishable from human body odor (Lundstrom *et al.*, 2008). When we directly compared how the brain processes *body odors* with how it processes perceptually similar *fake body odor*, thus controlling for the effects caused by the conscious percept of the body odor, we found that body odors activate an elaborate network residing outside the main olfactory system. Body odors activate four main areas: the posterior cingulate cortex, the occipital gyrus, the angular gyrus, and the anterior cingulate cortex (see Fig. 1.1).

This particular combination of cortical areas forms an interesting network. The posterior cingulate cortex (PCC) is known to regulate emotional responses and actions (Cato *et al.*, 2004; Maddock, 1999), and the anterior cingulate cortex is primarily associated with attention processing (Botvinick, *et al.*, 1999). The occipital cortex activation was located within areas of the primary visual cortex, which suggests that the neuronal processing of body odors is similar to what has been previously demonstrated for emotional visual stimuli of high ecological importance, such as pictures of spiders or snakes. For these visual images, the PCC works in conjunction with the anterior cingulate cortex to determine and process the emotional stimuli (Fredrikson *et al.*, 1995). Although these two latter cortical areas (the PCC and anterior cingulate cortex) were predicted, we cannot assign a causal relationship between them within this dataset. It is possible, however, that body odors, in comparison with common odors, receive a more or less automatic heightened attention by virtue of their signal value. Seen from an evolutionary perspective, signals carrying important information or information related to recurrent survival threats might have been selected by evolutionary pressure to receive preferential processing, or, more specifically, direct access to areas of the brain regulating emotional and attentional processing. Such preferential processing would allow the information contained within human body odors to have a direct impact on human behavior by either affecting the saliency or directly heightening attention to specific stimuli.

Body odors also triggered a strong response in the occipital cortex, the so-called primary visual cortex. That there is a link between odor processing and visual processing has been demonstrated in a range of neuroimaging studies exploring neuronal processing of odors (Djordjevic *et al.*, 2005; Gottfried *et al.*, 2004; Royet *et al.*, 1999, 2001; Zatorre *et al.*, 2000) in the absence of visual stimulation. The combination of frequent olfactory stimulation-induced visual activations in olfactory neuroimaging studies, the absence of visual stimulation in this study, and the subjects' inability to distinguish human body odor from fake body odor stimuli suggests that visual activation is not a direct derivate of body odor processing. Moreover, a review of the aforementioned articles demonstrates no obvious common denominator that could explain the visual activation other than the presence of an olfactory stimulus. It could be speculated that the activation of the visual system is indicative of a preparedness mechanism. The presence of an odor arguably signals the imminent presence of an object, be it an individual with respect to body odors or a nice meal with respect to common odors, and the resulting cognitive mechanisms may prime or prepare the visual system for visual stimuli. Studies of the function of the angular gyrus, an area intimately connected to the creation of a visual body construct, support this theory. Disruption of the neuronal signals within this area is known to either abolish or alter how the human brain interprets the perception of its own and other individuals' bodies (Arzy *et al.*, 2006; Blanke *et al.*, 2002, 2004, 2005). Whether the angular gyrus serves as an important node in a modality-independent system for body representation remains to be demonstrated, however. The topic of cross-modal perceptual priming on a neuronal level is an emerging field where much is still to be learned, and with the emergence of high field strength MRI scanners, the future is ripe for interesting discoveries.

IV. Neuronal Processing of the Smell of Fear

Humans, like many other animals, seem to be able to identify the emotional state of a conspecific based solely on his or her body odor. A recent study collected body odor samples from individuals who watched either funny or scary movie sequences. Participants were later asked, in a forced-choice detection task, to identify the emotional state of the donors. Remarkably, participants were able to accurately identify both happy and fearful emotional odors at levels above chance value (Chen and Haviland-Jones, 2000), though they performed much better with body odor samples from fearful donors. A subsequent study replicated some of the findings reported by Chen and Haviland-Jones (2000) in that

participants were able to identify a body odor as coming from a frightened individual (Ackerl *et al.*, 2002).

