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► **To cite this version:**

Camille Ferdenzi, Stéphane Richard Ortegón, Sylvain Delplanque, Nicolas Baldovini, Moustafa Bensafi. Interdisciplinary challenges for elucidating human olfactory attractiveness. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 2020, 375 (1800), pp.20190268. 10.1098/rstb.2019.0268 . hal-03065631

HAL Id: hal-03065631

<https://hal.science/hal-03065631v1>

Submitted on 15 Dec 2020

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Interdisciplinary challenges
for elucidating human olfactory attractiveness

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Abstract

Many species use chemicals to communicate. In humans, there is increasing evidence that chemicals conveyed by the body are extremely important in interpersonal relationships. However, many aspects of chemical communication remain to be explored to fully understand this function in humans. The aim of this article is to identify relevant challenges in this field, with a focus on human attractiveness in the context of reproduction, and to put forward roadmaps for future studies that will hopefully extend to a wider range of social interactions. The first challenge consists in not being limited to body (mal)odours from the axilla. Preliminary data on how the odour of the face and head is perceived are presented. Second, there is a crucial need to increase our knowledge of the chemical bases of human chemical communication. Third, cross-cultural approaches must not be overlooked, because they have a major input in understanding the universal and culture-specific aspects of chemical communication. Fourth, the influence of specific cultural practices such as contraceptive and fragrance use is likely to be prominent, and therefore needs to be well described. The fifth and last challenge for research projects in this field is the integration of different disciplines such as behavioural sciences, social sciences, neurosciences and microbiology.

Keywords (3-6 words)

Olfaction, Human attractiveness, Sex differences, Culture.

Introduction

The human body conveys a complex mixture of hundreds of chemical compounds (alcohols, carboxylic acids, ketones, aldehydes, esters, hydrocarbons, etc.), which are transformed from precursors secreted by excretory skin glands [1,2] through the action of skin bacteria (*Corynebacteria*, *Propionibacteria*, *Staphylococcus*) (see Natsch & Emter, this issue) and which constitute body odour. This chemical blend has a fixed fraction, which is genetically determined [3,4] and used as a marker of individuality [5,6]. It also possesses a variable fraction, which depends for example on diet [7,8], age [9] or physiological state [10,11]. There is empirical and societal evidence that odours produced by human bodies are not just some unwelcome emissions that a large proportion of individuals from many societies try to eliminate with the help of hygienic and cosmetic practices: They are sought, and they clearly affect daily interactions with others, especially the close ones. Scientific studies back up these observations by providing solid reasons to believe that chemical communication occurs in humans, i.e. communication through chemicals emitted by an emitter's body and perceived by a receiver through the olfactory and/or trigeminal systems.

Mother-infant communication, for example, is likely modulated by chemicals produced by the mother and perceived through the olfactory system of her baby. Indeed, mothers' areolar glands produce secretions that are attractive to newborns [12] and that are positively associated with breastfeeding success [13] (see Schaal, this issue). But human chemical communication has been most extensively studied in the context of mate choice, mostly by investigating perceived attractiveness and preferences for a potential reproductive partner. Studies using self-reports show that body odour is rated as a key factor in a person's attractiveness when compared with several sensory and behavioural characteristics of a potential partner [14], although mainly in female raters [14,15]. Studies in patients with olfactory disorders show that olfactory loss has serious adverse effects on the quality of social interactions (see Hummel, this issue), such as partnership insecurity or decreased sexual activity [16]. It must be pointed out here that a significant part of the research in this area has been driven and even drifted by the fascination of the scientific community as well

as the public by pheromones. In particular, many studies have focused on the behavioural effects of male steroid compounds, such as androstadienone. But the scientific justification for such a focus - to the detriment of all the other components of human biological odour - is highly debatable [17] and, although androstadienone is likely to have psychological effects [18,19], it does not seem to meet the concept of a sex pheromone [20,21] (see also Wyatt, this issue). In sum, while pheromones have been defined [22] and identified in several animal species (insects [23] and mammals [24,25]), their existence in humans has only been speculated and not rigorously demonstrated. In addition, their functional processing has been a subject of debate. Namely, the widespread belief that they would be processed through the accessory (vomeronasal organ VNO) rather than the main olfactory system has been challenged by the fact that i) occlusion or absence of VNO in humans has no effect on putative pheromone perception [26] and that ii) in other mammals (e.g., rabbit) pheromones are processed through the main (not the accessory) olfactory system [24,27,28].

