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Influence of gender and culture on the perception of acidic compounds of human body odor

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Abstract

There is increasing evidence that human body odor is involved in interpersonal communication. However, among the wide variety of substances excreted by the human body that might act as chemosignals, much attention has been granted to androstenes to the detriment of other categories. Here, we focused on the acidic fraction of human body odor. We investigated men and women's perceptual descriptions and detection thresholds of the sexually dimorphic (male) compound 3-hydroxy-3-methylhexanoic acid (HMHA) in two contrasted cultures, France and Madagascar. Perceptual responses to HMHA in both countries were very similar. HMHA proved to be more typical of body odor than another chemically-related major compound of human body odor 3MHA (3-methylhex-2-enoic acid also known as 3M2H). A significant portion of the samples studied (between 8 and 19%) was likely to be anosmic to HMHA (and to 3MHA: 25%). Although differences would be expected between men and women's perceptual responses to HMHA, based on the assumption that this compound would have a function in human partner choice, no sex differences were found for any of the perceptual variables. However, in Malagasy women, perceived intensity of HMHA was higher in participants who were in the fertile phase of the menstrual cycle. Whether HMHA is relevant in the perception of a potential partner thus requires further explorations, with more implicit approaches for example and/or by investigating the repercussions of HMHA specific anosmia on interpersonal relationships.

Keywords

Chemical communication; Social interaction; Odor threshold; Body odor; Cross-cultural study; Gender differences.

1. Introduction

There is increasing evidence that human body odor, a complex mixture of volatile compounds produced by bacterial transformation of sweat gland secretions, is involved in interpersonal communication. For instance, body odor provides information about genetic proximity through the major histocompatibility complex [1–3], about hormonal levels of male and female donors [4–7], about health condition [8–10], and about emotional state [11–13]. Such information is relevant for social interactions in general, and for mate choice and interpersonal attractiveness in particular [14]. How a person smells plays an important role in partner choice. This is indicated for example by the high rank of importance given to the person's odor among different sensory signals and personality traits [15], especially in women [15,16]. Moreover, losing one's sense of smell generates substantial disruption of social interactions and sexual behavior [17–19], which is an indirect proof of the importance of olfaction in social interactions.

To understand the mechanisms by which body odor plays a role in human attractiveness, some studies have chosen to focus on individual compounds of body odor. Among the wide variety of substances excreted by the human body, several androgen derivatives present in apocrine sweat have received much attention from scientists: 5-α-androst-16-en-3-one (Androstenone) [20,21], 5α-androst-16-en-3α-ol (Androstenol) [22,23] and androsta-4,16-dien-3-one (Androstadienone) [24–27]. The main grounds for believing that these compounds may have a function in sexual reproduction (sex pheromones), and therefore may have key roles in human attractiveness, are that they have been directly linked with the reproductive behavior of another mammal (Androstenone in pig [28]) and that they are emitted in a sexually dimorphic manner, with higher concentrations, on average, in men [29–31] although this remains debated [32]. These androgen steroids have been reported to have psychological and behavioral effects [33–36], but these occurred both in men and women [25,26] whereas sex pheromones would be expected to exhibit clear sex differences. Additionally, the scientific justification for focusing on this family of compounds has been called into question [37],

and the necessity to enlarge the scope of investigated molecules to better understand human chemical communication has been clearly expressed [25,37].

Androgen steroids represent only a small fraction of the compounds emitted by the human body, i.e. alcohols, carboxylic acids, ketones, aldehydes, esters, or hydrocarbons [38]. The possibility that, among this variety of compounds, some of them might act as chemosignals in humans remains poorly explored. The most straightforward way to investigate this is to search the literature for sexually dimorphic compounds other than androstenes. Targeting sexually dimorphic odorants is motivated by the fact that signals that are produced more by one sex are likely to be relevant to human reproduction and mate choice [39]: for example, sexually dimorphic facial and vocal traits predict human mate preferences and behaviors related to competition for mates [40], two aspects of sexual selection. Although the chemical composition of human body odor is not fully known [41] partly due to methodological limitations, some differences between the sexes have been reported. In particular, a study showed that men and women differ in the ratio of two precursors secreted in the armpit, leading to potentially more sulfurous onion-like odor in women's sweat and to more cheesy rancid odor in men's sweat [42], the latter being caused to a large extent by the carboxylic acid 3-hydroxy-3-methylhexanoic acid (HMHA). Men have the potential to produce more HMHA than women also because they possess a greater amount of *Corynebacteria* [43] who are responsible for the formation of HMHA [44]. We therefore chose to study this particular molecule belonging to the acidic fraction of human body odor.

Available knowledge about carboxylic acids is mainly provided by studies of the metabolism of malodors originating from the axilla. Volatile fatty acids are among the major (and most distinctive) constituents of human sweat malodor. Zeng and colleagues [45] identified (*E*)-3-methylhex-2-enoic acid (3MHA also known as E3M2H, 3M2H, or M2HA) as being a major contributor to the axillary odor, qualitatively and quantitatively; Natsch and colleagues [44,46] subsequently showed that 3MHA is found along with a chemically related compound also present in large amounts, HMHA. Only basic and few explorations of how these compounds are perceived have been conducted to date, despite their

predominance in human body odor. HMHA has been described with the terms "perspiration, animal, cheese, rancid" [42], evaluated as unpleasant [47] and the reported average thresholds are variable according to the method used: 0.18 ng/l (air dilution olfactometry, $N = 30$ raters [42]), 0.6×10^6 ng/l (aqueous odorous solution on glass rods, $N = 20$ [47]), and from 10 to 0.1 ppm depending on the enantiomer studied (R and S respectively, mineral oil solution in beakers, $N = 5$ [48]). Results regarding sex differences are scarce and inconsistent (thresholds described as "similar" in men and women [42] or statistically lower in women [47]). Further examination with larger samples is necessary to determine how these compounds are perceived, especially as a function of rater sex.

The aim of this study was thus to provide a fine-grained description of how HMHA, a major compound of human body odor, more typical of men, is perceived and how this perception varies as a function of rater sex. This is a prerequisite to future studies that will test behavioral effects of this underexplored body odor compound. Two approaches were used in two different cultural samples, in France and in Madagascar, because inclusion of participants outside the so-called WEIRD (Western, Educated, Industrialized, Rich, and Democratic [49]) populations are needed to properly understand and generalize psychological phenomena to the human species. A first study was conducted in a French sample of moderate size ($N = 40$), using HMHA but also two other major body odor compounds: another carboxylic acid 3MHA (no reports of sex differences to date) and a steroid (Androstenone) which has been widely studied and will therefore serve as a reference. Another reference was used: a floral odor (phenylethyl alcohol or PEA) for which we have measures of general olfactory acuity with published standards [50]. Detection abilities of men and women as well as their perceptual ratings (pleasantness, intensity etc.) and verbal descriptions were examined. A second study was conducted in a large Malagasy sample ($N = 280$), using HMHA. Perceptual and threshold data were collected too using simplified methods due to the experimental constraints, which were to test a large sample of participants and to embed this study in another larger project on odor perception. Because of its sexual dimorphism, the male compound HMHA is likely to have a particular relevance to women: we therefore hypothesized that women may have more acute detection abilities of HMHA,

and that – if we assume that this carboxylic acid is common to the human species – these differences may be independent of the cultural group.