One can speculate that body odors originating from a fearful individual possess an inherently higher level of relevance to the perceiver, as they might signal danger in the surrounding environment (Ohman *et al.*, 2001b). In other words, given the high survival value, fearful stimuli might have been selected for, by evolution, to enjoy the benefit of an automatically higher level of attention and prioritized access to processing (Ohman and Mineka, 2001; Tooby and Cosmides, 1990). This might explain why participants seem to have an easier time identifying and discriminating the body odor sampled from a fearful individual. Interestingly, a recent study investigating the ability of body odors to modulate the acoustic startle reflex seems to support this notion (Prehn *et al.*, 2006). The acoustic startle reflex is an evoked preattentive reflex that is modulated by the affective valence and the extent to which the foreground stimulus merits attention and that is often used to investigate the emotional effect of stimuli (Dawson *et al.*, 1999; Koch, 1999). Prehn *et al.* (2006) demonstrated that body odors sampled during a state of anxiety were able to modulate the startle response, whereas body odors collected during a neutral emotional state were not. Body odors collected during a high anxiety state might thus modulate emotional processing of relevant stimuli in the surroundings (but see, Miltner *et al.*, 1994). Indeed, Chen *et al.* (2006) demonstrated that exposure to body odor samples collected during fearful stimuli rendered participants to process a fearful content in a word association task more slowly and more accurately. It might seem that the heightened accuracy in cognitive processing that fearful body odors produced is in congruence with the notion that these odors are preferentially processed or, as Chen *et al.* (2006) argue, that they modulate cognitive performance. One might, however, take the opposite stance. An instantaneous response to a fearful stimulus is at the core of fear-evoked responses (cf. Mineka and Ohman, 2002). The underlying evolution of cognition is not clear, but there is little evidence supporting the view that it emerged to enhance responses in fearful or stressful situations. Rather than carefully evaluate available options and their potential outcomes, an individual has a greater chance at survival if they are able to act instantly, with only minimal cognitive effort. Hence, the evolutionary pressure should have been on the promotion of false positive, rather than false negative errors in response to fear: the former is costly energy-wise, but the latter is potentially deadly. In other words, fearful stimuli should enhance reaction time at the cost of accuracy as previously demonstrated for fearful visual stimuli (Flykt, 2006; Ohman *et al.*, 2001a,b). Based on this, the assumption that fearful stimuli should increase accuracy and prolong the response time to lexical judgments requiring cognitive processing seems less plausible. However, in defense of the cognitive view are recent behavioral and imaging data that seem to indicate that body odor samples collected during a fearful or high emotional state are not processed in a manner similar to visual fearful stimuli, which provoke a fast and immediate response, but rather seem to modulate the cognitive evaluation or processing of relevant stimuli.

When asked to rate faces with an ambiguous emotional expression, women tend to rate them as being more fearful when exposed to body odors collected from men in a fearful state compared to body odor samples collected from men in a happy state (Zhou and Chen, 2009). Related results were obtained in a study by Mujica-Parodi *et al.* (2009), who collected body odor samples from volunteers performing a tandem parachute jump for the first time or while exercising. Exposure to the body odor samples collected during the parachute jump made the participants better at discriminating between the emotional faces presented to them. Unfortunately, neither of these two experiments reports data for response speed, thus making it impossible to infer anything about the trade-off between speed and accuracy. However, the aforementioned behavioral studies seem to indicate that body odors signaling fear or high levels of anxiety indeed modulate cognitive processing and increase accuracy of

how certain salient stimuli in our surroundings are processed. This is contradictory to what is known for the processing of threatening visual stimuli, but in accordance with how the chemosensory system generally works. The speed of processing for chemosensory stimuli is significantly lower than that of visual or auditory stimuli (Wetter *et al.*, 2004). The estimated time difference between the onsets of the first perceptual and the first cognitive processing between the visual and olfactory system is as large as 200 and 400 ms, respectively (Olofsson *et al.*, 2008; Pause and Krauel, 2000). Relying on the olfactory system for early detection warning might therefore not be an optimal survival strategy for an individual, given how "slow" the brain is in processing chemosensory stimuli. However, since chemosensory stimuli are good at communicating messages over distance and remain reliable when the visual field is occluded, a good strategy would be to allow chemosensory stimuli to shape the slower and more deliberate processing rather than the initial and more rapid detection phase.

