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Prior exposure to Hedione, a model of pheromone, does not affect female ratings of male facial attractiveness or likeability

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ABSTRACT

The existence of pheromones in humans is controversial, partly because of definitional difficulties and partly because of the question of possible chemical substances. The synthetic compound Methyl dihydrojasmonate (Hedione) is potent to bind to vomeronasal-type 1 receptors (VN1R1s) and activate limbic areas of the brain in a sex-specific manner. However, one of the most important definitional points for a human pheromone effect has not yet been investigated, i.e., whether smelling Hedione, a model of pheromone, has a behavioral effect. We tested in females whether Hedione leads to altered perception of male social stimuli. Each of the included women were sensitive to Hedione and were tested around the time of ovulation in three consecutive sessions, during each they were exposed to either Hedione or Phenylethyl alcohol or Odorless air. We measured the speed of male face recognition (implicit priming task) and collected ratings of facial attractiveness and likeability of men (explicit task). Only about half of the women tested were sensitive to Hedione. Those women did not show any effect of Hedione exposure in the implicit priming task and moderate, but non-significant effects in the explicit task. We therefore assume that Hedione is not a potent model of pheromone in humans and this observation may be due to the fact that the artificially produced substance is not suited for signaling the proximity of other humans. Furthermore, the high rate of Hedione-specific anosmia leads to the hypothesis that a substantial proportion of individuals has a poor V1NR1 receptor expression.

1. Introduction

The idea that human behavior can be driven by chemosensory communication has been widespread in the consumer markets that promote vision of collective females' attraction to a man who has used a certain perfume but scientific evidence for the existence of human pheromones is debatable. One of the reasons for this is that the definition of the pheromone term is not uniform, the other refers to the question which substance may cause such an effect.

A first definition by Karlson and Lüscher [1] stated that the pheromones are "secreted to the outside by an individual and received by the second individual of the same species, in which they release a specific reaction". Further conceptual work emphasized the usefulness of the chemical signal to both parties [2] and distinguished four functional groups of pheromones, namely primers, signalers, modulators and releasers [3]. While primers and signalers have a subtle effect, such as indicating the presence of another individual of the same species, primers elicit physiological changes and potentially delayed behavioral effects. Releaser pheromones have the most rapid effects, instantly evoking behavioral response. Perhaps the strongest evidence for the existence of a releaser pheromone effect in humans can be found in newborns, where the natural breast odor of the mother causes a targeted movement towards the nipple and sucking behavior [4].

Other effects of odors were investigated with regard to human sexual behavior and revealed that sexual interest is moderated by olfactory cues in both sexes [5–7]. Derivatives of human sex hormones can, for example, alter physiological or behavioral responses. These steroids, namely 4,16-androstadien-3-one (AND) and estra-1,3,5(10), 16-tetraen-3-ol (EST) have been shown to influence mood, physiological arousal, visual perception and brain activity [8]. Effects of sexual orientation on AND perception have been reported with homosexual women exhibiting similar activation patterns of anterior hypothalamus

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to heterosexual men rather than heterosexual women [9]. Furthermore, when persons are asked to rate the gender of artificial objects, simultaneous exposure to EST results in attribution of femaleness, while exposure to AND results in attribution of maleness [10]. Another example comes from speed-dating events, where women exposed to AND presented more interest in a potential mate than women in a control condition [11]. An imaging study revealed cortical regions that are activated upon exposure to AND and EST [12]. They found activation of the anterior hypothalamus, a region that regulates sex hormone release via the hypothalamus-pituitary-gonad axis and that is rather atypical for non-social olfactory stimulation. This mechanism may describe the route from the peripheral perception of AND and EST to social or sexual behavior [13].

Despite these behavioral and neural effects of AND and EST, there is controversy about its pheromonal activity [14–17]. This is mainly motivated by the fact that there is no compelling evidence on the gender-specificity of AND, by the potential positivity bias in publishing results of behavioral effects, by small sample sizes and by the lack of systematic replication [17]. Hare and colleagues for instance reported null effects for the perception of gender-neutral faces and for the perception of attractiveness and unfaithfulness of faces during exposure to AND and EST [18].