2. Materials and Methods

2.1. Study 1 - France

2.1.1. Participants

Study 1 included 40 participants originating from the vicinity of Lyon, France (20 men, 20 women; $M \pm SD = 24.7 \pm 5.0$ years of age) who declared that they were heterosexual, with normal olfaction, not regular smokers, and non-pregnant (women). About two third of the women ($N = 12$) were taking hormonal contraception; among those who were not ($N = 8$), 2 were estimated as being in the fertile phase of their menstrual cycle (for the method, see [51]). Participants provided written informed consent prior to participation. They were tested individually and received monetary compensation for their participation. The study was conducted in accordance with the Declaration of Helsinki and experimental procedures were approved by the local Lyon Sud-Est II ethical review board.

2.1.2. Odorants

Four odorants were used: a floral odor, phenylethyl alcohol (PEA; Fluka®; CAS number: 60-12-8) and three body odor compounds, namely 3-hydroxy-3-methylhexanoic acid (HMHA; CAS: 58888-76-9), (*E*)-3-methylhex-2-enoic acid (3MHA; CAS: 27960-21-0) and 5α-androst-16-en-3-one (Androstenone; Sigma-Aldrich®; CAS: 18339-16-7). HMHA and 3MHA were synthesized for the purpose of the study using procedures adapted from published protocols (see Supplementary Material). 3MHA and racemic samples of HMHA were all >99% (GC purity). Pure liquid odorants

(HMHA, PEA) or stock solutions of odorants that initially were in crystal form (3MHA: 5 mg in 5 ml mineral oil; Androstenone: 5 mg in 4 ml mineral oil; dissolved by sonication) were diluted in mineral oil (Sigma-Aldrich®). For each odorant, a series of 16 dilutions was prepared, using a ratio of 1:2 (v/v) between each dilution step, starting at 400 ppm (HMHA), 300 ppm (3MHA), 200 ppm (Androstenone) and 40 000 ppm (PEA) for the highest concentrations. In the data analysis, the dilution numbers are used, e.g. for HMHA, dilution level 1 is 400 ppm, dilution level 2 is 200 ppm, dilution level 3 is 100 ppm, etc. until dilution level 16 which is 1.2×10^{-2}. Concentration ranges were chosen, based on existing literature [50,52] and on the results of a pilot study (N = 6 men, 8 women, aged 25-40 yrs), to limit ceiling and floor effects in detection abilities. Odorants and blanks (mineral oil only) were presented in 15 ml amber flasks (opening diameter: 1.7 cm; height: 5.8 cm; filled with 5 ml solution). Solutions were absorbed on a scentless polypropylene fabric (3 × 7 cm; 3 M, Valley, NE, USA) to optimize evaporation and air/oil partitioning.

2.1.3. Procedure

Each participant took part in two sessions (one hour each) scheduled at the exact same time of day (between 8 am and 5 pm), generally on 2 consecutive days. Each session included threshold detection and perceptual ratings of two odorants separated by 5-min breaks (HMHA followed by PEA, or 3MHA followed by Androstenone; the order of the sessions was randomly assigned). As HMHA and 3MHA were our target odorants, we placed them always first to reduce possible noise related to the influence of other odors presented before. Indeed, the psychological effects of Androstenone are well documented [33–36]). In addition, presenting the control condition (PEA) always last allows to keep it as stable as possible. The participants were instructed not to wear perfume or to smoke before the experiment, and not to eat or drink anything but water in the hour preceding the test. The testing session was postponed in case raters had a cold or a blocked nose. All tests were conducted individually in a well-ventilated room at Lyon University.

The threshold detection measurement was performed using a triple-forced-choice paradigm in a staircase ascending procedure [53]. Blindfolded participants started by smelling a blank to get

familiarized with the “no-odor” condition. Then, an experimenter equipped with cotton gloves started a series of trials occurring every 30 sec, starting with the lowest concentration. In each trial, she presented 3 flasks randomly (1 with an odor, 2 blanks) by placing them ~2 cm below the nostrils during ~3 sec: participants had to indicate which flask contained the odor. The experimenter increased concentrations until the participants had two consecutive correct answers, which triggered a reversal of the staircase (decreasing concentrations). The geometric mean of the last 4 staircase reversal points of a total of 7 reversals was used as the threshold estimate (dilution levels are used). When participants did not detect the highest concentration, they were supposedly anosmics for the tested odor.

After each odor threshold detection task, using the odor concentration one step above the participant’s individual threshold, participants were asked to provide perceptual ratings of the odor: pleasantness, familiarity, irritation, and intensity on scales from 1 (“not at all pleasant / familiar / irritating / intense”) to 7 (“very pleasant / familiar / irritating / intense”). They also had to identify, or at least describe, the odor. Additional ratings (odor categorization, rating of affective feelings) were performed but are not presented here for the sake of concision.

2.1.4. Data Analysis

Analyses were performed with Statistica 12, R 3.0.1 and JASP 0.9.2 depending on the statistical tests used. As most variables did not follow a normal distribution (according to Shapiro-Wilks tests), non-parametric statistics were used.

Thresholds. We first computed the average threshold at the group level, based on the individual threshold estimates (dilution level) and provided the corresponding concentration in ppm. The shape of the threshold distributions in the participant sample was tested using the Hartigan's dip test for unimodality in R. Sex differences in odor sensitivity were examined using Bayesian Mann-Whitney U tests to compare the mean thresholds, and using Fischer’s exact test to compare the threshold distributions. When threshold distributions were not normal but rather appeared bimodal (HMHA and Androstenone), subgroups of least and most sensitive participants were constituted by median split, and were then compared for the number of men and women in each subgroup using a Chi-square test.

Perceptual ratings. We first computed the average ratings of pleasantness, familiarity and irritation at

the group level. As we used for these ratings an odor at a concentration based on the individual detection ability, the ratings of intensity were not analyzed but only used as a control measure to ensure participants perceived something. Identification responses were analyzed by: i) removing adjectives that directly qualified the odor or its effects (e.g., “strong”, “relaxing”) and keping only source names (e.g., “sweat”) and adjectives that are directly linked to an odor source (e.g., “floral”), ii) grouping responses into the following categories: human or animal characteristics, chemical and medicinal products, fermentation or humidity, foods, cosmetic or floral, plants, or others. Percentages of responses pertaining to a given category were computed out of the total number of responses (some participants have provided more than one response). Sex differences in odor perceptual ratings were examined using Bayesian Mann-Whitney U tests to compare the mean ratings, and the number of responses originating from men and from women in each identification category were compared using Fischer’s exact test for small samples. Finally, when applicable, the perceptual ratings of the least and most sensitive subgroups were compared using Bayesian Mann-Whitney U tests.