Another section of research in this area provided significant advances in understanding human chemical communication by postulating that human body odour carries specific and relevant information about the individuals, which is transferred from one individual to another (chemosignalling; see [29]). Based on previous literature in non-human animals [e.g., 30], perceptual studies in humans have revealed preferences for biological odours that provide cues to biological quality of a potential sexual partner with regards to genetics (including the major histocompatibility complex MHC), reproductive status and health. People have been shown to prefer and choose MHC-dissimilar mates based on their body odour [31], at least in some populations [32], a mechanism believed to favour the production of MHC-heterozygous offspring who are more resistant to pathogens (see also Havlicek, this issue, and Croy, this issue). This outcome is also served by a preference for MHC-diverse (heterozygous) mates, which has been shown to be a more robust phenomenon in a recent meta-analysis (while mixed evidence was found – notably as a function of samples' ethnic heterogeneity – for MHC-dissimilarity) [33]. Preferences for other indicators of mate fitness, which have been evolved because of their beneficial effects on the

offspring (biological quality, contribution to child care), seem to be mediated by body odours. For example, women within the fertile phase of the menstrual cycle prefer the body odours of men with greater body bilateral symmetry (indicating a better developmental stability, which is a marker of good physical condition) [34], and for socially dominant men [35]. Men's preference for women's cues of fertility is another adaptive phenomenon that seems to be (in part) mediated by body odour, as shown by men's preference for odour samples collected during women's fertile phase of the menstrual cycle [11,36]. Additionally, human body odour communicates information about health status (see Olsson, this issue), which is one aspect of mate fitness. Compared with healthy donors, the odour of sick persons is more aversive [10] and more intensely activates brain networks involved in odour processing [37]. Information about body condition related to nutritional state is also conveyed by body odour [38], as well as about gender [39,40] and age [9]. Finally, body odours are involved in the communication of emotions (see also de Groot, this issue; Pause, this issue; meta-analysis in [41]) and of personality traits (such as dominance and neuroticism) [42], both of which being involved in the initiation and maintenance of romantic relationships [43].

In spite of these numerous pieces of evidence regarding the existence of a chemical communication in humans, especially in the context of mate choice, the mechanisms of such a communication are poorly documented to date. The aim of this article is to identify in the following sections five relevant challenges in the field and to put forward potential avenues for future studies to better understand chemical communication. The context of mate choice is used as a background here because it is the most largely documented, probably due to the fact that reproduction is a fundamental function in living organisms and to the rich evolutionary theoretical framework available in this domain. However, it must be kept in mind that the identified challenges also apply (and should be extended) to other social contexts. Current knowledge is almost exclusively based on one odour source, the axilla, and on several unpleasant odorous compounds ("malodours"): Challenge 1 therefore consists in going beyond malodours from the axilla. Especially, odour sources that have a behavioural

relevance in interactions with the actual or a potential mate (such as the hands or the face) should clearly be within the scope of investigation. We started facing this challenge and provide some new data on the perception of head/face odour from men and women.

Challenge 2 consists in increasing our knowledge of the chemistry of human body odour. Most of the studies mentioned in the previous paragraph use perceptual approaches, and little is known about the chemical bases of human chemosignalling. Exploring how this question was studied until today reveals several limitations, as well as heterogeneity and relative paucity of investigations. Challenge 3 is a warning against confining investigations to the usually studied WEIRD populations (Western, Educated, Industrialized, Rich, and Democratic countries) [44] and an explicit incentive to extend them to different cultures, which to date has only been done occasionally. This allows testing to what extent hypothesized mechanisms of odour-based attractiveness may be common to the human species and to identify cultural specificities. About cultural specificities, two major aspects constitute Challenge 4: contraception and fragrance use. These very widespread practices seem to interfere with or complement natural chemical communication. Finally, significant advances in the field will be possible only with the combined efforts from different disciplines: This constitutes Challenge 5. This last challenge presents how the conjunction of behavioural sciences, social sciences, neurosciences, and microbiology will help increasing our understanding of human chemical communication.