In animal research, the terminology of pheromones is strongly associated to peripheral chemosensory processing in a region called the vomeronasal organ (VNO), where receptors are expressed that serve the purpose of social chemical communication. In the VNO of rodents for instance, three large families of 7-transmembrane G-protein–coupled receptors exist: vomeronasal-type 1 receptors (V1r), vomeronasal-type 2 receptors (V2r) and formyl peptide receptor-like proteins (FPR) [19]. However, the story is different in humans. Whereas there are 240 functional vomeronasal-type 1 receptor genes (VN1Rs) in the rat and mouse genomes, only five intact VN1Rs have been found in the human and chimpanzee genomes [20–23]. Furthermore, the human VNO is not functional [24]. The absence of a functional VNO does not necessarily indicate loss of sensing and functioning of social chemosignals [24,25,26]. Messenger RNA for the VN1R gene has been found in cells of the human olfactory mucosa [21] which indicates that the human main olfactory epithelium (OE) could be involved in the sensing of social chemosignals. In addition to the “classical” VNO receptor types, another class of receptors, the trace amine-associated receptors (TAARs), known to communicate sex and stress level in mice, are also present in human OE. This further suggests the ability to detect social chemosignals in the absence of functional VNO [27].

In search of a potential human pheromone, a substance that activates VN1R1 seems to be relevant. Such a substance is Methyldihydrojasmonate (Hedione), which is a synthetic compound invented in 1958 to mirror the natural scent of jasmine [28]. Not only does Hedione bind to VN1R1, it has also been shown to activate the hypothalamus in a sex-differentiated manner. When exposed to Hedione, women – but not men – show an activation of the hypothalamus. Furthermore, Hedione as compared to the control odor Phenylethylalcohol (PEA; smelling like rose) elicited stronger activations in the hippocampus and amygdala, regions responsible for memory and emotional processing [29]. The binding to the VN1R1 receptor and the neuronal activation pattern suggest that Hedione has pheromone-like effects in humans. However, the behavior experiment is still pending. We therefore investigated whether exposure to Hedione results in altered perception of social stimuli. We hypothesized that exposure to Hedione will result in faster detection of social cues and enhanced perception of facial attractiveness.

2. Materials and methods

2.1. Ethics statement

The study was performed in accordance to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. Informed written consent was obtained from all participants. The study design and consent approach were approved by the Ethics Review Board at the TU Dresden (EK211052017).

2.2. Participants

Only females were invited to participate in this study because young females have been found to be more sensitive to odors [30–32], more responsive to olfactory cues than men in mating context [33] and present stronger neural activation when exposed to Hedione [29]. Initially we invited 33 healthy, heterosexual women aged between 19 and 33 years to participate in the study (M_{age}=24.09±3.96 years). Exclusion criteria were self-reported use of hormonal contraceptives (pill, hormone spiral, hormone patches), irregular menstruation cycle, existing pregnancy, active desire to conceive or breastfeeding, anorexia nervosa, acute or chronic inflammations or diseases in the nasopharyngeal area, as well as concomitant diseases with effects on the sense of smell (olfactory disturbance or olfactory loss). Additional exclusion criteria were hyposmia (Sniffin’ Sticks identification subtest < 12 points (according to [31] and symptoms of depression (> 13 points in the Becks Depression Inventory (BDI-II) [34]. Another exclusion criterion was the inability to perceive Hedione. In order to test this, the participants performed a simple threshold test based on the 3-alternative forced choice (3AFC) ascending threshold test staircase logic [31,32,35] by using 6 decreasing concentrations of Hedione (diluted 1:4) starting from 10%. Based on results in this test, we included 17 participants (M_{age}=24.8 ± 4.8 years) whose score was equal or higher to three, meaning that these women were able to perceive Hedione at concentrations of 0.625% dilution or less. The high fraction of women obtaining lowest possible score (1 point) suggests high prevalence of specific anosmia to Hedione. Ability to detect Hedione was not associated with age, $t(31)=-0.94$, $p=.36$ [95% CI: −4.13; 1.53] but it was positively correlated with odor identification abilities ($r = 0.43$, $p=.14$). Distribution of Hedion sensitivity is presented in Fig. 1. Participants excluded from the sample ($n = 16$; $M =$ 23.9±.75 years) were not different in terms of age from those who remained in the study sample ($n = 17$; $M = 24.3 \pm 1.16$ years; $t(31)=$ 0.39, $p=.77$ [95% CI:−3.27; 2.43]).