Two recent neuroimaging studies provide additional support for the notion that fear, or anxiety, can be communicated via our body odors (Mujica-Parodi *et al.*, 2009; Prehn-Kristensen *et al.*, 2009). Both studies sampled body odors from individuals undergoing a fear- or anxiety-inducing task as well as a physical exercise task as control. The aforementioned study by Mujica-Parodi *et al.* (2009) sampled body odors from individuals performing a tandem skydiving jump for their first time, whereas the study by Prehn-Kristensen *et al.* (2009) sampled body odors from individuals who were waiting for an important academic test. Although their design and analyses were quite similar, the studies produced different results. Mujica-Parodi and colleagues found that a central subcortical area, the amygdala (see Fig. 1.2), responded preferentially to the body odor sample collected during the skydiving jump when compared to the exercise sweat.

However, Prehn-Kristensen and colleagues found that a cortical network consisting of the fusiform gyrus, the insular cortex, PCC, and the precuneus responded preferentially to the anxiety sweat. Such large disparities between two studies so similar in design are, at first sight, hard to understand. However, this is an excellent example of how minor differences in the sampling of body odors have a large impact on the outcome. The body odor sampling by Mujica-Parodi *et al.* (2009), from volunteers performing a parachute tandem jump for the first time, who are presumably in a state of fear or at least very high anxiety, is quite different from the body odor sampled by Prehn-Kristensen *et al.* (2009), from students waiting to take an academic exam. It is probably safe to assume that jumping out of a plane would produce a more fearful state than waiting for an academic test, an act that is arguably more likely to induce high to moderately anxiety. Indeed, Mujica-Parodi and colleagues demonstrated by salivary cortisol measures that their subjects expressed at least very high levels of anxiety during the jump. The location of the main activity in the amygdala also supports the notion that it is indeed related to fear. The amygdala has repeatedly been linked to the processing of negative emotional stimuli (Morris *et al.*, 1999; Whalen *et al.*, 1998; Yamasaki *et al.*, 2002). Moreover, detection of threat-related stimuli and responses to them and other emotionally salient stimuli are mediated by the amygdala (LeDoux, 1992, 1996). However, although the amygdala is recognized as a major site of fear-plasticity (LeDoux, 2000), evidence suggests that it may not mediate feelings of fear *per se* (Dolan and Vuilleumier, 2003; LeDoux, 2000). Rather, the amygdala has been identified in all vertebrates studied to date as an important center in the identification of threats. In mice, the amygdala has been specifically identified as the main processing center of threat-related endogenous odors (Vyas *et al.*, 2007). One could postulate, therefore, that the amygdala should also be involved in the detection of threat-related olfactory stimuli in humans and not the processing of fear itself. The aforementioned study by Lundstrom *et al.* (2008) lends support to this notion. We demonstrated that smelling a stranger's body activated cerebral regions similar to those found to be active when viewing perceptually masked fearful faces

(Morris *et al.*, 1998; Whalen *et al.*, 1998). Despite a low conscious recognition of the body odor's source, a marked response in the amygdala, insular, and precuneus cortex of all participating subjects was noted (see Fig. 1.3). In other words, the detection of a body odor signaling an unknown individual (a stranger) in the near vicinity, or a body odor originating from an individual in a fearful state, could be hypothesized to act as a warning signal which would be processed by the amygdala.

Interestingly, the neuroimaging results obtained by Prehn-Kristensen and colleagues correspond to a great extent to the aforementioned results of body odor processing by Lundstrom *et al.* (2008). Activations were found in both studies within in the anterior and PCC as well as the insular and precuneus cortex. However, Prehn-Kristensen and colleagues' imaging design involved contrasting two natural body odors, whereas Lundstrom and colleagues contrasted natural body odors with a fake body odor consisting of natural odors. The control odor used in each study explains why these contrasts yield similar results.

