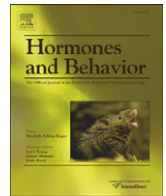




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The relationship between oral contraceptive use and sensitivity to olfactory stimuli

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ABSTRACT

The present study examined differences in olfactory sensitivity between 16 naturally cycling (NC) women and 17 women taking monophasic oral contraceptives (OCs) to six odors: lemon, peppermint, rose, musk, androstenone and androsterone. Thresholds were assessed twice for both groups of women (during the periovulatory and luteal phases of their cycles) via a forced-choice discrimination task. NC women in the periovulatory phase were significantly more sensitive to androstenone, androsterone, and musk than women taking OCs. These findings give support to odor-specific hormonal modulation of olfaction. Further, due to the social and possibly sexual nature of these odors, future work should address whether there is a relationship between decreased sensitivity to these odors and reported behavioral side effects among women taking OCs.

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Introduction

There are a number of physiological, perceptual, and behavioral changes that have been reported to co-occur with ovulation in women; these changes have largely been attributed to the hormonal fluctuations that characterize ovulation (i.e. the pre-ovulatory spikes in luteinizing hormone (LH) and estradiol) (e.g. [Fehring, 2002](#); [Gueguen, 2009](#); [Parlee, 1983](#)). Because women taking oral contraceptives (OCs) do not experience hormonal fluctuations as naturally cycling (NC) women do, and do not ovulate, they provide a particularly good opportunity to assess which of these mid-cycle changes are specifically related to hormonal influences ([Cohen and Katz, 1979](#); [Elkind-Hirsch et al., 1992](#)).

Approximately 82% of women between the ages of 15 and 44 in the United States have at one point in time regularly used an oral contraceptive pill as a form of birth control ([Mosher and Jones, 2010](#)). The combination pill, containing an estrogen and a progestin, is reportedly the most common form of the pill in use ([Sanders et al., 2001](#)). The combination pill targets the hypothalamus and pituitary, altering hormone levels, to prevent ovulation. The estrogen component suppresses the follicle stimulating hormone (FSH), preventing the development of a follicle, and the progestin component suppresses the LH surge necessary for ovulation ([Speroff and Darney, 2010](#)).

Exogenous hormones can have various physiological effects on women's bodies, such as inducing nausea and promoting weight gain, as well as putting women at risk for more serious health

problems, such as stroke ([Seibert et al., 2003](#)). Women taking OCs have also reported many behavioral side effects, such as emotional lability and decreased sexual desire ([Battaglia et al., 2012](#); [Caruso et al., 2004](#); [Sanders et al., 2001](#); [Warner Chilcott, 2009](#), but see [Alexander et al., 1990](#)).

Recent studies have elucidated the effects of OCs on the sensory systems, reporting increases in auditory and olfactory thresholds, indicating decreased auditory and olfactory sensitivity, among OC users as compared to nonusers ([Caruso et al., 2001, 2003](#); [Snihur and Hampson, 2012](#)). [Caruso et al. \(2001\)](#) tracked women's olfactory thresholds across their menstrual cycles, both before they began using OCs and then again during the period of use. Participants' thresholds were significantly higher after beginning a pill regimen. Before beginning use of OCs, the women showed fluctuations in sensitivity to the olfactory stimuli across their menstrual cycles—becoming more sensitive to many of the olfactory stimuli during the periovulatory and follicular phases of their cycles, as compared to the luteal phases. However, when on OCs, the women's thresholds rose to luteal phase levels, and remained at these levels throughout the months. It is presumed that the steroid hormones of the pill are responsible for the women's decreased olfactory sensitivity; however, the specific mechanism underlying these effects remains unclear. One possibility is that because thresholds rise to luteal phase levels, and the luteal phase of the cycle is characterized by heightened levels of progesterone, it is the progestin in the pill driving these effects ([Caruso et al., 2001](#)). It is also possible that the decrease in sensitivity is due to the decrease in estradiol in OC users, as NC women experience increases in estradiol throughout the follicular phase, and a sharp increase in estradiol just preceding ovulation, both of which are absent in OC users ([Cohen and Katz, 1979](#); [Elkind-Hirsch et al., 1992](#)).