Participants’ sociosexual orientation was measured with the Sociosexual Orientation Inventory (SOIR) and compared to normative data [36] to screen for outliers, confirming none of the subjects exhibited deviance from the mean sociosexuality of the population that could

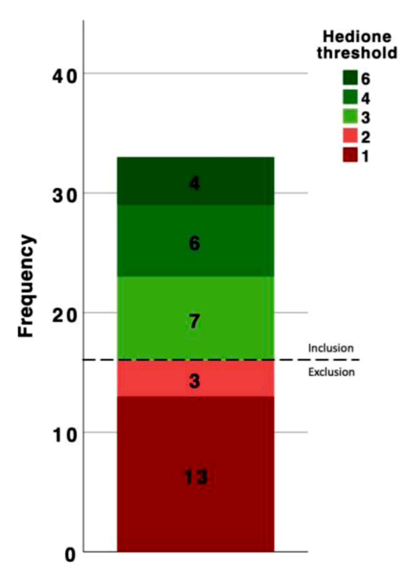

Fig. 1. Distribution of Hedione sensitivity in the initial sample (n = 33) of women invited to participate in the study. The high fraction of lowest possible score (1 point) suggests high prevalence of specific anosmia to Hedion.

potentially bias interpersonal attraction. Nine of the participants included in the final sample were in a stable relationship that lasted from 0.83 to 8 years ($M = 4.62 \pm 1.02$ years); two were left-handed.

2.3. Procedure

All participants attended three experimental sessions. All women were around ovulation at the time of the session to control for the possible hormonal bias. This was ensured by assessment of the individual menstrual cycle onset and cycle length which was used to calculate a probable date for the next ovulation. Urine ovulation tests performed daily at home by all participants (starting three days before the most probable day of ovulation) were used for precise determination of the test day. Before each session they were asked to refrain from smoking one hour prior to the meeting, not to wear perfumes on the testing day and not to eat or drink for at least half an hour before the session. None of the subjects in our sample reported regular smoking.

At each session, the participants were exposed to either Hedione (HC, Firmenich, Switzerland, Art Nr. 947,325), Phenylethylalcohol (PEA; 2-Phenylethanol ≥99%, Sigma-Aldrich, Deutschland; Bestellnummer #77,861), both used as a 5% solution in propylene glycol, or odorless air. Both fragrances have a flowery, pleasant smell. The order of the three sessions was randomized across the participants.

During the 30 min odor presentation phase, participants were seated in a comfortable chair placed in front of a monitor, which displayed tango contest videos. This was aimed to reduce boredom during odor presentation and to prime the participants uniformly to interpersonal, emotional contact and by that reduce the variability of the individual emotional state. While watching the video, the odor (or odorless air) was intranasally presented via a nasal tube which was connected to an inspiration-triggered olfactometer (Burghart, Wedel, Germany) that produced respiratory controlled air puffs with a minimal temporal interval of 5 s and a mean interval of 6 odor stimulations per minute. The participants were asked to rest and to concentrate on the odor. Every 10 min, participants were asked to rate odor intensity and pleasantness on a visual analogue scale (VAS) ranging from 1 (not intense / very unpleasant) to 9 (very intense / very pleasant). At the end of the odor presentation phase, participants were asked to rate to what extent they enjoyed the tango clip using VAS ranging from 1 (not at all) to 9 (very much).

Afterwards, the test phase started. Testing phase was scheduled after odorous stimulation to prioritize less artificial rating situation (without having the olfactory tubes in the nostrils). Therefore, attraction was assessed with an implicit priming and an explicit rating method. The implicit priming method assessed the speed of male facial recognition [37]. We presented 15 sets of stimuli: 5 computer generated male faces from the Social Perception Lab database of attractive male faces [38,39] and 10 distractors (bicycles, chairs and stairs) taken from the Geneva picture database [40]. Each stimulus was transformed in 10 steps with progressive pixilation until unrecognizable (for an example see Figure S1 in the Supplementary File 1). Each set was presented on the screen starting with the strongest pixilation and each image of each set was presented for 1000 ms with no inter stimulus interval. The subject was asked to press a button immediately when she identified the image and to provide a cued answer whether this was (1) a man (2) stairs, (3) a chair, (4) a bicycle. Order of pictures and answer format were randomized. In case, the image was a man, participants were asked to rate (explicit task) "how likeable is the man?" and "how attractive does he appear?" using a scale ranging from 1 (not at all) to 9 (very much).