As discussed above, body odors originate from various glandular sources and the mental and physical state of the individual has a large impact on which source is predominant at any given moment. In the samplings performed by Prehn-Kristensen and colleagues and Mujica-Parodi and colleagues, the emotional condition would have sampled predominantly from the apocrine glands and will be highly odorous while low in amount of sampled liquids. The exercise condition will sample predominantly from the eccrine glands and will have a weak odor but will also have a greater quantity of liquid. A contrast between these two conditions not only compares two emotional states, but also separates glandular excretions and two different amounts of stimulus. In the case of Prehn-Kristensen and colleagues' study, the contrast between anxiety sweat and exercise sweat would then result in cortical areas activated by sweat predominantly sampled from the apocrine glands when the perception of the body odor is controlled for, much like the design by Lundstrom *et al.* (2008). We would like to stress that this fact does not falsify or negate the obtained and published results. We are, however, arguing that the difference in the source of the body odors should be considered when interpreting the outcome. A more stringent control condition, although admittedly more cumbersome, would be to sample control body odor while participants perform a non-emotional task in the same physical state as during the experimental condition (see among others: Chen and Haviland-Jones, 1999; Chen *et al.*, 2006; Lundstrom *et al.*, 2008, 2009a). Nevertheless, the coherent message of these studies implies that humans, as do most other animals studied, have the ability to detect and process warning signals hidden within body odors. Moreover, it seems that these signals are able to modulate the cognitive processing of relevant stimuli in our surroundings. The natural human body odor consists of about 120 individual chemicals when sampled from a resting phase (Labows *et al.*, 1999). It would be of great interest to isolate which individual compound, or mixture of compounds, mediate these effects. Recent receptor studies in rodents imply that there is a single receptor transmitting these fear signals to the brain and that when it is rendered nonfunctional, the animal stops displaying fearful responses toward a natural threat odor (Kobayakawa *et al.*, 2007). It is not clear whether humans also express this receptor. If so, blocking the receptor or removing a component of the downstream pathway responsible for mitigating the warning signals might be a useful remedy in the treatment of social psychiatric disorders such as social phobia.

V. Are Body Odors Processed by the Main Olfactory System?

As discussed above, a network that is activated by body odor but unrelated to the conscious perception of a “body odor” is residing outside the main olfactory system has been identified (Lundstrom *et al.*, 2008; Prehn-Kristensen *et al.*, 2009). However, an important question left unanswered is whether body odors are processed within the common olfactory system. First,