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Hormonal modulation of olfaction has previously been evidenced in work focusing on sex differences in olfactory ability and in research examining changes in women's olfactory sensitivity across the menstrual cycle. The majority of research that has reported sex differences in olfactory sensitivity has shown that, compared to men, women are more sensitive to a range of odors and have greater accuracy in odor-identification (for review, see Doty and Cameron, 2009). However, there are disparities in the literature, where some have failed to find sex differences in sensitivity. This is similarly the case with olfactory fluctuations across the menstrual cycle. Although many studies have reported that women become more sensitive to odors during the ovulatory phases of their cycles, this does not appear to hold true for all odors. It has been suggested that these inconsistent findings are due to the nature of the odors used in the studies (for discussion, see Doty and Cameron, 2009). Whereas, for example, significant sex differences and menstrual phase differences have been found for sensitivity to citral, anise, Exalotide (musk), and coumarin, no differences have been found in regard to safrol, n-butanol, amyl-acetate (banana), and eucalyptus (Caruso et al., 2001; Le Magnen, 1952; Mair et al., 1978; Navarrete-Palacios et al., 2003; Oberg et al., 2002).

Lundstrom et al. (2006) provided data indicating that hormones may have differential effects on olfactory sensitivity, dependent upon the reproductive significance of the odor. Specifically, they showed women in the periovulatory phase of their cycles to be more sensitive to androstadienone, a social odor, than to phenyl-ethyl alcohol (PEA—the scent of roses); whereas women on OCs were more sensitive to PEA, an environmental odor, than the social odor. The authors suggest that these differences in olfactory sensitivity may be explained by differences in the hormonal profiles of the women, as women taking OCs do not ovulate, and thus increased sensitivity to odors of potential mates would not prove beneficial. However, this was a cross-sectional study, and NC women's time of ovulation was estimated, not directly measured via blood or urine analyses; therefore, more precise evaluation of this hypothesis is warranted.

The present study sought to further explore hormonal influences on odor sensitivity, and tested the claims that women taking OCs would have decreased olfactory sensitivity to a range of odors compared to NC women. The study also explored whether the discrepancies between these two groups of women would be particularly prominent during the periovulatory phase, when we predicted NC women would show increased sensitivity to these odors, whereas the women on OCs would maintain relatively stable olfactory thresholds throughout the month.

Method

Participants

Thirty-six participants (ages 18–22) were recruited for the present study: eighteen NC women and eighteen women taking a monophasic, combination (ethinyl estradiol and progestin) OC pill (see Table 1 for a comprehensive list of OCs used by participants). The NC women had either never taken OCs or had stopped taking OCs at least 3 months prior to the study. Similarly, women taking OCs had been doing so for at least 3 months prior to the first lab visit. Participants were recruited from a small Midwestern college via campus-wide email and direct approach. All participants were monetarily compensated (\$15 for NC women, \$10 for women taking OCs) at the conclusion of their second visit to the lab. Two NC women and one woman taking OCs were later excluded from analyses. One NC woman and one woman taking OCs were excluded because they were unable to come into lab for the second olfactory assessment; the second NC woman's data were later excluded because she had nasal congestion at the time of the olfactory assessment.

Table 1

Comprehensive list of the brand names of the oral contraceptives (OCs) used by women in the study ($n = 17$). Manufacturer and dosage of the OC are provided in parentheses.