Challenge 1: Beyond the axilla

Although many areas of the body produce a smell, most studies on human chemical communication have investigated odours from the axilla. This can be explained in part by the belief that axilla has taken over the communication role from the anogenital region due to the upright human posture [45], but also by cosmetic motives (necessity to understand the formation of malodours to better neutralize them), and by the fact that in adults it is one of the most odorous body regions (richest in apocrine sweat glands) and one of the easiest to

collect (discreet sampling, limited contamination by exogenous odours). Other odour sources, largely ignored so far, may be relevant though.

For example, the perception of vaginal and breath odours has been occasionally investigated as a function of hormonal status and gender. Vaginal odours were found to have lower intensity and unpleasantness during the late follicular phase (near ovulation) of female donors, compared to the other phases of the menstrual cycle [46]. The authors however raise some doubts regarding a possible function of vaginal odours in attraction because they remained in the unpleasant pole of hedonic valence even around ovulation. Breath odour of men and women were categorized as male or female at a better than chance frequency [39], which seems to be driven by the propensity to rate male odours as more intense and less pleasant than female odours (see also [47]). Another study found that individuals can be discriminated on the basis of olfactory cues from their hands; female raters' performance in this task was improved when the two donors were genetically unrelated, and differed on their diet [48]. More recently, a comprehensive approach consisted in comparing the responses of men exposed to women's tears *versus* a control saline solution [49]. Without conscious perception of an odour, tears caused men's sexual arousal to decrease, which was associated with a decrease in physiological arousal and in the activation of the cerebral substrates of sexual arousal (but see [50] and the following debate [51,52]). Another study from the same group (see Sobel, this issue) focused on a widespread social practice: greeting by handshaking [53]. This behaviour may be used to sample conspecifics' chemosignals since participants increased the sniffing of their own hands after a handshake. How hand sniffing behaviour after greeting a person of the opposite sex could be related with evaluation processes of a potential reproductive partner is an aspect that should be investigated further. Finally, other body odour sources have been investigated for other purposes than studying human attractiveness to conspecifics. These studies often favour analytical views of the emitted odour over behavioural approaches. Their aims range from *i*) managing malodorous emanations (e.g., from feet [54], urine [55], flatus [56], but also related to aging [57]), *ii*) diagnosing diseases (e.g., cancer, from breath [58]), *iii*) forensic applications (e.g. odours

from hands [59], internal organs [60]), to *iv*) understanding the spreading of diseases (due to blood-sucking insects attracted by human hand odour [61] or feet odour [62]).

Returning to body odour attractiveness, it is crucial to consider odours that may be meaningful during interactions with the partner, namely odours emitted by body parts that are sampled voluntarily or – more likely – in a non-conscious manner. This includes more particularly the head (face, hair, neck, mouth), the hands, the axilla and the genital areas. Here, we present the results of a perceptual study comparing the odour of the head and of the axilla (for Methods details see Supplementary Material). Young heterosexual adults, of European descent and non-smokers, took part either as donors (N=16 men and 16 women, including 8 non-pill users and 8 pill users) or as raters (N=16 men and 17 women, including 9 non-pill users and 8 pill users). Donors followed a strict food/hygiene protocol and sampled the odour of their axilla and their head (face, neck, and scalp) over 6 days. Raters evaluated the attractiveness and intensity of opposite-sex odour samples on continuous scales, and described them by choosing the most appropriate terms among a list of both positive and negative descriptors from a list of 22 items (Table S1). Qualitative variations can be described as a function of gender (Fig. 1.a, descriptors highlighted by colours). Men's odours were perceived as sweatier than female samples (axilla and head), but also more fatty/oily (head). Women's axillary odours were more earthy/mouldy/musty and smelled more like vomit than male samples, and their head odour was more floral, woody, heavy and mineral/metallic. Odour sources also differed (Fig. 1.a, descriptors highlighted by dots). Compared to axillary odour, head odour was heavier and more mineral/metallic in women, and more fatty/oily and earthy/mouldy/musty in men. On average, head and axillary odours did not differ in intensity or attractiveness, which were moderate (Fig. 1.b). A principal component analysis (PCA) conducted on the individual's qualitative profiles showed that the highest part of the variance (30% and 36% for axilla and head odours respectively, first factor) was explained by valence as shown by the contribution of descriptors such as "floral", "perfume/soap" vs. "sweat", "heavy", "cat urine" (see Fig. 2.a.1 and 2.b.1). The second factor (14% and 11% of the total variance respectively) could be interpreted as