let us define what the human olfactory cortex entails. The olfactory sensory pathway starts with the receptor cells where odor molecules interact with receptors embedded in the olfactory mucosa situated on the roof of the nasal cavity. Their axons join in the olfactory nerve and project to the tufted and mitral cells of the olfactory bulb. The largest recipient of input from the olfactory bulb is the piriform cortex but only relatively recently was the greater neuronal olfactory network identified. Zatorre *et al.* (1992) were the first to outline the olfactory brain in humans. According to their findings, smelling odors result in brain activations in an area lying on the inferior junction of the frontal and temporal lobes, corresponding to the piriform cortex, and in another area in the right orbitofrontal cortex. Zatorre and colleagues proposed that these regions constitute the primary and secondary olfactory cortex, respectively. Later neuroimaging studies have verified Zatorre and colleagues' initial results. However, besides the piriform cortex, several other structures are involved in olfactory processing in various degrees. These structures include the olfactory tubercle, the periamygdaloid cortex, the anterior cortical nucleus, and the nucleus of the lateral olfactory tract of the amygdala (Carmichael *et al.*, 1994). From these set of anatomical structures receiving direct projections from the olfactory bulb, hence sometimes referred to as primary olfactory sensory areas, inputs are sent to another series of structures. These include the orbitofrontal cortex, the agranular insula, the hippocampus, the thalamus, medial and lateral hypothalamus, and ventral striatum and pallidum (Carmichael *et al.*, 1994). The region that receives the major cortico-cortical projections from the piriform cortex is the caudal orbitofrontal cortex (Carmichael *et al.*, 1994; Rolls *et al.*, 1996), and as such has traditionally been considered to constitute the secondary, or higher order, olfactory cortex. Interestingly, of the five published functional neuroimaging studies that have used intact body odor stimuli, none have reported activity within what is commonly referred to as olfactory cortex, namely the piriform cortex and the caudal orbitofrontal cortex (Lundstrom *et al.*, 2008, 2009a; Mujica-Parodi *et al.*, 2009; Prehn-Kristensen *et al.*, 2009; Zhou and Chen, 2008). In addition, if we view also minor projection areas from the olfactory bulb extending within the orbitofrontal cortex, the higher order olfactory cortex, there is only one study describing activation due to body odor perception. Zhou and Chen (2008) reports that body odors sampled while subjects were watching erotic videos activated the lateral orbitofrontal cortex. Although this area receives projections from the piriform cortex (Carmichael *et al.*, 1994), it is infrequently reported as active in olfactory neuroimaging studies. However, a recent study demonstrated that this area processes odor mixtures (Boyle *et al.*, 2008); the greater the disparity of odors within a mixture, the greater the signal within this area. Whether the results reported by Zhou and Chen (2008) are to some extent mediated by the disparity between the body odors and the single compound odor they used to contrast against, or whether the results are a result of body odor processing remains to be determined. Nevertheless, the basic fact remains that five neuroimaging studies, which have used a variety of methods and presented body odor stimuli reported as clearly perceived, have failed to activate the areas of the human brain that process common odors. One could argue that the conscious perception of body odors recruits areas outside the main olfactory system and that this mechanism is too transient to be detected by the olfactory cortices, areas with a demonstrated susceptibility to habitation effects (Poellinger *et al.*, 2001; Wilson, 2000). Alternatively, one could argue that this is the result of the conscious trade-off made in neuroimaging analyses between risk of false positive and risk of false negative. Modern neuroimaging analyses correct only for false positive errors, whereas no correction exists for false negatives. In other words, lack of significant activity in a neuroimaging study can never be taken as evidence for the hypothesis that a specific area is not involved in the task at hand. However, the first argument can be rejected based on the clear activations in olfactory processing cortical areas for a nonendogenous control odor (fake body odor). In two studies, we presented a control odor consisting of nonendogenous components, which subjects identified as a natural body odor (Lundstrom *et al.*, 2008, 2009a). If the lack of activation in olfactory cortices is due to its cognitive processing, the same would hold for

the nonendogenous control odor, which participants mistook for a natural body odor. Although statistically feasible, it is unlikely that five independent neuroimaging studies would produce five sets of similarly false negative results.

This lack of dependence on conscious awareness of the nature of the stimulus suggests that a biological model should be sought to explain the lack of noticeable processing in odor cortex. Tentative evidence for an early separation between the neuronal processing of endogenous odors and common odors can be found in the nonhuman animal literature. Two separate functional subsystems exist in the rodent olfactory system; one system is dedicated to the processing of common odors while another system produces innate responses to endogenous odors (Boehm *et al.*, 2005; Kobayakawa *et al.*, 2007). Whether body odors are processed mainly, or only, outside the main olfactory system in humans should be the focus of future studies.

As discussed above, several neuroimaging (Lundstrom *et al.*, 2008, 2009a; Prehn-Kristensen *et al.*, 2009) and behavioral results seem to be independent of conscious awareness of abilities. The ability to identify the body odors from either oneself (Lundstrom *et al.*, 2008) or one's sister (Lundstrom *et al.*, 2009a) is extremely high but participants express a very low conscious awareness. In most of the instances, although subjects are able to identify their own body odor and their sister's with 92% and 85% accuracy, respectively, subjects state that they are merely guessing. It is not clear where this disparity between the conscious estimate of one's ability to identify certain body odors and actual performance originates from. However, the anatomical organization of the olfactory pathway has one feature that is unique among our senses and might account for this discrepancy. The olfactory pathway lacks an early thalamic relay to transfer peripheral input into the brain. Whereas all the other senses project from the receptors to the brain-stem and from there to the thalamus for further transfer to the primary sensory areas, the olfactory system projects directly from the receptors to the olfactory bulb and primary olfactory cortical areas (Carmichael *et al.*, 1994). The need of thalamic processing for conscious awareness was recently suggested (McAlonan *et al.*, 2008), implying that the late downstream contribution of the thalamus in olfactory processing might render it a mostly nonconscious process. The functional implications of this “negative” feature of the olfactory system remain, however, unknown (Plailly *et al.*, 2008).