Here we give additional information regarding the Bayesian Mann-Whitney U tests. The null hypothesis was that there is no difference in sensitivity and odor ratings between men and women / no difference in odor ratings between high and low sensitivity groups (H_0 : effect size $\delta = 0$). We used a one-sided hypothesis, which states that only positive values of δ are possible (higher scores in women / in people with high sensitivity), except for PEA for which no direction for the sex differences was hypothesized. δ was assigned a Cauchy prior distribution with $r = 1/\sqrt{2}$, truncated to allow only positive effect size values in the case of HMHA, 3MHA and Androstenone. Analysis of the results is based on the Bayes factor which offers an assessment of evidence on a continuous scale. BF_{10} quantifies the relative predictive performance of hypothesis H_1 over H_0: Bayes factor equal to 1 signifies that both hypotheses are supported equally by the data, and the larger the BF_{10} becomes, the more support is gained for H_1 (see [54]). Bayes factor between 1 and 3 indicates weak support for H_1, between 3 and 10 constitutes a moderate evidence for H_1, and more than 10 is considered as strong evidence for H_1; BF_{10} between 1/3 (0.333) and 1 indicates weak support for H_0, between 1/10 and 1/3 constitutes a moderate evidence for H_0, and below 1/10 is considered as strong evidence for H_0.

2.2. Study 2 - Madagascar

2.2.1. Participants

Study 2 included 280 University students originating from Antananarivo, Madagascar (175 men, 105 women; $M \pm SD = 21.4 \pm 3.2$ years of age). All participants took part in the threshold tasks, but only part of them did the perceptual ratings (see below for the description of the tasks): $N = 173$ for HMHA ratings and $N = 115$ for PEA. The vast majority of participants was non-smoker ($N = 270$). Four women were taking hormonal contraception; among those who were not ($N = 91$; $N = 10$ missing data), some were estimated as being in the fertile phase of their menstrual cycle [51] (see details in the Data Analysis Section). Participants provided written informed consent prior to participation. They were tested collectively and received a meal in compensation for their participation. The study was conducted in accordance with the Declaration of Helsinki and experimental procedures were approved by the Ethical Committee of the Ministry of Health of Madagascar.

2.2.2. Odorants

Although the threshold and the perceptual rating task included a variety of odorants, here we chose to present only the data regarding HMHA and PEA also used in Study 1 (the other odorants were used for the purpose of another study, not presented here). In the threshold task, HMHA was the last of 6 different odors presented; threshold to PEA was not measured. In the perceptual rating task, HMHA and PEA were presented in random order among other different odors: 7 odors were presented to each participant, constituting one of three different sub-lists made from a total of seventeen different odors; HMHA was included in all sub-lists while PEA was included in only one and was therefore evaluated by a smaller sample of participants. For the threshold task, a series of 5 dilutions was prepared, using a ratio of 1:10 (v/v) between each dilution step, starting at 100 ppm for the highest concentration. The concentration range (100 to 0.01 ppm) is similar to Study 1 (400 ppm to 0.0122 ppm) except that the two highest concentrations steps (400 and 200 ppm) were removed and that the interval between the

steps is larger. For the perceptual rating task, a single concentration of HMHA was used (1000 ppm) and PEA was used at concentration 266×10^4 ppm. As in Study 1, odorants were diluted in mineral oil and presented in 15 ml amber flasks.

2.2.3. Procedure

Participants took part in a one-hour session that included a threshold detection task of 6 odors including HMHA, followed by perceptual ratings of 7 odors including HMHA and in some cases PEA. As in Study 1, the participants were instructed not to wear perfume or to smoke on the day of the experiment, and not to eat or drink anything but water in the hour preceding the test. The testing session was postponed in case raters had a cold or a blocked nose. All tests were conducted collectively in a classroom at the University of Antananarivo and participants performed the task autonomously. The language used in the written documents (instructions, questionnaires) was French, but oral instructions were given in Malagasy and the participants could answer in French or Malagasy. The threshold detection measurement was performed using a sequence of five 4-alternative forced choice tests, following the procedure described in [55]. The detection test consisted in five rows of four flasks. In each row, only one flask contained HMHA, the others contained mineral oil (blanks), and each row had a different concentration of HMHA. The participants had to sniff each of the four flasks in a row for ~3 sec per flask, and then indicated which flask differed from the other three, i.e. which flask contained the odor. Each concentration was presented only once, and concentrations were presented in ascending order. Participants were recommended to make a short break between the different odorants and to sniff into the crook of their arm as a sort of reset. The individual detection threshold for HMHA was the lowest concentration of HMHA that the individual identified correctly, provided all higher concentrations were correctly detected as well: here, we assume that an individual who can detect an odor at a given concentration should make no mistake at higher concentrations. When participants did not detect the highest concentration, they were supposedly anosmics for the tested odor.

The perceptual rating task was performed by asking the participants to sniff the flask containing the odorant (HMHA, PEA) for ~3 sec. Then, they were asked to rate the odor for pleasantness, familiarity,

intensity and edibility (not analyzed here) on 1-to-7 scales similarly to Study 1. Finally, participants were asked to freely identify and/or describe the odor. The threshold and perceptual rating tasks were separated by a break during which participants filled a questionnaire (on food behavior, not analyzed here).

2.2.4. Data Analysis

The same analyses as in Study 1 were conducted for the thresholds (means and distributions) and the perceptual ratings (pleasantness and familiarity as in Study 1, and intensity); data were most of the time not normally distributed. As the Malagasy sample was larger, the analysis of sex differences in anosmia rate and in identification responses could be performed using a Chi-square test (instead of Fischer's exact test for small samples in Study 1). It must be noted that, although the threshold distribution was not bimodal, for the sake of comparability with Study 1 the most and least sensitive groups were compared (median split: $N = 84$ participants with threshold > 1 and $N = 143$ participants with threshold = 1). In Study 2 the sample sizes were sufficient to compare (with Bayesian Mann-Whitney U tests) responses of women not taking hormonal contraception according to their menstrual cycle phase, i.e. "no pill non-fertile" women versus "no pill fertile" women: $N = 57$ vs. 20 (HMHA threshold, successful detection), $N = 65$ vs. 24 (HMHA perceptual ratings) and $N = 23$ vs. 14 (PEA perceptual ratings). The sample size of the pill users was too small to be compared ($N = 4$).

3. Results

3.1. Study 1 - France

3.1.1. Perception of HMHA

Thresholds. The average detection threshold was 6.30 ± 2.75 (dilution level) which corresponds to a concentration of 12.5 ppm of HMHA in mineral oil. Three participants (8%) were unable to detect

HMHA at the concentrations we used (ND in **Fig. 1.a1**). This is most likely a specific anosmia since they otherwise successfully detected PEA and Androstenone. Two of them also detected 3MHA but not the third participant. The distribution of HMHA detection thresholds significantly differed from a unimodal distribution ($Dn = 0.08$, $p = 0.043$) and its overall shape suggests a bimodal distribution, with a group of more sensitive participants (threshold < 25 ppm) and a group of less sensitive participants (threshold > 25 ppm) (**Fig. 1.a1**). Regarding sex differences, 2 men versus 1 woman were unable to detect HMHA. Among the 37 participants who were able to detect it, no sex difference was found on the distributions ($p = 0.835$; **Fig. 1.a1**). Regarding the average threshold, no evidence in favor of either hypothesis, i.e. no sex difference or women's higher sensitivity, was found ($BF_{+0} = 0.494$) (**Fig. 2.a1**). The most sensitive group comprised a higher proportion of women ($N = 11$ versus 7 men; $N = 8$ women versus 11 men in the least sensitive group) but this difference was not significant ($\chi^2(1) = 1.34$, $p = 0.248$).