Oral contraceptive brand name and dosage	Number of participants
Yaz (Bayer)/Gianvi (generic, Teva Pharmaceuticals) (3 mg of drospirenone and 0.02 mg of ethinyl estradiol)	6
Loestrin 24Fe (Warner Chilcott) (1 mg of norethindrone acetate and 0.02 mg of ethinyl estradiol)	4
Microgestin 1.5/30 (Watson Pharmaceuticals, Inc.) (1.5 mg of norethindrone/0.03 mg of ethinyl estradiol)	2
Levora (Watson Pharmaceuticals, Inc.) (0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol)	1
Sronyx (Watson Pharmaceuticals, Inc.) (0.1 mg of levonorgestrel and 0.02 mg of ethinyl estradiol)	1
Yasmin (Bayer) (3 mg of drospirenone and 0.03 mg of ethinyl estradiol)	1
Necon 1/35 (Watson Pharmaceuticals, Inc.) (1 mg of norethindrone and 0.035 mg of ethinyl estradiol)	1
Desogen (Merck & Co., Inc.) (0.15 mg of desogestrel and 0.03 mg of ethinyl estradiol)	1

Materials

Time of ovulation for NC women was determined with Answer Quick & Simple One-Step Ovulation Tests (Church & Dwight Co., Inc., Princeton, NJ, USA). Each ovulation test kit contained seven test sticks with luteinizing hormone (LH) antibodies designed to detect the LH surge that occurs approximately 24–36 hours before ovulation. According to the manufacturer, these tests have a 98% accuracy at detecting the LH surge, and thus at predicting ovulation. During each laboratory session, olfactory thresholds were determined for four general odors: lemon (McCormick Pure Lemon Extract, McCormick & Co., Inc. Hunt Valley, MD, USA), peppermint (Tone's Imitation Peppermint flavor, ACH Food Companies, Inc. Memphis, TN, USA), rose (Rose Water, Nielson-Massey Vanilla's, Inc. Waukegan, IL, USA), and musk (Mystic Memories' Witch Fae Perfume Oil with Genuine Amethyst, Mayfield Heights, OH, USA) odorants, as well as 5 α -androst-16-en-3-one (androst-16-en-3-one), an androgen metabolite found in male bodily secretions (i.e. axillary secretions, urine, etc.), and androsterone, another androgen metabolite (Applied Pheromones Research, Laguna Niguel, CA, USA).

Procedure

All participants signed a consent form approved by the local Institutional Review Board (IRB). NC women were asked to provide the date of onset of their previous menstrual cycle, as well as an estimate of their average length of cycle. Their range of possible ovulatory days was calculated, using date charts that were included with each ovulation kit. Approximately 4 days prior to their expected ovulation date, women were asked to begin taking urinary LH tests each morning. Once participants received a positive result, indicating an LH surge, they were asked to come into the lab within the following 24–48 hours (at expected time of ovulation). LH results were all self-report and not directly observed by the experimenter, thus we cannot rule out that women misrepresented or misinterpreted the results of the tests. At the conclusion of the first lab visit, each woman was asked to come into the lab for the second olfactory assessment approximately 1 week later (the luteal testing phase).

Women taking OCs provided the start date of their last pill pack, the brand name of their OCs, and the number of inactive pills included in their pill-pack. Women taking OCs were asked to come into the lab at similar temporal intervals to those of NC women; for convenience, we refer to these intervals as periovulatory and luteal, although these women were not cycling. Thus, their first olfactory assessment was approximately 7–11 days after beginning a pill-pack ("periovulatory"), and their second assessment was approximately 1 week following their first (approx. day 14–17 of the pill-pack). Previous studies

have tested women taking OCs using a similar temporal testing sequence (e.g. Caruso et al., 2001).

Olfactory thresholds were determined by way of a forced-choice discrimination task, a commonly employed method for determining olfactory thresholds (adapted from Hummel et al., 1997, 2005). Lemon, peppermint, rose and musk were each diluted in a geometric series (ratio of 1:2) of ten dilutions and placed into vials in an ascending staircase (0.2375 μL –0.125 mL) (adapted from Chopra et al., 2008; Hummel et al., 1997). Androstene and androsterone were also diluted in a geometric series (ratio 1:10), into seven dilutions (0.1 μM –10 mM) (Knecht et al., 2003). Beginning with the lowest concentration, subjects were presented with three vials: two containing the solvent that the odor was dissolved in (water for lemon, peppermint, and rose; odorless safflower oil for musk, androstene, and androsterone), and a third vial containing the odor, diluted in its respective solvent.

