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Olfactory processing and odor specificity: a meta-analysis of menstrual cycle variation in olfactory sensitivity

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Abstract: Cycle-correlated variation in olfactory threshold, with women becoming more sensitive to odors mid-cycle, is somewhat supported by the literature but the evidence is not entirely consistent, with several studies finding no, or mixed, effects. It has been argued that cyclic shifts in olfactory threshold might be limited to odors relevant to the mating context.

We aimed to test whether the evidence currently available points in the direction of odor-specific or, rather, general changes in olfactory sensitivity and, if the former is the case, to what group of odorants in particular. We carried out a meta-analysis of relevant studies which together used a variety of different odorants, including some found in food, body odor, and some that occur in neither of these. First we tested whether there appears to be an overall effect when all studies are included. Next, we hypothesised that if cyclic changes in olfactory processing are odor-specific and tuned to biologically relevant odors, we should find changes in detection thresholds only for odorants found in body odor, or for those that are perceptually similar to it. In contrast, if threshold patterns are linked to more general fluctuations in odor processing across the cycle, we would not expect changes in relation to any particular odorant group.

The results support the view that there is significant cycle-correlated variation. Thresholds were in general significantly lower in the fertile than the non-fertile phases, with effect sizes consistently in this direction. This same conclusion applied to both 'food' and 'musky' odorants, despite their different evolutionary significance, and to the androgen steroids (androstadienone, androstenone, and androsterone), but could not be applied to phenyl-ethyl alcohol.

The results indicate that olfactory sensitivity may be a non-adaptive by-product of the general physiological fluctuations or differences in neural processing experienced across the cycle to a broad spectrum of odorants, rather than being specifically selected for mate choice-related odors.

Key words: menstrual cycle, mate choice, odor threshold, human oestrus, olfaction

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Introduction

In recent years, researchers interested in the evolutionary underpinnings of human behaviour have recorded in women a variety of behavioural and perceptual changes associated with menstrual cycle phase (review in Gangestad and Thornhill 2008). The cyclic shifts in sensory perception seem to cut across sensory modalities (Doty et al. 1982; Dye 1992; Kuga et al. 1999) and may be linked to general physiological fluctuations or differences in neural processing experienced across the menstrual cycle. Doty and Cameron (2009) reviewed the ways through which such a general effect would be possible. They put forward the idea that cyclic changes may reflect fluctuations in hormones other than the primary ovarian steroids, suggesting the potential involvement of the corticotropic releasing hormone (CRH) – adrenocorticotropic hormone (ACTH) – adrenal axis. Alternatively, they propose that these shifts may be controlled by central nervous system centres or networks such as those that control various other rhythms (e.g. Rusak and Zucker 1979), for instance specific or non-specific effects of neurotransmitters or other neuroactive substances that fluctuate on a monthly basis.

Of the various sensory modalities, among the most hotly debated is cyclic variation in olfactory thresholds for both social (i.e. human body odor-related) and non-social odors (review in Doty and Cameron 2009). The suggestion that olfactory detection thresholds vary across the menstrual cycle was first reported over 50 years ago (Le Magnen 1952). In one study, he measured thresholds for pentadecalactone (Exaltolide) across ten menstrual cycles of five women with two – to three – day intervals. In general, he found an increase in sensitivity (decrease in odor threshold) in all cycles following menstruation but, at the same time, the individual cycles varied considerably in the timing and magnitude of this increase. For instance, while in some cases sensitivity peaked shortly after menstruation, in others it took longer. Moreover, he also noted a second peak in sensitivity during the late luteal phase in three cases. However, no such changes in sensitivity to safrole, guaiacol, amyl salicylate, or pyridine were noted in a smaller number of tested women, except for a mixture of cholesterol and testosterone. Hence, it would seem that menstrual cycle-related changes in olfactory sensitivity would pertain exclusively to musky-smelling odorants, suggesting that they might be of special ecological significance to humans.