pathogenic threat, since for both odour sources the terms related to organic decay “vomit” and “faecal” contribute importantly to this dimension (Fig. 2.a.1 and 2.b.1; in opposition to “mineral/metallic” for head odour, Fig. 2.b.1). Examination of how odour donors are represented in these 2-dimensional spaces (Fig. 2.a.2 and 2.b.2) suggests that there is a higher variability between individuals, i.e., spatial distance between them, with regards to the negatively connoted descriptors (left side of the graphs) than for the positive descriptors (right side of the graphs). This was true both for head odours (bottom graph, Fig. 2.b.2) and even more for axillary odours (top graph, Fig. 2.a.2) for which men and women seem to present different patterns of unpleasant features. The diversity in body odour quality between individuals may thus rest upon chemical compounds that are rather unpleasant, especially in the axilla. A relevant question for research in the coming years is whether olfactory attractiveness is based on some (to be defined) pleasant attributes, or on the absence of some (to be defined, too) unpleasant attributes that are cues of poor health / of other unwanted features in a reproductive partner, or on both (the second option being supported by the fact that diversity is higher within the unpleasant pole of descriptors).

Interestingly, head and axillary odour attractiveness were highly correlated in women ($r=0.87$, $p<0.0001$) and significantly less in men ($r=0.40$, $p=0.128$; Fig. 1.c; comparison between rs: $p=0.028$). It cannot be excluded that a bias could have accounted for these results: a potential greater use of perfumed cosmetics in women may have homogenized the olfactory signature of different body parts (through residual compounds diffusing all over the body for example, despite the hygienic restriction protocol we applied) rendering axillary and head odour more similar than in participants using less fragrant products. But another possibility that would be worth exploring in the future is that the odour of the head could convey different cues than the axilla in male donors. Some of the most interesting questions to address in the future are: which information is conveyed by each odour source? by which mechanisms? and which odour source has more weight in determining the attractiveness of a potential reproductive partner?

Associated with another set of studies showing that odours of the breast, a body area rich in sebaceous glands as is the face, may serve mother-infant communication [12,13], the unique data presented above support the idea that more effort should be made to investigate odours produced in the facial area due to their potentially relevant informative content. While axillary odours mostly originate in the bacterial transformation of compounds conveyed by apocrine sweat, the face and scalp possess a high concentration of sebaceous glands (and some apocrine glands) and probably host a different microflora, which is likely to result in odours differing in quality compared to the axilla. Whether these odours differently impact potential partners' attractiveness remains to be tested, with comprehensive approaches including the testing of behavioural effects. Qualitative measures using descriptive terms is a useful approach to investigate the sensory profiles of body odours (see also [63]), but also to describe their intra- and inter-individual variations (gender differences, variations according to hormonal status), and eventually to link the odours' perceptual and chemical profiles.

Challenge 2: Body odour chemistry

In humans and other mammals, the study of chemical communication is much more recent than in other organisms such as plants or insects [64]. In the last two decades, the chemical composition of human scents has received increasing interest in areas such as medical diagnosis [65] and disease prevention [66,67], forensics [59,60], emergency search [68], and more occasionally in the field of cognitive psychology and affective neuroscience (e.g. communication of emotions [69,70]). The chemical underpinnings of human chemical communication remain mostly unknown, likely because explorations of the characteristics of human scent using analytical chemistry are very heterogeneous and generally confined to very specific issues such as malodour management [57,71,72].

The chemicals emitted by the human body are volatile organic compounds (VOCs, which are targeted when investigating communication through the olfactory system), but also semi- and non-volatile compounds that emanate from the skin, urine, sperm, vaginal