The three vials were presented in random order to the participant, who was asked to report which of the three vials (1st, 2nd, or 3rd) she believed to smell the most different from the other two. As the presentation of the triplets continued, the concentration of the odor increased with each set presented until the subject correctly identified the vial containing the odorant. Following an initial correct response, the concentration was raised one more step to the next triplet. Two consecutive correct responses triggered a reversal, and the previous triplets were then presented in a descending staircase. When the participant again correctly identified the vial containing the odorant during the reversal, this concentration level was recorded as the participant's threshold for that odor. If participants correctly identified an odor in two consecutive concentration presentations but then did not correctly identify the vial containing the odorant in the reversal, the concentration was increased until correctly identified once more, and at this point another reversal would begin. During data entry, the two consecutive threshold amounts correctly identified were averaged with the concentration that was correctly identified twice (in the initial presentation and in the reversal).

This procedure was repeated for each odor. Once the threshold was obtained for an odor, the participant was asked to label the scent and to provide an affective rating (pleasant, unpleasant, or neutral). In order to attempt to control for habituation and, in some cases, possible sensitization, participants were asked to smell coffee beans after each completed odor presentation. The following responses were accepted as "correct" for the odor-labeling task: lemon (lemon, citrus), peppermint (peppermint, mint), rose (rose, floral, flowers), and musk (musk, musky odor). Subjects were requested to provide labels for androstene and androsterone, so as not to indicate that these odors were unique; however, as there are no "correct" or "incorrect" responses, these data were not included in analyses.

The same procedure was repeated for the second assessment of thresholds; however, the order of general odor presentation was randomized in the second assessment, in order to control for memory effects. A number of participants did not correctly identify the odorant-containing vial in the first or second trial for androstene and androsterone. Thus, in order to ensure that participants were not anosmic, at the conclusion of the second trial the participant was presented with these odorants in increased concentrations (androstene: 0.42 g; androsterone: 0.57 g). No participants were deemed anosmic to either odor. For data entry, these participants' thresholds were entered as 100 mM, which would have been the next concentration step in the geometric series, following 10 mM. All procedures were done in accordance with a procedure approved by the local IRB.

Results

Olfactory sensitivity

2 \times 2 (cycle phase [periovulatory vs. luteal] \times OC status [NC vs. using OCs]) mixed factor analyses of variances (ANOVAs) were

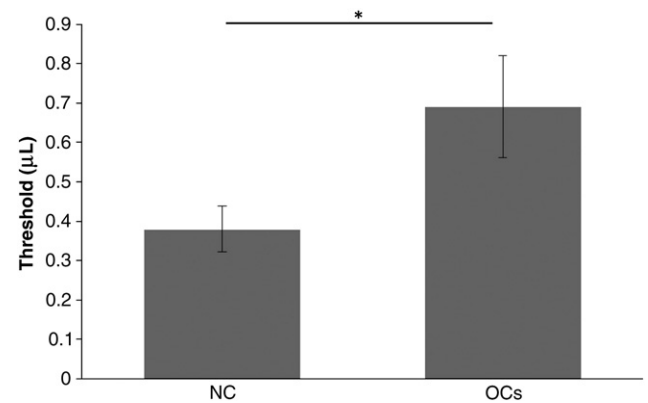


Fig. 1. Mean detection thresholds (\pm SE) for musk for naturally cycling (NC) women ($n=16$) and women taking oral contraceptives (OCs) ($n=17$). NC women were more sensitive to musk than women taking OCs ($*p<0.05$, $\eta_p^2=0.13$).

conducted to assess differences in olfactory thresholds for lemon, peppermint, musk, and rose. Of the four odors assessed, significant effects of OC use or cycle phase were found only for musk. No significant effects were found when analyzing data for sensitivity to lemon, peppermint, or rose ($p>0.05$ for all main effects and interactions).