In contrast to the findings of Le Magnen (1952), Mair et al. (1978), who employed a signal detection paradigm, reported women's better performance during ovulation compared to menstruation for pentadecalactone (Exaltolide) as well as for coumarin and cinnamyl butyrate (but not amyl acetate). Other researchers have also noted significant cyclic variation in sensitivity not only to pentadecalactone (Good et al. 1976; Vierling and Rock 1967), but also to other musk-smelling odorants, such as 5α-androst-16-en-3-one (androstenone; e.g. Renfro and Hoffmann 2013; Sueda et al. 2003) or musk-ketone (Caruso et al. 2001), as well as those that are not considered to be of biological relevance to humans, such as ammonia, anise essence, citral, eugenol (clove odor), furfural, or pyridine (e.g. Caruso et al. 2001; Doty et al. 1981). Navarrete-Palacios et al. (2003) also reported menstrual cycle-related fluctuations in amyl acetate thresh-

olds, contrary to the findings of Mair et al. (1978). On the other hand, some researchers have not found any significant changes in sensitivity to androstenone, citral, pure lemon extract, n-butanol, nicotine, pure peppermint extract, phenylethyl alcohol, or rose water (Hummel et al. 1991; McNeil et al. 2013; Pause et al. 1996; Renfro and Hoffmann 2013).

A major contribution to the debate comes from Doty et al. (1981), who, employing a signal detection paradigm, tested odor detection performance for furfural every other day across 2 consecutive menstrual cycles of both oral contraceptive non-users and users. Furthermore, concomitant measures of body temperature, blood pressure, heart rate, nasal airflow, and respiration rate were also taken as well as levels of estradiol, estrone, follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, and testosterone. To handle problems related to averaging data across menstrual cycles of different lengths, the authors used a procedure devised by Doty (1979). They found three peaks in average olfactory sensitivity: in the middle of the cycle (around ovulation), in the middle of the luteal phase, and in the second half of the menstrual phase. Remarkably, these fluctuations were observed in both oral contraceptive non-users and users, suggesting that there may not be a causal relationship between levels of gonadal hormones and hypophyseal gonadotropins and olfactory thresholds but, rather, a correlation.

In a subsequent study, Doty et al. (1982) aimed to test whether similar shifts in olfactory sensitivity could be found for phenylethyl alcohol in one oral contraceptive user across two menstrual cycles, along with shifts in auditory thresholds. Of the variables relevant to the present topic, measures of odor detection performance, body temperature, heart rate, plasma FSH, LH, progesterone, and total estrogens were taken twice a day. Most notably, they observed a positive correlation between body temperature and olfactory sensitivity.

Thus, cycle-correlated variation in olfactory threshold, with women becoming more sensitive to odors mid-cycle, is somewhat supported by the literature but the evidence is not entirely consistent, with several studies finding no, or mixed, effects. A major question that arises is whether the evidence currently available points in the direction of odor-specific or, rather, general changes in olfactory sensitivity. Furthermore, if the former is the case, what group(s) of odorants in particular are affected? For example, might increased mid-cycle sensitivity be specific to musky-smelling odorants and the androstenes, which may possess biological relevance through an influence on mate choice? Consistent with this idea, Lundström et al. (2005) found that menstrual cycle stage influenced sensitivity to a biologically-relevant odorant androsta-4,16,-dien-3-one (androstadienone), but not to phenylethyl alcohol (PEA, rose odor). Similarly, Renfro and Hoffmann (2013) reported cyclic variation in sensitivity to androstenone and 3α-hydroxy-5α-androstan-17-one (androsterone), but not to pure lemon or peppermint extract, or rose water.

Here we aimed to further test whether the menstrual cycle influences odor sensitivity and, if so, whether the extent of such changes might be predicted by the biological significance of the odorants used. To do this, we carried out a meta-analysis of relevant studies which together used a variety of different odorants, including some found in food,

some found in body odor, and some that occur in neither of these. First we tested whether there appears to be an overall effect when all studies are included. Next, we hypothesised that if cyclic changes in olfactory processing are odor-specific and tuned to biologically relevant odors, we should find changes in detection thresholds only for odorants found in body odor, or for those that are perceptually similar to it. In contrast, if threshold patterns are linked to more general fluctuations in odor processing across the cycle (cf. Becker et al. 1982), we would not expect changes in relation to any particular odorant group.