Perceptual evaluations. HMHA was perceived as rather unpleasant (average pleasantness ratings: 3.05 ± 0.17 on a scale from 1 to 7), mildly familiar (3.49 ± 0.27) and not very irritating (3.03 ± 0.27). Identification responses mainly referred to chemical products (39%), human or animal characteristics (21%), fermentation or humidity (14%) and food (14%) (see details in **Table 1**). Bayesian analyses provided moderate evidence for the absence of sex differences (pleasantness: $BF_{+0} = 0.185$; familiarity: $BF_{+0} = 0.135$; irritation: $BF_{+0} = 0.162$) (**Fig. 2.a1**). Men and women did not differ in their identification responses as well (chemical, human/animal, fermentation/humidity, food: $df = 1$; all $ps = 1.0$). Finally, there was no evidence in favor or against the existence of differences in pleasantness ($BF_{+0} = 0.849$), familiarity ($BF_{+0} = 0.403$) or irritation ($BF_{+0} = 0.587$) ratings of HMHA by the most and least sensitive groups.

3.1.2. Perception of 3MHA

Thresholds. The average detection threshold was 6.67 ± 1.98 which corresponds to a concentration of 9.4 ppm of 3MHA in mineral oil. Ten participants (25%) were unable to detect 3MHA at the concentrations we used (ND in **Fig. 1b**), including one man who was also unable to detect HMHA.

The distribution of 3MHA detection thresholds did not differ from a unimodal distribution ($Dn = 0.07$, $p = 0.352$). There were no sex differences in the proportion of non-detectors (5 men and 5 women), or in threshold distributions ($p = 0.625$; **Fig. 1b**), and there was moderate evidence in favor of the absence of sex differences for the average threshold ($BF_{+0} = 0.258$) (**Fig. 2b**).

Perceptual evaluations. 3MHA was perceived as rather unpleasant (3.37 ± 1.47 on a scale from 1 to 7), mildly familiar (3.77 ± 1.85) and not very irritating (3.23 ± 1.76) and was described with terms referring to chemical products (41%), fermentation or humidity (20%), plants (15%), and human or animal characteristics (9%) (see **Table 1**). There was moderate evidence for the absence of sex differences for pleasantness ratings ($BF_{+0} = 0.164$), and no evidence in favor or against the existence of sex differences for familiarity ($BF_{+0} = 0.335$) and irritation ($BF_{+0} = 0.358$) (**Fig. 2b**). No sex differences were found in identification responses ($df = 1$, $ps > 0.302$).

3.1.3. Perception of Androstenone

Thresholds. The average detection threshold was 11.04 ± 4.17 which corresponds to a concentration of 0.2 ppm of Androstenone in mineral oil. One man (3%) was unable to detect Androstenone at the concentrations we used (ND in **Fig. 1c**). The distribution of Androstenone detection thresholds significantly differed from a unimodal distribution ($Dn = 0.09$, $p = 0.021$), and we therefore compared the most and least sensitive groups obtained by median-split. No sex differences were found in threshold distributions ($p = 0.190$; **Fig. 1c**) and the most and least sensitive groups only marginally differed in the number of men/women (12 men, 7 women in the least sensitive group, 7 men and 13 women in the most sensitive group: $\chi^2(1) = 3.09$, $p = 0.079$). Regarding the average threshold, no evidence in favor of either hypothesis, i.e. no sex difference or women's higher sensitivity, was found ($BF_{+0} = 0.577$) (**Fig.2c**).

Perceptual evaluations. Androstenone was perceived as moderately unpleasant (3.74 ± 1.62 on a scale from 1 to 7), a little familiar (4.05 ± 1.64), not irritating (2.42 ± 1.59) and described with terms referring to chemical products (26%), human or animal characteristics (19%), plants (17%), and cosmetic or floral (13%) (see **Table 1**). There was moderate evidence for the absence of sex differences for pleasantness and irritation ratings ($BF_{+0} = 0.175$ and 0.273 respectively), and no

evidence in favor or against the existence of sex differences for familiarity (BF_{+0} = 2.199) (**Fig. 2c**). Women (N = 10, vs. 22 other responses) described Androstenone with human/animal descriptors more frequently than men (N = 3, vs. 34 other responses; p = .028); no sex differences were found for the other categories (ps > .0988) in the identification task. Finally, there was no evidence in favor or against the existence of differences between the most and least sensitive groups in terms of pleasantness (BF_{+0} = 1.317) and familiarity (BF_{+0} = 0.861), but a strong evidence (BF_{+0} = 0.086) that the most sensitive group rated Androstenone as less irritating (1.85 ± 1.09) than the least sensitive group (3.06 ± 1.83).

3.1.4. Perception of PEA

Thresholds. The average detection threshold was 11.68 ± 2.61 which corresponds to a concentration of 39.1 ppm of PEA in mineral oil. All participants were able to detect PEA at one of the concentrations used. The distribution of PEA detection thresholds did not differ from a unimodal distribution (Dn = 0.06, p = 0.282). There were no sex differences in threshold distributions (p = 0.213; **Fig. 1d**), and moderate evidence in favor of the absence of sex differences for the average threshold (BF_{10} = 0.291) (**Fig. 2d**).

Perceptual evaluations. PEA was perceived as rather pleasant (4.85 ± 1.31 on a scale from 1 to 7), quite familiar (4.43 ± 1.77), not irritating (2.35 ± 1.59) and was described with terms referring to plants (38%, almost exclusively flowers), human or animal characteristics (18%), cosmetic or floral (15%), and chemical products (13%) (see **Table 1**). There was evidence in favor of women rating PEA as more pleasant (moderate: BF_{10} = 3.985; mean rating 5.35 ± 0.93 vs. 4.35 ± 1.46 in men) and less irritating (strong evidence: BF_{10} = 34.09; mean rating 1.55 ± 1.05 vs. 3.15 ± 1.66 in men) (but no evidence in favor of presence or absence of sex differences for familiarity ratings: BF_{10} = 0.384) (**Fig. 2d**). Regarding the odor descriptions, women qualified PEA as a flower odor more often than men did (13 responses out of 23 vs. 10 responses out of 37; Fischer's exact test: p = .030), while men described PEA with human/animal attributes while women almost never did (10 responses out of 37 vs. 1 response out of 23; Fischer's exact test: p = .039).