secretions, sweat and breath. Various sampling methods have been used to analyse human body odour (see [67] for a review), including i) solvent extraction, where compounds are collected on a medium (e.g., cotton, gaze, glass) and then extracted with a solvent (e.g., hexane, dichloromethane, ether), ii) solid-phase micro-extraction (SPME) and stir-bar sorptive extraction (SBSE), where volatiles are trapped on an adsorbing polymer coated on a small glass fibre or a stir bar, and then liberated by thermal desorption for analysis, and iii) other types of VOC-traps for the dynamic headspace adsorption on various porous polymers (e.g., Tenax, Porapak Q). Analysis is then often performed with Gas Chromatography - Mass Spectrometry (GC-MS), which combines the excellent resolutive capacity of GC with the power of MS for structure identification (usually assisted by the use of mass spectra databases). GC-MS is particularly adapted to highly volatile compounds of low molecular weight and polarity (as are most of animal scent compounds). Alternatives include liquid chromatography LC-MS [73] more adapted for detection of non-volatile compounds, proton-transfer-reaction PTR-(Q or QTOF)-MS [69] allowing for real-time quantification of VOCs (see Williams, this issue), selected ion flow tube SIFT-MS [74], or multi-capillary column-ion mobility spectrometry MCC-IMS [75]. Each method has its advantages and drawbacks, such as isolation of irrelevant compounds with solvent extraction (compounds that are not volatile at natural body temperature) or SPME (artefacts originating from the trapping polymer) [76]. Choosing the most suited technique must be carefully weighted [77] depending on the studied substrate (human scents are complex and diverse) and the pursued goal (e.g., understanding individual's full chemical signature for forensic applications *versus* investigating olfactory detection of airborne attractive compounds). Indeed, two different methods may provide very different outcomes, as shown for example by a comparison of SPME and solvent extraction, which revealed only 15 molecules in common (against 92 and 58 compounds found with each technique respectively [78]). To comprehensively and exhaustively understand human body odour, using complementary techniques and comparing them as it has been done in plant science [79,80] can prove to be useful [76,78,81,82], although inevitably costly and time-consuming.

To date, the knowledge about the chemical composition of human body odour remains heterogeneous and incomplete. Diverse methods are used for sampling (collection time from a few minutes to several hours; during daytime or night-time; contact or non-contact; diverse media such as sterile gauze, cotton, wool, viscose, glass beads, t-shirts [83–85]), and for analysing (see above). Outcomes are therefore hardly comparable, which is worsened by the small number of donors involved and by the large number of VOCs found [68]. These VOCs are sometimes listed without discussing their origin: it has been estimated that nearly one third of the molecules reported in mammals are either misnamed or not likely to have been produced by the studied organisms [86], therefore emphasizing the need for a critical attitude towards the origins and roles of the compounds found. The complexity and fluctuations of human body odour (due to diet, physiological state, interindividual genetic variability, and exogenous compounds introduced by using drugs and cosmetics) constitute a serious challenge. Exogenous compounds related to fragranced cosmetics are difficult to eliminate even with a specific hygiene protocol before sampling [78,87] and others are due to contaminations of the samples at every stage of the processing, indicating that special precaution should be taken to diminish this risk [77]. In sum, more research is needed in this area, always with extreme care at all stages of processing especially regarding undesirable contamination, and standardization of methodologies would be welcome. To do so, recruiting volunteers having a natural/perfume-free lifestyle could help obtaining more relevant chemical profiles. Also, repeated measures in time for a given individual would be helpful. Replications of previous studies are needed too, as in other fields of science, which could be facilitated by open-access practices [88] that allow for cross-analyses and reduction of redundant experiments. Finally, significant progress could be achieved on chemical profiles characterization with the help of new generations of artificial noses, namely electronic devices mimicking the nose and detecting odorants through sensors. The field of artificial olfaction has recently achieved a significant expansion, and offers increasingly performant devices based on bio-inspired sensors [89]. Historically used for quality control of the environment or of food and beverages, artificial noses are increasingly employed in

disease diagnosis and could very well extend their applications to detection of body odour compounds.

Challenge 3: Cross-cultural studies

The study of how body odours may be involved in human reproductive function should not be limited to the usually studied WEIRD populations [44]. Including different populations allows testing to what extent hypothesized mechanisms of odour-based attractiveness may be common to the human species, and to describe cultural specificities. For example, it has been proposed that if human body odour contains compounds that are relevant in human attractiveness, then olfactory receptor genes responsible for their detection would be highly conserved in the human species [17]. In light of this, the extensively studied putative pheromones androstenone and androstadienone seem to be poorly credible candidates. Indeed, at least one in five people cannot detect them [20,90] and strong genetically-based interindividual variability has been described for their perceived quality [91]. In line with this, a significant part of the population (80–95% of Asians, *versus* 0–3% of Europeans and Africans) possesses a non-functional variant of the ABCC11 gene, which has a key function in the formation of body odour, resulting in the absence of androgen (and carboxylic acid) compounds and to a much weaker body odour [92]. These molecules may thus not be as relevant in human mate choice as scientists once thought.