Materials and Methods

We carried out a literature search (using the search engine Google Scholar) with the two search terms "olfactory threshold" and "menstrual cycle", then sifted through the results for relevant and suitable studies. The requirements for inclusion into the meta-analysis were that a study had measured olfactory thresholds with the menstrual cycle phase as a time variable, and reported (a) an effect statistic or (b) an effect for which a statistic could be calculated from the findings (based on this criterion, we have not included the study by Grillo et al. (2001); however, this study reported lower periovulatory thresholds for a number of odorants consistent with the pattern of results obtained in this meta-analysis, thus exclusion of this study should not have altered our conclusions). For the same reason, we could only include results for androstenone and androsterone from the study by Renfro and Hoffmann (2013). All the studies have been published in peer-reviewed scientific journals. All were reported in English with the exception of Sueda et al. (2003), which was translated from Japanese. Data from a total of thirteen independent studies were included in the analysis (274 females). In two studies that used both a within-subject and a between-subject design (Navarrete-Palacios et al. 2003; Renfro and Hoffmann 2013), we chose to use data from the within-subject design because this better controls for possible confounding variables related to interindividual differences in olfactory processing.

A summary of the studies included in the meta-analyses, giving details on the odorants used, concentrations, perceived quality, volatility (as defined by vapor pressure) sample sizes, the techniques used to estimate olfactory thresholds, and the frequency and timing of measurements taken, is shown in Table 1. Although there is some variability in technique, more than half of the studies used some form of staircase forced – choice technique without feedback, now a standard practice in olfactory psychophysical testing (Keller and Vosshall 2004).

We conducted two initial fixed-effect meta-analyses to determine whether: (1) there is variation in thresholds across the cycle (including all studies), and (2) differences occurred specifically between fertile and non-fertile cycle phases. Where appropriate, we here condensed the effects of several odorants used in single studies by averaging the respective effect sizes (Schmidt 1990). Next, we compared whether changes occurred across the cycle in studies that included: (3) odors associated with foods (namely pure anise essence, amyl acetate, citral, eugenol, cinnamyl butyrate, coumarin, vanillin, and n-butanol), (4a) odors that smell musky (namely androstadienone, androstenone, musk ketone, pentadecalactone) and (4b) musky odors excluding

Table 1. Summary of studies included in the meta-analysis

Table gives details of odorants used, the subset in which they have been included for the purposes of the meta-analysis, concentration(s) used, perceived quality irrespective of concentration, volatility as defined by vapor pressure (if known or applicable), sample sizes (N), olfactory threshold techniques employed and frequency and timing of measurements taken. The quality descriptions have been taken from Burdock (2009) and vapor pressure data from the publicly accessible PubChem Project Database (NCBI 2014), unless stated otherwise. Higher values of vapor pressure indicate a tendency of a substance to vaporize more readily and odorants with a vapor pressure greater than 0.1 mm Hg at 25°C are considered volatile (Vo and Morris 2014). †Number of participants and analyses actually used in the meta-analysis.

Study	Odorant(s) (subset)	Concentration(s)	Perceived quality	Vapor pressure [mm Hg] at 25°C	N	Threshold technique	Schedule
(1) Amoore et al. (1975)	Pentadecalactone (Exaltolide) (musky)	Binary dilution steps, each step being half the concentration of the step before. Starting from step 0 for the saturated solution (1.1 ppm, w/v), steps 4–16 were tested.	Extraordinarily persistent, musk-like odor	$2.61*10^{-5}$ (Bedoukian 2014)	22 (total) 9 complete data (3 + 6 hormonal contraceptive non- + users)†	3AFC (Whissell-Buechy and Amoore 1973). Done twice at each dilution step. Threshold: highest consecutive dilution correctly chosen. No feedback.	19 subsequent days within 1 month (excluding weekends) Data divided for statistical analysis into 7 four-day intervals: menstrual, early/late follicular, ovulatory, early, mid-, and late luteal
(2) Caruso et al. (2001)	Ammonia	Liquid diluted to 22% in distilled water		$7.51*10^{3}$ (volatile)	60	Rhinomanometry and olfactometry. Threshold: smallest volume of air at which odor is perceived.	3 measures: follicular (day 5–8), periovular (13–16), luteal (18–23)
	Pure anise essence (food)	Undiluted					
	Citral (food)	Undiluted	Strong, lemon-like odor	$9.13*10^{-2}$			
	Pure clove essence (food)	Undiluted					
	Musk-ketone (musky)	Undiluted	Fine, warm, light, sweet musky odor, closest to natural musks (Bedoukian 1986:301–303)	$5.84*10^{-7}$			
	Pyridine	Pure liquid substance	Characteristic, penetrating odor	20.8 (volatile)			

Table 1. cont.