3.2. Study 2 - Madagascar

3.2.1. Perception of HMHA

Thresholds. The average detection threshold was 1.53 which corresponds to a concentration of 100 ppm of HMHA in mineral oil. Fifty-three participants (19%) were unable to detect HMHA (ND in **Fig. 1.a2**). Regarding sex differences, 37 men out of 139 (21%) versus 16 women out of 88 (15%) were unable to detect HMHA at the concentrations we used: the difference was not significant ($\chi^2 = 1.35$, $p = 0.245$). No sex difference was found either on thresholds distributions ($p = 0.746$; **Fig. 1.a2**) and no evidence in favor or against the existence of sex differences was found for the average threshold ($BF_{+0} = 1.011$) (**Fig. 2.a2**). Comparison as a function of menstrual cycle phase did not allow to conclude in favor or against the existence of differences between the no pill non-fertile and the no pill fertile groups ($BF_{+0} = 0.982$) (**Fig. 3a**). Finally, the most and least sensitive groups did not differ in sex distribution (38 women and 46 men vs. 51 women and 92 men, respectively; $\chi^2(1) = 2.03$, $p = 0.154$).

Perceptual evaluations. HMHA was perceived as rather unpleasant (average pleasantness ratings: 2.96 ± 1.25 on a scale from 1 to 7), little familiar (3.11 ± 1.55) and quite strong (4.64 ± 1.17). Identification responses mainly referred to foods (27%), human or animal characteristics (26%), chemical products (23%), and fermentation/humidity (16%) (see **Table 1**). There was evidence in favor of no sex differences in pleasantness (strong evidence: $BF_{+0} = 0.055$) and familiarity ratings (moderate evidence: $BF_{+0} = 0.100$) (but no evidence in favor of presence or absence of sex differences for intensity ratings: $BF_{+0} = 0.449$) (**Fig. 2.a2**). Men and women did not differ in their identification responses (foods, human/animal, chemical, fermentation: ($\chi^2 < 0.60$, $ps > 0.440$). Regarding the perceptual responses of non-fertile and fertile women not taking the pill, there was moderate evidence in favor of fertile women perceiving HMHA as more intense ($BF_{+0} = 3.584$; mean rating 5.13 ± 1.15 vs. 4.52 ± 1.26 in non-fertile women), but no evidence in favor of presence or absence of differences

for familiarity (BF_{+0} = 0.435) and moderate evidence for the absence of differences for pleasantness (BF_{+0} = 0.130) (**Fig. 3a**). There was moderate evidence for the absence of difference between the most and least sensitive groups' evaluations of HMHA pleasantness (BF_{+0} = 0.270), familiarity (BF_{+0} = 0.113) and intensity (BF_{+0} = 0.187).

3.2.2. Perception of PEA

Perceptual evaluations. PEA was perceived as slightly unpleasant (average pleasantness ratings: 3.50 ± 1.28 on a scale from 1 to 7), little familiar (3.22 ± 1.71) and quite strong (4.53 ± 1.22). Identification responses mainly referred to plants (40%, mostly flowers), chemical products (13%), foods (14%), and fermentation (7%) (see **Table 1**). There was no evidence of sex differences for pleasantness, familiarity or intensity ratings, but, instead, moderate evidence in favor of no sex differences at least for familiarity and intensity (BF_{10} = 0.239 and 0.223 respectively; pleasantness: BF_{10} = 0.374). Regarding the odor descriptions, as in the French sample of Study 1, women qualified PEA as a flower odor more often than men did (19 responses out of 34 vs. 22 responses out of 69; $\chi^2(1) = 5.47$, $p = .019$). Finally, there was moderate evidence that perceptual responses of non-fertile and fertile women not taking the pill did not differ on pleasantness (BF_{10} = 0.249) and intensity (BF_{10} = 0.320), but no evidence in favor or against the existence of sex differences was obtained for familiarity (BF_{10} = 1.366) (**Fig. 3b**).

4. Discussion

With this study, our aim was to increase knowledge about the perception of a major constituent of human body odor: 3-hydroxy-3-methylhexanoic acid or HMHA. The acidic fraction of human odor has been rarely explored in perceptual studies compared to other families of compounds such as the androstenes. Using psychophysical threshold evaluations and perceptual ratings in participants from two groups differing by culture (France and Madagascar) and size, we found that i) a significant

portion of the population is likely to be anosmic to HMHA and to a closely related compound, 3MHA, ii) HMHA is described in very similar ways in both cultures, and iii) there was no statistical evidence that women have more acute detection abilities or intensified perception of HMHA compared to men, however there were differences in perceived intensity within the group of women as a function of menstrual cycle.

An important result of our study is the large inter-individual variability of sensitivity to HMHA and 3MHA. First, prevalence of anosmia is high: 8% and 19% for HMHA in France and Madagascar respectively, and 25% for 3MHA in France. Those percentages are concordant with the literature: 21% and 17% for 3MHA in previous studies [45,56], corresponding respectively to the participants who were not able to detect the odor at the highest concentration used (0.194 ppm), and to one of six authors who reported that he could not perceive this odor; to our knowledge, no previous report exists for HMHA. Second, variability also expresses in the presence of two subgroups of participants with low and high sensitivity (bimodal distribution) among the French individuals who detected HMHA. Although this bimodality was not replicated in Madagascar due to the lower sensitivity of the test (5 concentrations differing by a ratio of 1:10 versus 16 concentrations differing by a ratio of 1:2), future research should investigate this bimodality further. Other body-related compounds, Androstadienone and Androstenone, present such a dichotomy as evidenced by i) bimodal distribution of the thresholds (see the results for Androstenone in our study, and other studies [57,58]), and ii) association between lower sensitivity and pleasant/woody/fragrant descriptions on the one hand, and between higher sensitivity and unpleasant/urinous/musky descriptions on the other hand, due to genetic variation of a particular olfactory receptor gene OR7D4 [59]. In our study, the participants with the lowest detection abilities rated the odor as more irritating, which suggests that detection abilities for Androstenone may be based on trigeminal rather than olfactory perception as suggested in another study on Androstenone [60]. Regarding HMHA, the two groups did not rate the odor differently in terms of pleasantness, familiarity, or irritation (as shown in the large Malagasy sample; the smaller French sample provided inconclusive results): But how they differ on other dimensions such as odor-related behaviors (effect of the odor on cognitive / social tasks) remains to be explored,

as well as the possible genetic polymorphism behind such a phenotypic variability. Finally, it must be noted that both countries probably had equivalent sensitivity to HMHA, although average thresholds seem to be quite different (12.5 ppm in France vs. 100 ppm in Madagascar). Indeed, it most likely reflects a difference in the concentration steps: in Madagascar, the step under 100 ppm is 10 ppm, meaning that a threshold of 12.5 ppm (as in France) would automatically end up in the 100 ppm category if tested with the method used in Madagascar.