Considering the more complex body odour in its entirety, cross-cultural studies remain scarce. Anthropologists have pointed out ethnicity-related differences in body odour judgments, such as the fact that white and black people perceive the other group as “foul-smelling” [93]. A proposed explanation was that such an olfactory classification of people demarcates social groups and contributes to maintaining boundaries between them. However, whether this has biological and perceptual grounds remains under-studied to date probably because this is an ethically sensitive topic. A few studies compared Asian, African and Caucasian people on several aspects, though. African participants were found to have the largest apocrine glands and highest levels of sweat secretion, while Asian participants

have fewer apocrine glands and a lower level of axillary odour [94]. The emission of some carboxylic acids also differs between ethnic groups [95], and differences related to donors' ethnicity were reported in terms of pleasantness and intensity ratings [96], which are likely genetic, although diet- and hygiene-related influences cannot be excluded.

Cultural norms and practices may indeed influence body odour emission and perception. For example, rules of interpersonal distances during social interactions (theory of proxemics [97]) vary according to culture [98] and may have a role in chemical communication, as hypothesized in some cultural comparisons of body odour perception [99,100]. Cultural variations do also exist in emotional responses to odours [101,102] and in the language used to evoke odours (see Majid, this issue). Cultural variations in cosmetic and drug practices may also be influential, as detailed hereafter.

Challenge 4: Pill and fragrance use

Cultural practices are known to interact with body odour emission and perception: hormonal contraception and cosmetic practices are among the most significant ones. Using hormonal contraceptives seems to cause counter-adaptive effects, such as inverting preferences related to the immune system (preference for the smell of individuals with a similar MHC [103], while the reverse could be expected in naturally cycling women on the basis of some studies [31]; but see [33]). Studies using various smells [104,105] and body odours [106] show that olfactory sensitivity of pill users is equivalent to that of non-pill users in the luteal (non-fertile) phase of their menstrual cycle, both groups having lower sensitivity than non-pill users in the follicular (fertile) phase of their cycle. The same pattern occurs for body odour emission, with body odour attractiveness being highest around ovulation [11] and lowest in the luteal phase and in women using the pill [36]. Hormonal contraception use is very widespread in Western societies (41% of French women aged 15-49 years [107]) and its influence on mate preferences [108] and more largely on the brain and behaviour [109] is being increasingly studied. Therefore, how it interferes with olfactory attractiveness of a

partner and how initiation/cessation of it impacts the relationship deserves more attention in the future.

Another practice that might influence chemical communication is the ancient and widespread use of fragranced daily hygiene products. Masking or embellishing people's body odour is one of the major functions of this practice, but the nature of perfume-body odour interactions is complex and to date not fully understood, all the more so as most studies on human chemical communication require perfume removal in donors to focus on the biological odour and to limit exogenous variations in body odour samples. There are chemical interactions with perfume depending on the person's natural odour type [110], potentially leading to the formation of new aromatic compounds [111]. There is some evidence that fragrance has a disruptive effect on judgments of masculinity [112], personality traits [113] and gender [114], and that it modifies other social judgments such as perceived likeability and friendliness [115]. Some experiments support the idea, however, that fragrances may interact with body odour in a complementary manner. Individual's natural olfactory signature is conserved even when they use perfume, as shown by a discrimination task [116] and the use of fragrance creates individually-specific odour mixtures leading to the maintenance of the interindividual variability [117]. Comparing people's own perfume *versus* a fragrance imposed by the experimenter, several studies show that people choose perfumes in an individual fashion to complement their own natural scent [116,117]. This is very consistent with the fact that individual preferences for perfume ingredients (for use on self) correlate with a person's MHC genotype [118,119]. Perfumes selected for oneself may thus enhance the individual genetic/olfactory signature (see also [120] for a discussion of perfume-body odour interaction being an example of culture-gene coevolution), and the selection of perfume by a biologically related individual (sister vs. girlfriend or oneself) enhances the attractiveness of the perfume / men's body odour blend [121]. Human body odour is very complex in itself, and understanding the hardly predictable perceptual quality that emerges when it is mixed with a perfume represents an additional significant challenge for the field of human chemical communication. In the future, a

particular attention should be paid to the fact that not only conscious processes (as measured by raters' verbal responses, in the studies cited above), but also non-conscious processes, are likely to result in fragrance-related changes in social behaviours. To finally widen the scope of investigation, other hygienic practices may be worth considering to understand the impact of human behaviours aimed at odour control, such as how, and how often people wash their body.