In order to make full use of the carefully screened participants, we also performed an implicit and explicit test for maternal feelings that are also suspected to be impacted by pheromones. Those methods and results (all non-significant) are presented for reasons of transparency in the supplementary material.

Before and after each session, mood was assessed with the Positive and Negative Affect Schedule PANAS [41].

The study was operated with the E-prime3 software (Psychology Software Tools, Inc., Sharpsburg, USA). The protocol scheme is presented in Fig. 2.

2.4. Statistical analyses

Statistical analyses were performed with SPSS statistical package version 25 with the level of significance set to $\alpha=0.05$. Tango film ratings were compared across the three experimental conditions using a repeated measurement ANOVA. Ratings of odor pleasantness and intensity during the exposure were examined using repeated measurement ANOVA with session (Hedione vs. PEA vs. odorless air) and measurement timepoint (10 mins vs. 20 mins vs. 30 mins) as within subject factors. Changes in positive and negative affect as a function of odor exposure were analyzed with repeated measurement ANOVA with session (Hedione vs. PEA vs. odorless air) and measurement timepoint (before vs. after exposure) as within subject factors.

For the implicit task, mean reaction time scores for the five targets (male faces) and 10 distractors were computed per session and participant and thereafter analyzed using repeated measurement ANOVA with 3 sessions x 2 objects (male faces vs distractors).

The two explicit ratings were analyzed with two repeated measurement ANOVAs with 3 sessions.

3. Results

Odor exposure did not significantly influence tango film rating, $F(2,28)=0.32$, $p = 73$. Odors were rated as similarly pleasant (all $Fs<1.37$, $ps<0.25$, $\eta^2<0.09$) and intense (all $Fs<2.64$, $ps<0.09$, $\eta^2<0.16$) during the three measurement timepoints (Figure S2 in the Supplementary File 1). There was no significant change in positive affect (all $Fs<0.47$, $ps<0.62$, $\eta^2<0.04$), however, negative affect was significantly reduced after odor exposure ($F(1,28)=20.1$, $p=.001$, $\eta^2=0.59$). There was no significant main effect of odor, $F(2,28)=0.57$, $p = 57$, $\eta^2=0.04$ and no significant odor by session interaction effect, $F(2,28)= 1.47$, $p = 25$, $\eta^2=0.10$ on negative affect.

The implicit task revealed a significant main effect of object ($F(1,14)=42.18$, $p<.001$, $\eta2=0.75$), showing that women reacted faster to male faces ($M = 6.58 \pm .22$) as compared to the distractors ($M = 5.75 \pm .18$). No significant main effect of session ($F(2,28)=0.45$, $p=.64$, $\eta2=0.03$) and no significant interaction ($F(2,28)=0.21$, $p=.82$, $\eta2=0.01$) were observed (Fig. 3).

Within the two models testing attractiveness and liking ratings of men faces in the explicit task, we consistently found non-significant within-participants effect of odor, suggesting that mens` faces were recognized as similarly attractive, $F(2,28)=1.97$, $p=.16$, n2=0.12 and likeable, $F(1.46,20.42)=0.37$, $p=.70$, n2=0.03 (Greenhouse-Geisser corrected for violation of the sphericity assumption) across the three odor exposures (Fig. 4).

4. Discussion

The results of the current study failed to show behavioral effects of exposure to Hedione as the model of pheromone. After being exposed to Hedione, women were not more vigilant to male faces and rated those faces as equally attractive and likeable as after exposure to odorless air or PEA.