Study	Odorant(s) (subset)	Concentration(s)	Perceived quality	Vapor pressure [mm Hg] at 25°C	N	Threshold technique	Schedule
(3) Doty et al. (1981)	Furfural	Custom-prepared for each individual and detectable 55% – 75% of the time during pilot trials. Range between $7.23*10^{-6}$ and $7.35*10^{-5}$ v/v.	Quality rarely recognised at concentrations employed here (below recognition threshold) (Arctander 1969)	2.21 (volatile)	9	Signal detection paradigm, 350 trials (175 blank). On a given trial diluent (blank) presented first, followed either by diluent or odorant. Rate confidence in whether an odorant presented. Feedback given.	Measures taken repeatedly every other day across 2 consecutive menstrual cycles.
(4) Good et al. (1976)	Pentadecalactone (Exaltolide) (musky)		See above		3	Signal detection paradigm:100 trials (50 blank); report if stimulus is odorant or blank. Feedback given.	2 measures: mid-cycle, menses
(5) Hummel et al. (1991)	Androstenone (musky)	Dilutions prepared successively by adding 40 ml of propylene glycol (double-distilled water for nicotine) to 40 ml of the preceding solution. Maximum concentrations: 1.44 mmol/l (androstenone), 4130 mmol/l (PEA), 151 mmol/l (nicotine)	Sweaty, urinous; sweet, floral; odorless (Bremner et al. 2003; Gower et al. 1998; Wysocki and Beauchamp 1984)		14	Ascending staircase (Wysocki and Beauchamp 1984), 3AFC, concentrations increase until 3 correctly discerned in succession, lowest is noted. Repeated. Threshold: mean of 2 lowest concentrations. No feedback.	Cycle split into 5 phases (two preovulatory, ovulatory, two postovulatory)
	Nicotine			$3.8*10^{-2}$			
	Phenylethyl Alcohol (PEA)		Characteristic rose-like odor	$8.68*10^{-2}$			
(6) Lundström et al. (2005)	Androstadienone (musky)	Geometric series dilutions in propylene glycol ranging from 0.091 μM (dilution 16) to 3000 μM (dilution 1)	Putrid, sweaty, urinous (Jacob et al. 2006)		22	Ascending staircase, 3AFC, concentrations increase until 2 correctly discerned in succession, triggering a reversal. 7 reversals. Threshold: mean of concentrations at the last 4 reversals. No feedback. (Hummel et al. 1997)	2 measures: fertile, non-fertile
	Phenylethyl Alcohol (PEA)	Geometric series dilutions in propylene glycol ranging from 16.3 μM (dilution 16) to 0.54 M (dilution 1)	See above	See above			

Table 1. cont.

Study	Odorant(s) (subset)	Concentration(s)	Perceived quality	Vapor pressure [mm Hg] at 25°C	N	Threshold technique	Schedule
(7) Mair et al. (1978)	Amyl acetate (AA) (food)	Dilution in dibutyl phthalate, 0.038 mM	Fruity, banana, sweet, fragrant, powerful odor	3.5 (volatile)	12 (all with Exaltolide; 6 with AA, 6 with coumarin and CB)	Signal detection paradigm: 60 trials (30 blank), report if stimulus was odorant or blank. Feedback given.	2 measures: ovulation, menses For Exaltolide, individuals tested on up to 3 successive days around ovulation until a clear increase in sensitivity observed.
	Cinnamyl butyrate (CB) (food)	Dilution in dibutyl phthalate, 0.78 mM	Fruity, slightly floral odor	$1*10^{-3}$			
	Coumarin (food)	Dilution in dibutyl phthalate, 0.96 mM	Sweet, fresh, hay-like odor similar to vanilla seeds	$9.8*10^{-4}$			
	Pentadecalactone (Exaltolide) (musky)	Dilution in dibutyl phthalate, 1.6 mM	See above	$2.61*10^{-5}$ (Bedoukian 2014)			
(8) McNeil et al. (2013)	N-butanol (food)	16 geometric series dilutions (Hummel et al. 1997)	Fusel- or banana-like sweet odor	7.0 (volatile)	17	Ascending staircase, 3AFC, concentrations increase until 2 correctly discerned in succession, triggering a reversal. 7 reversals. Threshold: mean of concentrations at the last 4 reversals. No feedback. (Hummel et al. 1997)	3 measures: early follicular – menstruation (days 1–5), late follicular – ovulation (days 11–14), mid-luteal (days 21–26); tailored to individual cycle length
(9) Navarrete-Palacios et al. (2003)	Amyl acetate (food)	Series of 8 half log concentrations, ranging from −log 9.5 to −log 6.0	See above	See above	15	Staircase, 4AFC, 2 odorants, 2 blanks. No feedback.	4 measures: menses, follicular, ovulatory, luteal
(10) Pause et al. (1996)	Citral (food)	Series of 14 half decimal log steps (diluted in diethyl phthalate), maximum: 1:2 (v/v) dilution, minimum: 1:6 300 000 (v/v).	See above	See above	5	Staircase, 3AFC. Threshold: lowest of 2 consecutive concentrations for which 4 successive correct identifications occurred. No feedback.	3 measures: follicular, ovulatory, luteal