Challenge 5: Interdisciplinarity

Inputs from different disciplines is obviously required to understand chemical communication. Beyond the necessity to multiply analytical chemistry approaches (discussed in Challenge 2), other approaches using measures of overt behaviour, theoretical frameworks of the social sciences, neuroscientific methods and analysis of the skin microbiome will undoubtedly be beneficial to the field.

Human chemical communication has been studied using mostly verbal descriptions of how body odour samples are perceived, either with rating scales (pleasantness, intensity, attractiveness, etc.) or with preference tasks (see Introduction). Indirect tasks have also been used, requiring social stimuli (e.g., faces [20], real persons [122]) to be rated after being primed by or in the presence of a body odour or a body odour compound. However, how chemosignals influence our biology and cognition, and ultimately our behaviours, is likely to be a covert process, which is not necessarily measurable with conscious verbal methods. Future research would certainly gain in developing paradigms to measure overt behaviours. For example, motor behaviours are sometimes (but rarely) measured, especially when language is lacking: e.g., head orientation of infants towards odours spatially distributed [123], or reach-to-grasp action towards an object in children with autism [124]. Other motor behaviours appear to be relevant, such as odour sampling behaviours, measured indirectly, e.g., by recording the frequency with which someone brings his/her own hand near the face after hand-shaking [53], or directly, e.g., by recording airflow variations in the nostrils (sniffing behaviour [125]). The latter, however, has never been used to our knowledge in the

context of social communication in humans (but see [126] for non-human hominids). Ideally, behaviours displayed in real social interactions (e.g., speed dating experiment, see [122]) and indicating attraction or repulsion towards someone would be very informative. However, although being highly ecologically valid, such approaches face numerous experimental biases, such as uncontrolled sensory and behavioural factors inherent to the interacting person. Therefore, crafty alternatives could be developed, such as associating the diffusion of body odours with artificial standardized individuals, using virtual avatars [127] or physically present manikins [128].

Besides these methodological perspectives in terms of outcome variables, taking advantage of the theoretical frameworks provided by social sciences would help having a more integrated view. Some models have been proposed to conceptualize social interactions, such as the perceptual model of intergroup relations (PMIR) [129]. The PMIR can be fed with several existing research on human body odour from various disciplines [130], to explain how olfaction mediates the interactions between group belonging (gender, culture/ethnicity, religion, social status) and intergroup perception/relationships. Although this model can be recruited for many types of social interactions (colleagues, friends, strangers, etc.), in the case of reproduction and mate choice, gender-related aspects are of major interest. Indeed, this framework can help modelling how one's particular biological odour influences his/her gender identity (e.g., level of gender conformity/nonconformity [131]), as well as the reverse, i.e., how one can modulate his/her gender identity by manipulating the odour blend conveyed by his/her body (through hygienic and cosmetic practices). This in turn may have implications for the relationships with other individuals, depending on their gender (e.g., implications for sexual orientation). Tightly related to this, the concept of stereotype is also worth considering as it may have a considerable influence on body odour perception. Gender stereotypes have seldom been investigated in the field of social olfaction (see [132] for perfumes, and [96,133] for body odour), despite being a potential significant source of cognitive modulation of body odour perception.

To understand the mechanisms by which chemicals emitted by a potential mate influence receivers' responses, we need to have a better knowledge of the central processing of these chemosignals. The neural networks involved in the perception of social chemosignals have been explored mostly for androstadienone, which was found to activate – even in the absence of conscious perception – a brain network that is not exclusively associated with olfaction and that is related to social cognition and attention [134,135]. Differences were found in the hypothalamus as a function of perceiver's sex [136, but see 137] and sexual orientation [138,139], and interpreted as being the underpinnings of sex-differentiated behavioural responses. In more naturalistic approaches, it was found that body odours induced increased neural activity in a large network including cingulate cortex, occipital and angular gyri, but not the primary olfactory areas [140]. Different networks are recruited depending on the origin of the body odour: network for processing fearful stimuli (stranger *versus* friend odour) [140], kin recognition (sister *versus* friend odour) [141] and rewarding stimuli (infant's odour) [142]. More directly related with body odour attractiveness, exposure to sadness tears [49] and to body odour of sexually aroused donors [143] modulate activations in the brain substrates of sexual arousal (namely fusiform gyrus and hypothalamus). Further research is needed to identify the neural networks involved in body odour attractiveness processing, considering for example other odour sources than the axilla (see Challenge 1).