Such variations in the ability to detect body odor compounds have been discussed in the past with regards to their behavioral relevance. Namely, it has been argued that, if the ability to detect them has not been conserved on the course of evolution, then their importance in the regulation of human behaviors can be questioned [37]. Following this reasoning, relatively high percentage of anosmia for Androstenone and carboxylic acids investigated in the present study tend to discredit their potential adaptive importance. However, in the context of social interactions, and more specifically in partner choice, this diversity might have been in contrary positively selected or at least subject to balancing selection. Little is known about the selective force acting on odor perception in humans regarding social interaction and mate choice, but one can suggest that diversity of perception and production of body odor might help to limit gene-flow and admixture in a context of strong group selection. A possible way to address this question in the future would be to evaluate whether insensitive individuals display any particularities in terms of reproductive function, including reproductive success, or more generally in terms of social interactions. Even if not vital, the consequences of not perceiving these compounds may be very concrete: insensitive individuals are probably not aware that they produce these smells, and they do not perceive this information in other individuals. As they are among the major constituents of body odor, this may influence hygienic/cosmetic practices and social interactions. This hypothesis remains to be tested in the future.

Perceptually, HMHA was described in a very similar way in France and Madagascar, with nearly one quarter of the participants using references to sweat, body parts (axilla, feet, skin), body excretions, persons and clothes, and animal sources. This is concordant with descriptions reported in another

smaller-scale study (perspiration, animal, cheese, rancid [42]). We identified other dimensions of the HMHA odor quality. It evoked chemical products in both countries (probably due to the odor presentation in the form of a solution in a bottle) and, interestingly, fermented products and humidity. In comparison, descriptions of 3MHA resemble those of HMHA with the following exceptions. References to fermentation and humidity are more frequent for 3MHA than for HMHA (which is consistent with the descriptions obtained in other studies: acrid, musty [45], acidic and rancid [42]). 3MHA elicits less references to human sources and seems to have a floral/vegetal aspect for some participants, which suggests that HMHA is more evocative of human body odor than 3MHA and thereby contributes more to the body odor percept. Food sources are also mentioned, with cultural variations (a diversity of fruits in Madagascar; aromatic herbs and condiments in France). When it comes to Androstenone, descriptions are consistent with the diversity reported in the literature, with references going from sweat and musk to flowers, wood and cosmetics [57,59].

Regarding our main question about sex differences in the perception of the odorous compound more typical of males, HMHA, we found no evidence that women outperform men in either quantitative (threshold, prevalence of anosmia) or qualitative perception (perceptual ratings, odor description). This was found on a moderate (France, $N = 20$ men, 20 women) as well as on a large sample size (Madagascar, $N = 175$ men, 105 women). Previous threshold comparisons between sexes with small samples provided mixed outcomes, i.e. either no sex differences based on a descriptive approach [42] or better detection abilities of women compared to men [47]. However, when we had a sample large enough to statistically test the effect of menstrual cycle phase (Madagascar), we found that women estimated in the fertile phase of the cycle perceived HMHA as more intense than women in the non-fertile phase. This is consistent with previous reports of finer sensitivity to complex body odors [51] or body odor compounds [61] around ovulation in naturally cycling women, and can be related with a possible adaptive function in human reproduction: women are probably finer-tuned to social cues conveyed by males when conception risk is higher. Whether this is limited to body odor compounds (versus other odor types) is a question that remains to be tested further before being generalizable; however, we provided a first piece of evidence by showing that intensity ratings of the same fertile

versus non-fertile participants differed for HMHA but not for a floral odor, PEA. Although in our study such a difference does not occur with HMHA thresholds, it could be revealed using a threshold test with higher sensitivity (such as the one used in the French sample).

To conclude, this study provides new findings related to underexplored chemical compounds from human body odor. In particular, it offers new data about how carboxylic acids that are major compounds of human body odor, HMHA and 3MHA, are perceived. A strength of this study is that for HMHA, which proved to be more typical of body odor than 3MHA, data were obtained through different methodological approaches in two very different participants' samples. On the one hand, convergent conclusions were obtained in terms of perceptual dimensions (pleasantness, familiarity, description of the odor sources); one the other hand, several results depended on the methodological choices made for each sample. Indeed, a compromise often needs to be made – in terms of time of testing – between the precision of the measure (especially for threshold, which is highly time-consuming) and the number of participants, and such a compromise inevitably has consequences on the research outcomes. Here, the fact that the number of concentrations in the threshold task was higher in the French sample than in the Malagasy sample (16 vs. 5) was appropriate to detect a bimodality in the former, but not in the latter. Also, the more limited range of concentrations used in Madagascar may not have covered the whole spectra of sensitivities: It is very likely that a portion of the population could have successfully detected HMHA at higher concentrations than 100 ppm, and that this would explain the higher percentage of non-detection in Study 2 compared with Study 1. In turn, to investigate inter-subject variability, a larger sample size is preferable, and this allowed us to find differences as a function of menstrual cycle in the large Malagasy sample. Finally, there are other factors of variability between the countries, related to differences in the methodology, such as the influence of odor presentation order on the participants' responses (e.g., effects of other odors presented before, or olfactory fatigue). About the fact that women's perception of HMHA did not clearly differ from that of men, it cannot be totally excluded though that this compound may have a role in human partner choice. Women perceived it (but not a control odor) as more intense during the fertile phase of their cycle, which could indicate that this compound is relevant in the perception of a

potential partner. Also, HMHA could be relevant both to men and women in the sexual selection process (intrasexual competition between men and men-women intersexual attraction). Future studies should test this, but also the behavioral effects of this odor, using more implicit approaches. Although no sex differences were found in the explicit perception of HMHA, the possibility that it influences person perception in a more implicit manner is worth being considered. Finally, from the broader perspective of understanding which odorous compounds produced by the human body may influence social interactions, it must be kept in mind that the ecological validity of investigating single molecules is limited: The perspectives proposed above should definitively involve testing the effects of target molecules when they are presented in mixtures, which corresponds to more realistic contexts.

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Figure Legends

Figure 1. Distributions of the detection thresholds in women and men, expressed in parts per million ppm (odor concentration) for **(a1)** HMHA in France, (**a2**) HMHA in Madagascar, and **(b)** 3MHA, **(c)** Androstenone and **(d)** PEA in France; ND: Not Detected.

Figure 2. Box-plots of the thresholds, pleasantness, familiarity and irritation or intensity ratings in women and men for **(a1)** HMHA in France, (**a2**) HMHA in Madagascar, and **(b)** 3MHA, **(c)** Androstenone and **(d)** PEA in France. #: evidence for group differences (Bayesian Mann-Whitney U tests).

Figure 3. Box-plots of the thresholds, pleasantness, familiarity and intensity ratings in women and men for **(a)** HMHA and (**b**) PEA in Madagascar. #: evidence for group differences (Bayesian Mann-Whitney U tests).