Sensitivity to musk was affected by OC status, $F(1,31)=4.62$, $p=0.04$, $\eta_p^2=0.13$ (Fig. 1), such that NC women were significantly more sensitive to musk than women who were taking OCs. Although there was not a significant interaction between OC status and cycle phase, follow-up t -tests were performed on an *a priori* basis. Follow-up t -tests revealed NC women in the periovulatory phase were significantly more sensitive to musk than women on OCs, $t(31)=-2.06$, $p=0.048$, $d=0.70$, and a medium effect for NC women to maintain this increased sensitivity in the luteal phase was revealed, but this effect did not reach significance, $t(31)=-1.74$, $p=0.092$, $d=0.60$.

Social odor perception

2 \times 2 (cycle phase \times OC status) mixed factor ANOVAs were performed on data for androstene and androsterone sensitivity. Significant main effects for OC status, $F(1, 31)=8.07$, $p=0.008$, $\eta_p^2=0.21$ and cycle phase, $F(1, 31)=6.00$, $p=0.02$, $\eta_p^2=.16$ were found for sensitivity to androstene. Although there was not a significant interaction between OC status and cycle phase, follow-up t -tests were performed on an *a priori* basis. As displayed in Fig. 2, follow-up planned comparisons showed NC women in the periovulatory phase were significantly more sensitive to the odor than women taking OCs, $t(31)=-3.00$, $p=0.005$, $d=1.05$; additionally, a medium effect for NC women to maintain this increased sensitivity in the luteal phase was revealed, but this effect did not reach significance, $t(31)=-1.93$, $p=0.062$, $d=0.67$. Paired t -tests revealed that NC women became significantly less sensitive to androstene in the luteal phase of their cycles, $t(15)=-2.36$, $p=0.032$, $d=0.64$; women taking OCs did not significantly differ in sensitivity across their cycles, $t(16)=-1.22$, $p=0.239$, $d=0.31$.

A medium-large effect of OC status was found for sensitivity to androsterone, although the effect did not reach significance, $F(1, 31)=4.01$, $p=0.054$, $\eta_p^2=0.12$. Follow-up planned comparisons revealed that NC women were significantly more sensitive to androsterone during the periovulatory phase, $t(31)=-2.28$, $p=0.029$, $d=0.81$; however, there was no significant difference in thresholds between NC women and women taking OCs found in the luteal phase, $t(31)=-0.543$, $p=0.591$, $d=0.19$ (Fig. 3).

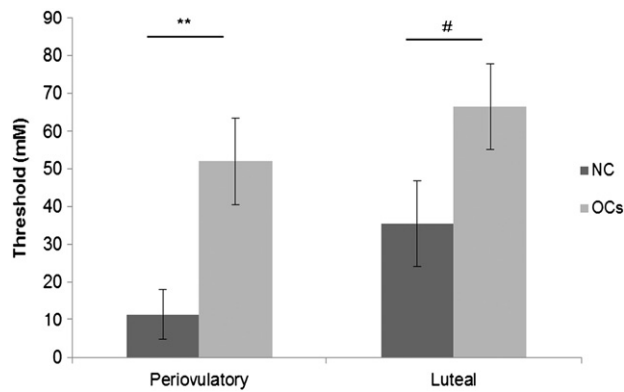


Fig. 2. Mean detection thresholds (\pm SE) for androstenone for naturally cycling (NC) women ($n=16$) and women taking oral contraceptives (OCs) ($n=17$). NC women in the perioovulatory phase were more sensitive to androstenone than women taking OCs ($**p<0.01$, $d=1.05$). There was a moderate effect for NC women in the luteal phase to be more sensitive to androstenone than women taking OCs, but it did not reach statistical significance ($#p<0.1$, $d=0.67$).

Odor labeling

Chi-square tests were conducted to assess differences in labeling accuracy of lemon, peppermint, rose, and musk between NC women and women taking OCs. No significant differences in accuracy of label were revealed for lemon, rose, musk, or peppermint during the luteal phase. However there was a significant difference in accuracy of label for the peppermint odor, $\chi^2(1, 32)=4.63$, $p=0.042$, with more NC women giving an incorrect label during the perioovulatory phase. No other differences in labeling were found during the perioovulatory phase.

Affective ratings

Chi-square tests were conducted to assess differences in affective ratings (pleasant, neutral, unpleasant) of all odors between NC women and women taking OCs.