While neuroscientific approaches provide an invaluable methodological asset to understand how receivers process potentially relevant chemosignals, there is a need to better understand how these chemosignals are produced and the mechanisms by which they convey information that is relevant to mate choice (and more generally to other social interactions). In this perspective, analytical chemistry has been identified as key discipline in Challenge 1, but biochemistry and microbiology are at least as important. Indeed, microorganisms are key contributors to the formation of human body odour. Precursor molecules that are present in the (odourless) secretions of skin glands (apocrine, eccrine, apoecrine, and sebaceous glands) are transformed through enzymatic activity of the resident bacteria into compounds

than are more or less volatile. This process has been mostly explored for one production site: the axilla [1,144–148]. The main families of bacteria identified on the skin are Coryneform bacteria, Propionibacteria and Staphylococci [1,149], with more men having a coryneform-dominant microflora (two thirds, vs. one third of the women) [150]. Different types of bacteria have been found to produce different compounds, resulting in various odour types: Corynebacteria are responsible for the production of carboxylic acids (such as 3-methyl-2-hexenoic acid and 3-hydroxy-3-methylhexanoic acid) and androgen steroids (such as 5 α -androst-16-en-3-one, 5 α -androst-16-en-3 α -ol and 4,16-androstadien-3-one) that contribute to a typical pungent axillary odour, while a more acid and sulphur-like odour is given by Staphylococci through the production of short-chain fatty acids and thio-alcohols (such as 3-methyl-3-sulfanylhexan-1-ol) [1,71,148]. The axilla is an ideal field of exploration in this regard because it contains a high concentration of all types of skin glands, hosts a dense population of microorganisms and produces numerous volatile compounds. Other odour-producing areas of the body, however, are likely less prolific and thus more difficult to investigate, but they probably constitute an unescapable challenge for future research in human chemical communication. Deeper explorations would also be welcome regarding individual differences but also factors of variations in time and their potential influence on interpersonal behaviour.

Conclusion

Chemical communication in humans is a relatively new field of research, with most of the research effort being concentrated in the last two decades. Major advances have been made, but many aspects of remain poorly understood for various reasons, including the fact that this is a recent topic, that focus has been made on some odours to the detriment of others, and on some social contexts to the detriment of others (e.g., mate choice vs. other types of social interactions such as parent-child, friends etc.) and that researchers are facing numerous technical, methodological and disciplinary limitations. The challenges developed in this article do not concern blank areas of research, which shows that progress is being

constantly made. Rather, they are destined to provide guiding principles for future studies contributing to elucidate the social function of odours in various contexts of social interactions.

Acknowledgments

We would like to thank Mariam Khidasheli, Ines Mehu-Blantar, Alexia Lamblin, as well as Myriam Troccaz, Christian Starkenman and Isabelle Cayeux (Firmenich), for their respective inputs in terms of bibliography, data collection, and methodology. We are also very grateful to two anonymous reviewers for their valuable and constructive comments on an earlier version of the manuscript.

Funding

This research was financed by grants from the Fondation Fyssen Paris (173867, to CF), the French National Research Agency (ANR-12-PDOC-0016, to CF), the Swiss National Science Foundation (100014_130036), and from the National Centre of Competence in Research “Affective Sciences” (51NF40-104897).

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Figure legends

Fig. 1 Perception of human body odour from the axilla and head of women (top, green, N=16) and men (bottom, blue, N=16). **(a)** Descriptive profiles (in percentage of times each descriptor was chosen): terms differing by more than 5% between men and women are highlighted (in green when higher in women, in blue when higher in men) and frames indicate a difference >10%; terms differing by more than 5% and 10% between head and axilla are indicated by empty and plain dots respectively. **(b)** Average intensity and attractiveness ratings (Mean \pm SEM) for axillary and head odours, compared by paired-sample t-tests. **(c)** Pearson correlations between axillary and head odours' attractiveness.

Fig. 2 Principal Component Analyses on the descriptive data of **(a)** the axilla and **(b)** the head odour of women (green, N=16) and men (blue, N=16). The figures represent the projections of the variables (descriptive terms, a.1 & b.1) and of the cases (odour donors, a.2 & b.2) on the first bi-dimensional spaces that explained nearly half of the variance.