VI. Kin Recognition via Body Odors

The ability to identify kin is ubiquitous among phyla and it is thought of as a vital evolutionary tool to promote one's genes by facilitating both nepotism and inbreeding avoidance (Lieberman *et al.*, 2007). It has long been known that we are able to make accurate judgments about kinship based solely on body odor composition (Lundstrom *et al.*, 2009a; Porter, 1998; Porter and Moore, 1981; Weisfeld *et al.*, 2003). The exact mediating mechanism behind kin recognition has yet to be elucidated, but it is believed that the signal within human body odors which facilitates this ability is determined by the human leukocyte antigen (HLA; in nonhuman animals, major histocompatibility complex, MHC), a highly polymorphic subset of the human genome involved in immunologic responses (Klein, 1986; Ober *et al.*, 1997; Penn *et al.*, 2002; Potts and Wakeland, 1993). The HLA is an immunologically important group of genes that regulates the discrimination of self/nonself within the immune system. The HLA has been demonstrated to be a good determinant of genetic similarity between two individuals due to being one of the most dimorphic gene complexes (Klein, 1986). Rodents have the ability to discriminate minute differences in MHC composition found in body odor, and discriminate kin and the degree of gene similarity (Beauchamp and Yamazaki, 2003; Eggert *et al.*, 1998; Hepper and Cleland, 1999; Mateo and Johnston, 2000, 2003; Yamazaki *et al.*, 2000). It is believed that the kin

recognition mechanism is piggybacking on the more explored HLA/MHC-based mechanism.

The ability to discriminate very small differences in MHC composition is used in selection of mating partners where evidence suggests that the highest mating preference is for partners that are dissimilar in their genetic composition (Beauchamp and Yamazaki, 2003; Yamazaki *et al.*, 1993, 2000). Although the detailed genetic basis of this connection between MHC and mate preferences is not well understood, each individual's evolutionary drive to produce viable and fit offspring is believed to be the underlying cause (Apanius *et al.*, 1997; Penn and Potts, 1998a; Penn *et al.*, 2002). The evolutionary pressure to develop mechanisms for genetic similarity/dissimilarity judgments of potential mating partners could thus be hypothesized to be extremely high. Recent evidence promotes the idea that humans also have the ability to detect differences in HLA composition (Ober, 1999; Ober *et al.*, 1999; Sandro Carvalho Santos *et al.*, 2005; Wedekind and Furi, 1997; Weitkamp and Ober, 1999; Wedekind *et al.*, 1995).

The neuronal base for this ability was long unknown until Pause *et al.* (2006) demonstrated that the human brain is able to discriminate between minor differences in HLA composition based on EEG recordings also in the absence of a conscious awareness of this ability. However, although the likely mechanism mediating kin recognition is HLA identification, how the brain can perform this task is not known. In other animals, it has been suggested that this is done by the so-called self-recognition, or armpit mechanism (Mateo and Johnston, 2000, 2003). In other words, the animal identifies a kin by comparing the HLA/MHC composition with his or her own. Interestingly, the results from a recent neuroimaging study by Lundstrom *et al.* (2009a) support the notion that this mechanism is at play also in humans. When the cerebral activity was compared between when subjects identified the body odor of their siblings and that when they identified the body odor of a friend, that is, both were body odor stimuli but one was originating from a kin and the other from a nonkin, it was found that a neuronal network generally consistent with studies attempting to map the neuronal substrates of self-referential mental tasks was activated (Goldberg *et al.*, 2006; Gusnard *et al.*, 2001; Platek *et al.*, 2005). This suggests that kin recognition in human is based on the so-called self-referential mechanism, akin to other animals.