No significant differences were revealed in affective ratings of lemon, rose, musk, or androsterone. Analyses showed significantly more NC women in the perioovulatory phase to rate peppermint as unpleasant, $\chi^2(2, 32)=7.26$, $p=0.026$. Additionally, more women taking OCs rated androstenone as unpleasant, whereas more NC women in the luteal phase rated the odor as neutral, $\chi^2(2, 26)=7.07$, $p=0.029$.

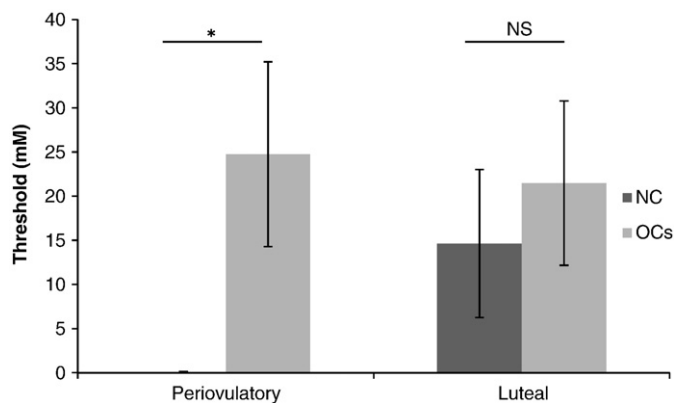


Fig. 3. Mean detection thresholds (\pm SE) for androsterone for naturally cycling (NC) women ($n=16$) and women taking oral contraceptives (OCs) ($n=17$). NC women in the perioovulatory phase were more sensitive to androsterone than women taking OCs ($*p<0.05$, $d=0.81$). NC women in the luteal phase were not more sensitive to androsterone than women taking OCs ($p=0.59$, $d=0.19$).

Discussion

The present study showed NC women to be significantly more sensitive to a musk odorant and to androstenone and androsterone than women who were taking OCs. Follow-up analyses revealed the differences between these two groups of women to be more pronounced during the perioovulatory phase of the NC women's cycles, as the differences between groups did not reach statistical significance in the luteal phase of the women's cycles. Although the luteal phase was always the second olfactory assessment, and thus the participant's second exposure to these odors, it is unlikely that the observed decrease in sensitivity would be due to habituation effects, as similar results with the putative pheromone androstadienone have been found previously in a cross-sectional study (Lundstrom et al., 2006). Further, it has been shown that rather than habituation, sensitization occurs with repeated exposure to androstenone (Wysocki et al., 1989).

Le Magnen (1952) found that women were significantly more sensitive than men to the musk-like odor, exalotide, as well as to the smell of testosterone; he proposed that he found these similarities in perception to these two odors because musk closely resembles sex hormones (as discussed in Doty and Cameron, 2009). Indeed, musk has similar odorous qualities to the scents naturally secreted by men, and thus it is not surprising that similar sensitivity patterns were found between it and the two androgen-metabolites, androstenone and androsterone, used in the study.

Hormonal state did not affect sensitivity to lemon, peppermint, or rose. These results corroborate previous studies, which suggest that hormonal modulation of olfactory sensitivity is dependent upon the nature of the specific odorant (Mair et al., 1978; for review, see Doty and Cameron, 2009).

No uniform patterns were found in regards to affective ratings and labeling of the odors. More NC women in the perioovulatory phase rated peppermint as unpleasant and more women taking OCs rated androstenone as unpleasant in the luteal testing time; however, overall, the odors were rated as pleasant/neutral, with very few of the participants rating any of them as unpleasant. This is most likely due to the odors being presented in such low concentrations. There was additionally no pattern revealed in labeling accuracy of the odors.