Studies on the effects of putative pheromones, namely EST and AND on perception of facial attractiveness showed mixed results. Olfactory preference for EST and AND has been found to correlate with visual preferences for feminine and masculine faces [11,42] while exposure to EST has been found to modulate the perception of vocal and facial attractiveness around the menstrual cycle [43], suggesting convergence between visual appearance and chemosensory signals in communication of mate quality [43]. More recently, contradictory findings suggested the effects of human putative pheromones are not sex-specific and that

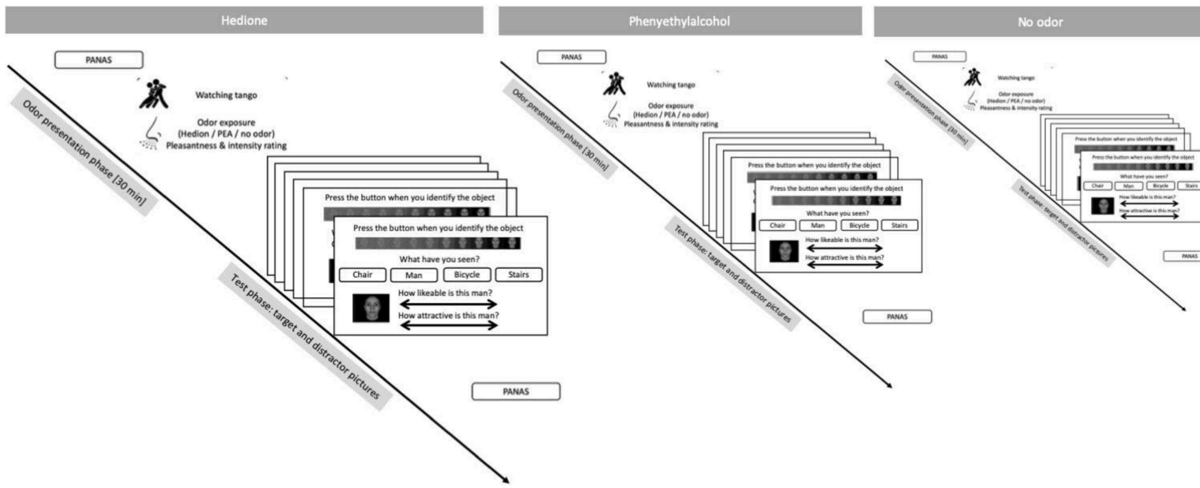

Fig. 2.. Study design summary. Note that all factors are within-subject.

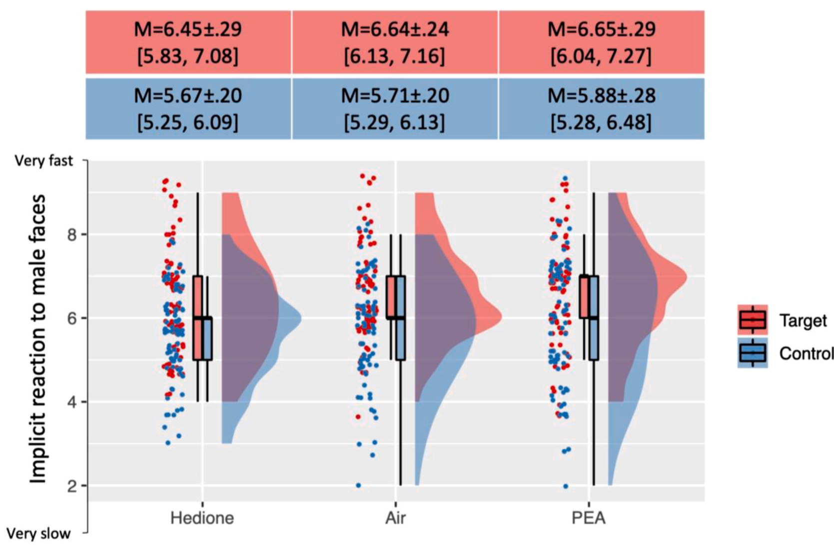

Fig. 3.. Distribution of the implicit task scores for men's pictures. Table at the top panel presents mean ± standard error and [95% confidence intervals].

exposure to EST and AND does not impact facial perception of gender, attractiveness or unfaithfulness [11,18,44]. The null results of our study add Hedione to list of questionable substances that act potentially not as human pheromones. In our opinion, there are two plausible explanatory models for the observed null effects: (1) the study was not perfectly well suited to study pheromonal effects of Hedione, or (2) Hedione does not have pheromonal properties.