VII. The Stimulus Delivery Problem

The understanding of the neuronal processing of body odors is in its infancy and much remains unclear. Although there is now a substantial amount of behavioral studies investigating body odor processing, the first functional neuroimaging study of body odor processing was published as late as 2008. The reason for this scarcity is twofold. First, the field of olfactory perception, from which most researchers focusing on body odor processing originate from, is itself a small scientific field, especially in comparison with its larger siblings, the fields of visual and auditory perception. Second, the few studying body odor processing must contend with the incompatibility of chemosensory stimulus delivery and functional magnetic resonance imaging (fMRI). The technique of choice for most neuroimaging studies, fMRI boasts faster acquisition times and better resolution at a lower cost than the rival technique, positron emission tomography (PET). fMRI is based on the simple principle that the brain acts similar to any other muscle of the human body. When a muscle is working, it needs oxygen and nutrition, both of which are delivered through the bloodstream. fMRI assesses the minute differences in the degree of magnetism between oxygenized and deoxygenized hemoglobin by inducing a very strong and shifting magnetic field. Unfortunately, the high magnetic field strengths required to pick up these very weak signals make it impossible to have any ferrous metal inside the room where the scanner is located. This is not a significant problem for visual and auditory research since visual and

auditory stimuli can be triggered from a distance, rapidly presented to a subject lying in the scanner, and just as rapidly removed. In contrast, chemosensory stimuli are chemical compounds whose size and density make rapid appearance and disappearance difficult. Despite this inherent difference between stimuli, olfactory stimuli must also be transported to the subject from outside the scanner and presented with a rapid onset and offset. The only way of accomplishing this is using an olfactometer (Kobal, 1981), a device capable of delivering odors in a controlled way without causing any thermal or tactile discomfort for the subject inside the scanner. Unfortunately, only a limited few are commercially available; all are limited to the presentation of liquid odorants and are therefore ill suited for the delivery of body odors. This means that the interested researcher needs to invest the time and money in building one himself or herself (Lorig *et al.*, 1999; Lundstrom *et al.*, 2009b), a task that can be daunting for many.

VIII. Conclusion

To conclude, behavioral studies using body odors as stimuli suggest that the complex mixture constituting human body odors is processed in a unique way due to the high behavioral relevance. Research suggest that endogenous chemical compounds within the body odors communicate various kinds of information that our sensory systems are able to extract and utilize. The mere fact that we are able to distinguish between individuals based solely on their body odors (Russell, 1976) and that our brains evoke differential responses to the stimulation of body odors originating from individuals with minute differences in their immunological composition demonstrates this capacity (Lundstrom and Jones-Gotman, 2009; Lundstrom *et al.*, 2009a; Pause *et al.*, 2006). What was once a divisive question in the scientific community, whether humans do use chemosignals in some form of social communication, can now be considered an undisputed statement (Beauchamp, 2000). What remains controversial is the chemical composition and appropriate label for the chemosignals themselves (cf. Beauchamp *et al.*, 1979; Doty, 2003). Specifically, whether or not humans communicate using so-called “pheromones” to communicate is still a matter of great debate. Body odor processing, however, is not an effect attributable to any specific compound, or “pheromone.” A plethora of behavioral and neuroimaging data gathered from both human and nonhuman animal research strongly suggests that body odors contain signals detectable by and beneficial to conspecifics. Whether the effects of these signals are innate or learned, or whether they result from an interaction of both, is likely signal-dependant and remains to be elucidated.

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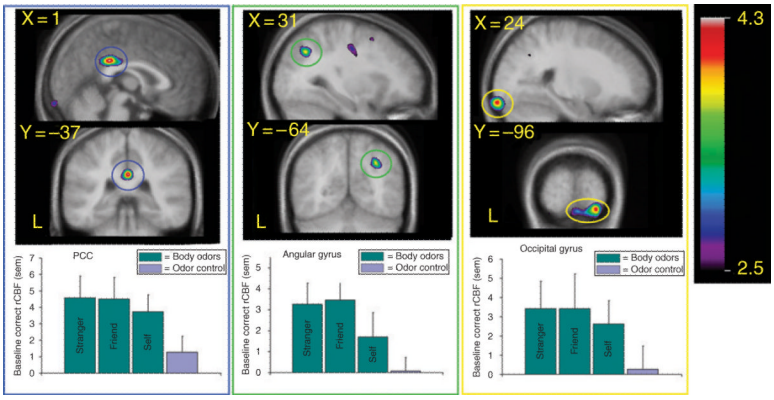

Figure 1.1.