Interestingly, for many of the odors, women taking OCs' olfactory sensitivity decreased from the first session compared to second, which could account for why analyses did not reveal significant interactions between OC status and cycle phase. The present data are not the first to suggest that women taking OCs may have olfactory fluctuations similar to those of NC women (Doty et al., 1981). Though these results may initially appear to contradict the proposed mechanism of hormonal modulation of olfactory sensitivity, this is not necessarily the case. These fluctuations could indeed be due to the direct impact of the exogenous hormones on olfactory function, or due to a secondary physiological effect, such as an increase in body temperature, which has been linked to both OC use as well as olfactory fluctuations. Neither of these possibilities would discount the suggested underlying mechanism of circulating ovarian steroids modulating olfaction (as discussed in Doty and Cameron, 2009). Further, although women taking monophasic OCs are assumed to maintain stable hormone levels throughout the month, dosage effects have been reported, such that women may not have steady levels of the progestins and estrogens in their blood until after many days of OC usage. For example, for both Yaz® and LoEstrin® 24 Fe, the two most commonly used OCs in the present study, it has been reported that steady-states of estrogens and progestins are not reached until approximately halfway through the pill cycle. Therefore, in these cases, women have a much lower serum concentration of the progestins and estrogens in their blood the first week of use as compared to the last week of use (Bayer HealthCare Pharmaceuticals Inc., 2012; Warner Chilcott, 2009).

A possible secondary explanation for why significant interactions between cycle phase and OC usage were not found is that NC

women were not only more sensitive to the odors than the OC women in the periovulatory phases, but also (although not significantly) in the luteal phases of their cycles. Again, this effect does not preclude the proposed mechanism of circulating ovarian steroids modulating the women's olfactory sensitivity. For example, although it is difficult to directly compare progestational activity in NC women and women taking OCs, it is possible, due to the levels of progestins that OCs induce in the blood, and the relative binding affinity of these progestins for the progesterone receptor, that the women taking OCs are exposed to greater progestational activity than NC women (Bayer HealthCare Pharmaceuticals Inc., 2012; Sitruk-Ware, 2006; Warner Chilcott, 2009; as compared to Marsh et al., 2011 or Stricker et al., 2006). However, a study more directly assessing this matter would be necessary to make any direct claims regarding this hypothesis.

Implications

In the present study, hormonal status was found to only affect olfactory sensitivity to the social odors, musk, androsterone and androstenone. Thus, these results lend support to the notion of odor-specific ovarian hormonal modulation of olfaction.

A documented complaint among women taking OCs is a decrease in sexual desire (Battaglia et al., 2012; Caruso et al., 2004). A prospective study found that 14% of women switched OCs and 47% discontinued use within a 12-month period, with the best predictor for switching/discontinuation being adverse emotional/sexual side effects (Sanders et al., 2001). It has been reported that NC women have the greatest sexual motivation mid-cycle, around the time of ovulation (Adams et al., 1978; Harvey, 1987). This is presumed to be proximally due to hormonal changes that occur at this time, and distally due to evolutionarily beneficial reasons, as women are most likely to conceive in the ovulatory phase, and should therefore show more receptive and proceptive sexual behavior during this time (Gueguen, 2009). Others have shown that women prefer more masculine, symmetrical faces and prefer the scent of men with symmetrical faces around time of ovulation (Thornhill and Gangestad, 1999). NC women do not show this preference in the luteal phase of their cycles, and this preference is also not found amongst women taking OCs (Thornhill and Gangestad, 1999).

Previous work has found that women rate a man's scent as a particularly important factor in selecting a potential mate—of greater importance than a man's physical appearance and voice, as well as many other factors, such as how many friends he has or how much money he earns (Herz and Inzlicht, 2002). The present study provides support for the claim that OC use could impair general ability to perceive socially-relevant odors. These data prime the question of whether women's decreased ability to detect these odors is a contributing factor to reported decreased sexual desire among a portion of women taking OCs and/or if OC usage could have detrimental effects on partner preference.

Future studies should evaluate if the changes in olfactory sensitivity identified here are also seen in progestin-only pill users, in order to help elucidate which hormones are driving these effects. In addition, so as to more clearly evaluate if decreased perception of these odors could have behavioral implications, future research should attempt to replicate this work and enquire into participants' levels of sexual desire, examining the possibility of a correlation between these two domains.

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