Figure 1

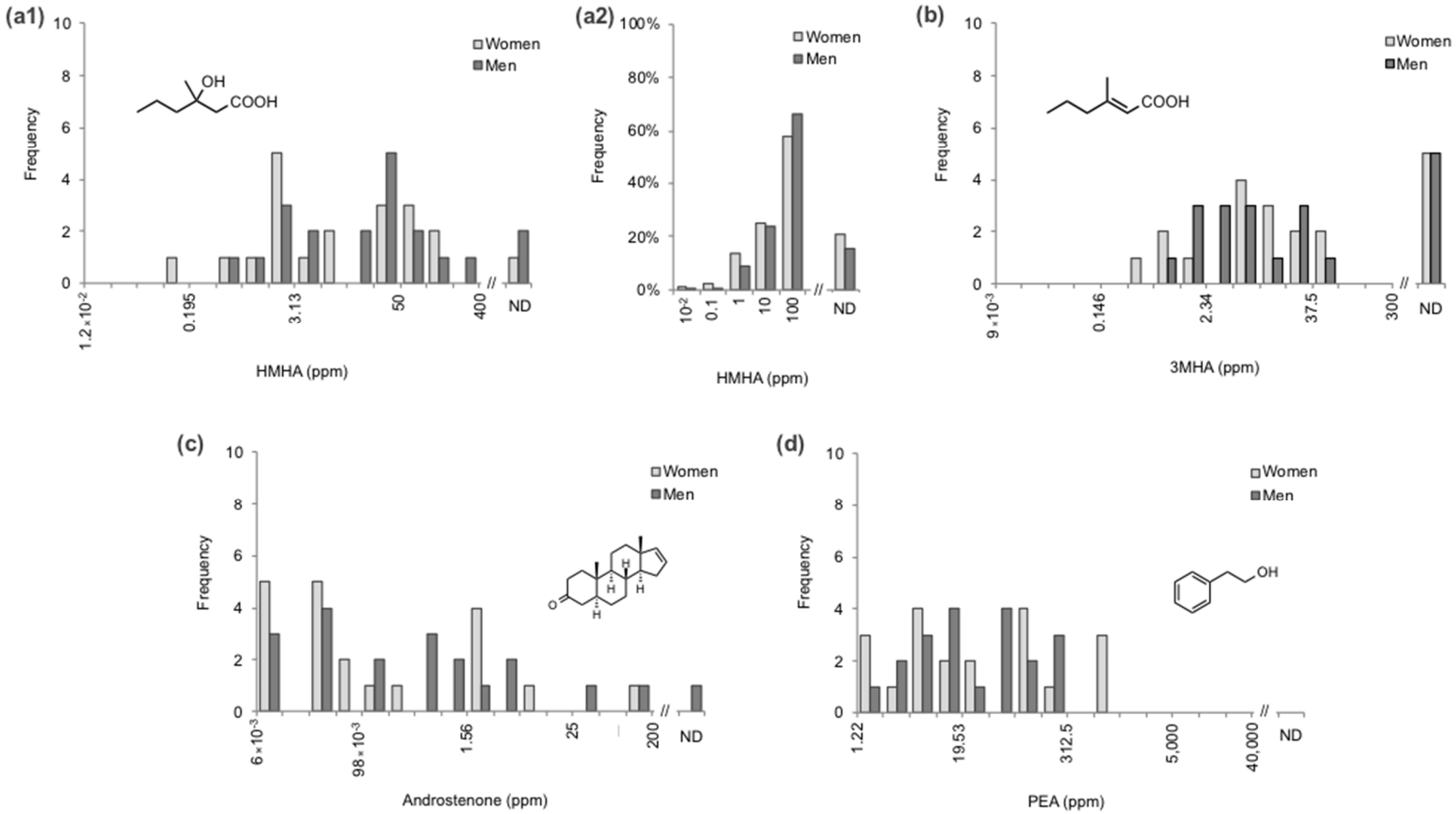
(a1)
Women
Men
OH
COOH
Frequency
HMHA (ppm)
1.2×10-2
0.195
3.13
50
400
ND
(a2)
Women
Men
Frequency
HMHA (ppm)
10-2
0.1
1
10
100
ND
(b)
Women
Men
COOH
Frequency
3MHA (ppm)
9×10-3
0.146
2.34
37.5
300
ND
(c)
Women
Men
Frequency
Androstenone (ppm)
6×10-3
98×10-3
1.56
25
200
ND
(d)
Women
Men
OH
Frequency
PEA (ppm)
1.22
19.53
312.5
5,000
40,000
ND

Figure 2

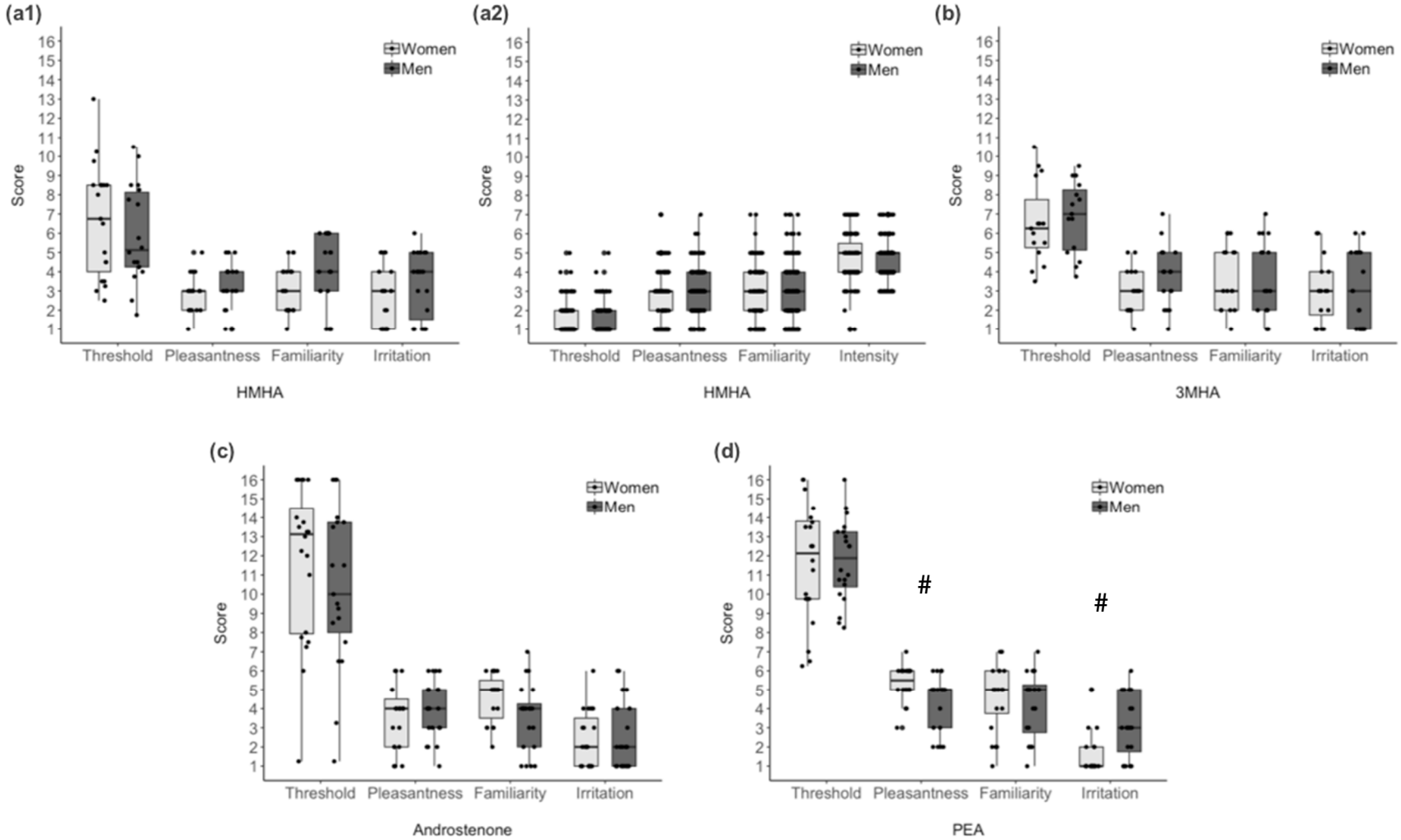
(a1)
Women
Men
Score
Threshold
Pleasantness
Familiarity
Irritation
HMHA
(a2)
Women
Men
Score
Threshold
Pleasantness
Familiarity
Intensity
HMHA
(b)
Women
Men
Score
Threshold
Pleasantness
Familiarity
Irritation
3MHA
(c)
Women
Men
Score
Threshold
Pleasantness
Familiarity
Irritation
Androstenone
(d)
Women
Men
#
#
Score
Threshold
Pleasantness
Familiarity
Irritation
PEA