Statistical parametric maps (*t* statistics as represented by the color scale) of group averaged rCBF responses to processing of body odors superimposed on group averaged anatomical MRI. Blue circles mark increased rCBF in the posterior cingulate cortex (PCC), green circles mark increased rCBF response in the left angular gyrus, and yellow circles mark an increased rCBF response in the right occipital cortex. Coordinates denote center of activation and slice expressed according to the MNI world coordinates system. Left in upper row of pictures represents posterior and left in middle figures represents left side (L). Graphs under each statistical parametric map represent extracted baseline-corrected rCBF values within the activation peak, in each odor category. Error bars represent standard error of the mean (SEM). Reproduced with permission from Oxford University Press.

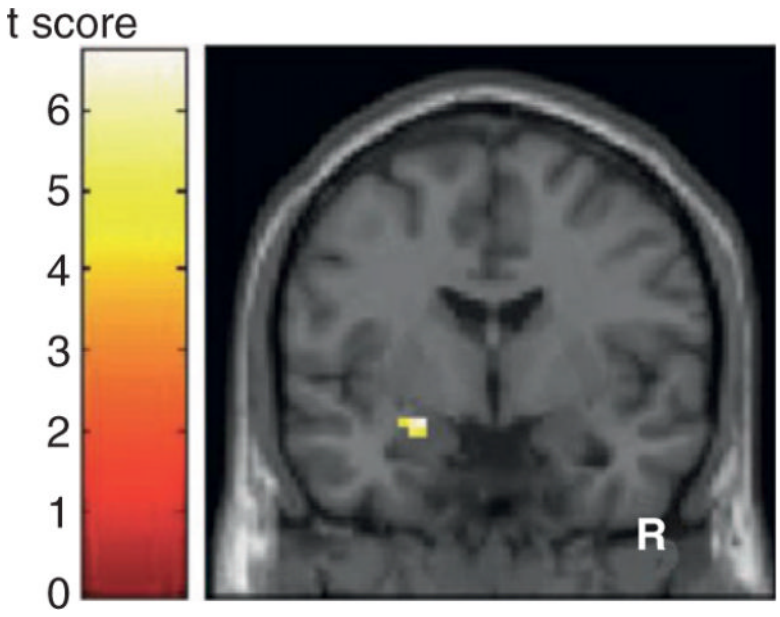

Figure 1.2.
Statistical parametric maps (*t* statistics as represented by the color scale) of group averaged BOLD responses to the processing of fear-related body odors. Note the significant activation in the left amygdala. Reproduced with permission from the authors.

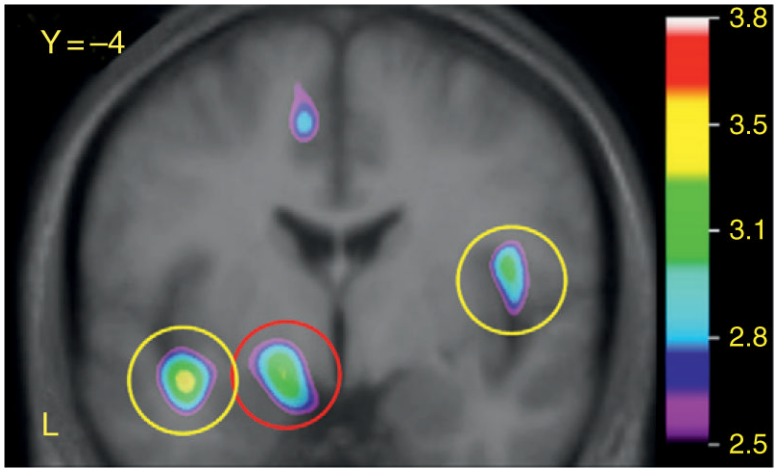

Figure 1.3.
Group averaged rCBF response showed in statistical parametric map (*t* statistics as represented by the color scale) to the processing of the body odor of a stranger. Yellow circles mark bilateral increased rCBF in the insular cortex and red circles mark increased rCBF response in the amygdala. Left in figure represents left side (L). Reproduced with permission from Oxford University Press.