Let us first take a closer look at the first explanatory model. Our final sample size did only allow us to detect large statistical effects [17], whereas the effect of Hedione on facial perception may actually be subtle. To capture these potentially small statistical effects a larger sample size would be required. However, the effect size of the implicit task was very small and explained only 1% of the variance. This makes a significant effect of Hedione unlikely, even if the sample size is considerably increased. The situation is different for the explicit rating of attractiveness. Here, the effect the odor exposure explained 12% of the total variance, which resembles medium effects. This leads us to our second limitation, namely the operationalization of behavioral effects in terms of the facial perception paradigm. One may argue, that this was not well suited to evoke behavioral effects. However, this seems unlikely considering the robust evidence from other studies showing that a) pleasant odors foster face recognition [45,46], b) unpleasant odors improve detection of happy faces in a distracting crowd [47], and that c) pleasant odors increase ratings of facial attractiveness [11,46,48-50,51,52,53-56]. More specifically, male faces are attractive when female participants smell subjectively pleasant male perfume [50,57], suggesting that synthethic odors used to mask natural axillary odors influence attractiveness perception. A potential improvement for further studies is to take measurements during (not after) exposure to Hedione, which might render effects of larger magnitude. It would also be of interest to study the potential longitudinal behavioral effects and potential side effects of exposure to Hedione.

Our second explanation of the null effects refers to the properties of Hedione. Hedione is a substance potent to activate VN1R receptors and limbic areas of the brain [29], but in contrast to AND and EST, it is not released by the human body. Hence, this artificial odor is most likely not conditioned to communicate the proximity of another human. However, it seems to be body-associated odors that influence attractiveness. The presence of body odors predicts attraction [58]. The ratings of facial attractiveness are influenced by simultaneous presentation of natural body odors: when participants are presented to subjectively pleasant axillary odor they also rate the faces as more attractive [52,55,59]. To advance our understanding of the VR1N receptor function, naturally emitted compounds that activate this receptor type need to be identified.

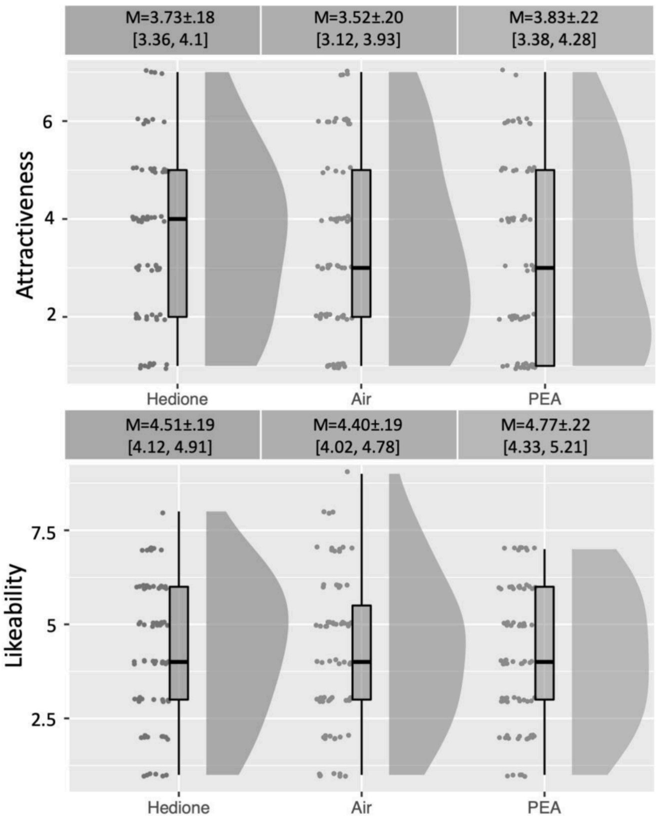

Fig. 4.. Distribution of the explicit task ratings for men's pictures.

In addition, further studies are required to gauge the translation of neural activation [29] into behavior.

Interestingly, we found a bimodal distribution of the Hedione perception. Almost half of the women we tested initially, were not able to detect Hedione at low concentrations, corresponding the rates of Androstenone-specific anosmia [60]. This high rate of Hedione-specific anosmia suggests that the V1NR1 receptor expression is poor in a substantial proportion of healthy young women which may indicate that this type of receptor has no important function for human behavior.

The current study failed to demonstrate that Hedione, an odorant potent to activate VN1R receptor but not naturally emitted by human body, exhibits pheromonal effects on facial perception in young heterosexual women. This null effect delineates future directions in the search for human pheromones focused on identifying odorant that signal the presence of other humans and activate VN1R.

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Declaration of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2021.113458.

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