Figure 3

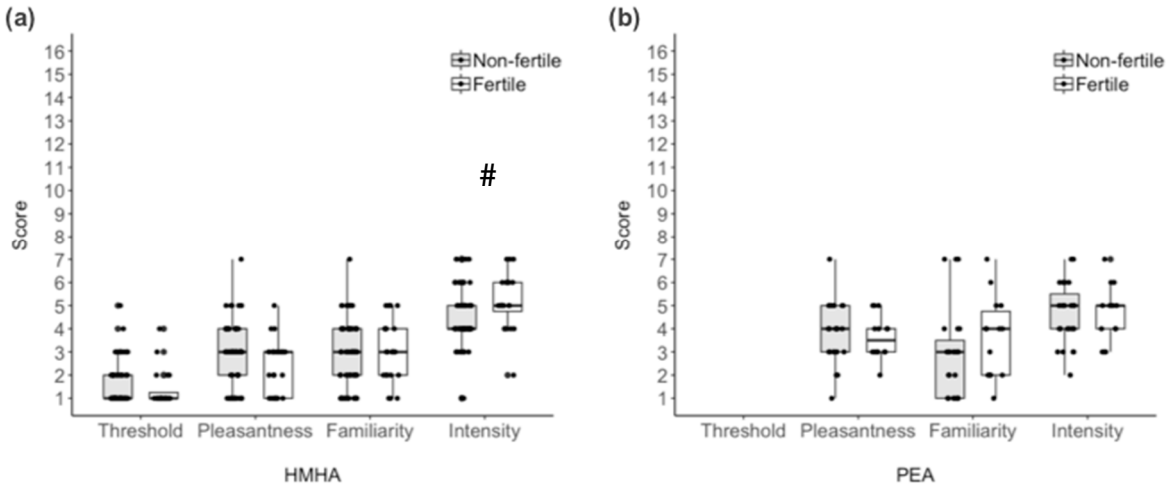
(a)
Non-fertile
Fertile
#
Score
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Threshold
Pleasantness
Familiarity
Intensity
HMHA
(b)
Non-fertile
Fertile
Score
Threshold
Pleasantness
Familiarity
Intensity
PEA

Table 1

Table 1. Identification responses of the odor compounds HMHA, 3MHA, Androstenone and PEA, in the French sample (N = 40) and when applicable in the Malagasy sample (N = 173 for HMHA, N = 115 for PEA). Only odor sources (e.g., "sweat") were retained for analysis, not odor characteristics (e.g., "strong"). Responses were sorted in categories and percentages indicate the number of sources pertaining to that category out of the total number of sources. * indicate the most frequently cited items. Incl.: including.

Odor	Descriptions
HMHA 3-hydroxy-3-methylhexanoic acid	**France** Chemical and medicinal products (39%): *cleaning product/detergent*, ammonia*, ink*, acetone, formalin, alcohol, hospital, plastic, hand sanitizer, paint, bleach, white spirit* Human or animal characteristics (21%): *sweat*, feet*, person, skin, leather* Fermentation or humidity (14%): *undergrowth*, rotten/overripe fruit*, moisture, manure* Foods (14%): *aromatic herbs (incl. thyme, rosemary)*, olive, onion/garlic, butter/cheese* **Madagascar** Foods (27%): *fruits (incl. jujube, tamarind, banana, apple)*, spices and condiments (incl. garlic, cinnamon, curry, clove, ketchup, mustard, pepper)*, fish, vegetables* Human or animal characteristics (26%): *sweat*, axilla*, human excretions/secretions (incl. feces, urine, cerumen)*, dirty clothes, person, feet, animal,* Chemical and medicinal products (23%): *medicine (incl. betadine/cough syrup)*, alcohol*, glue*, polish, machine oil, gasoline, paint, plastic* Fermentation or humidity (16%): *mold*, rotten/fermented/expired food*, wet things, old things*
3MHA (*E*)-3-methyl-hex-2-enoic acid	**France** Chemical products (41%): *cleaning product*, tar*, ink*, medicine, ammonia, chlorine, hospital, alcohol, glue, paint, gasoline* Fermentation or humidity (20%): *undergrowth*, fermented food*, mold, moist, manure, attic/cellar, dead leaf* Plants (15%): *flower (incl. lavender)*, plant, stem* Human or animal characteristics (9%): *homeless person*, sweat, animal*
Androstenone 5α-androst-16-en-3-one	**France** Chemical products (26%): *alcohol*, cleaning product*, iodine*, gasoline, plastic, solvent, ink, hospital* Human or animal characteristics (19%): *sweat*, animal*, leather*, musk* Plants (17%): *wood*, flower*, seaweed, grass* Cosmetic or floral (13%): *soap*, perfume/fragrance*, lotion, shampoo, bathroom*
PEA phenylethyl alcohol	**France** Plants (38%): *flower (incl. rose, lavender, lily, dandelion)*, wood* Human or animal characteristics (18%): *sweat*, grandmother, shoe, musk, fur, farm, goat, sheep, dirty hair* Cosmetic or floral (15%): *perfume*, floral waters*, soap* Chemical products (13%): *ink*, perchlorethylene, chlorine, chemical, cleaning product* **Madagascar** Plants (40%): *flower (incl. rose, iris, nasturtium, frangipani, hazo)*, aloe vera, plant, wood, tree, leaf* Chemical products (30%): *ink*, medicine*, plastic*, glue*, disinfectant, insecticide, polystyrene, chemical, varnish* Foods (14%): *honey*, fruits*, candies*, oil, spices, tea, vanilla, shrimps* Fermentation (7%): *rotten/fermented/stale food*, stagnating water*