Table 1. cont.

Study	Odorant(s) (subset)	Concentration(s)	Perceived quality	Vapor pressure [mm Hg] at 25°C	N	Threshold technique	Schedule
(11) Renfro and Hoffmann (2013)	Androstenone Androsterone	7 geometric series dilutions in safflower oil (ratio 1:10), ranging from 0.1 μM to 10 mM	See above Fruity (grapey), camphoraceous or aromatic, urine-like, musky or odorless (De Rovira 2008:542)	See above $2.79 * 10^{-8}$ (Raghava 2011)	16	Staircase, 3 AFC. Concentrations increase until correctly identified, then the next higher one presented. If again correct, reversed. If again correct at reversal, taken as threshold. If incorrect at reversal, increase until correctly identified. Reversed. Threshold: average consecutive correct identifications and reversal.	2 measures: perio-vulatory, luteal (approximately one week after first visit)
(12) Sueda et al. (2003)	Androstenone (musky)		See above		19	Staircase, 3AFC (3-way forced choice; no feedback)	4 measures: menses, follicular, ovulatory, luteal
	Phenylethyl Alcohol		See above	See above			
	Vanillin (food)		Characteristic, creamy, vanilla-like odor	$1.18*10^{-4}$			
(13) Vierling and Rock (1967)	Pentadecalactone (Exaltolide) (musky)	Stock solution of 1 mg of Exaltolide in 10 ml absolute ethanol diluted with distilled water to yield 5 dilutions containing 10^{-3} (1), 10^{-5}, 10^{-7}, 10^{-9}, 10^{-11} mg of Exaltolide per ml of water	See above	$2.61*10^{-5}$ (Bedoukian 2014)	73	9 flasks with 5 ascending concentrations (5–1), 4 blanks; after smelling each report if stimulus was odorant or blank. Threshold: individual scored 1–5 according to concentration detected.	2–4 times, arbitrary days in cycle

the androstenes, i.e. musky odors that are not found in human body odor. Finally, we assessed the specific effects on thresholds for (5) PEA, and (6) the androstenes, since these were each used in several studies.

We calculated effect sizes (*r*) for individual studies using transformations from Rosenthal and DiMatteo (2001). In cases where *p* values were reported in the absence of a test statistic, each *p* value was converted to its associated one-tailed standard normal deviate *Z*, and then to an effect size calculated using the formula $r=\sqrt{Z^2/N}$ (Rosenthal and DiMatteo 2001). Where a result was reported as not statistically significant, but it was not possible to calculate an effect size, we set an effect size at zero, which is considered a conservative procedure. For analyses 1–4, where single studies had tested more than one odorant, effect sizes were averaged within-study. Effect sizes for each study were weighted according to N-3 (Rosenthal and DiMatteo 2001). We estimated between-study heterogeneity by calculating values of *Q*, which follows a chi-square distribution with *k-1* degrees of freedom, where *k* is the number of studies (Wolf 1986), under the null hypothesis that all studies share a common effect size (Hedges and Olkin 1985). Rosenthal's failsafe N, the number of filed, new or unretrieved studies showing null effects which would be needed to produce an overall effect (Rosenthal 1991), was calculated as $N= (\Sigma Z)^2 /2.706 - k$ (where k=number of studies).

Results

Results of the individual analyses are shown in Table 2. Analysis 1 shows that detection thresholds are subject to variation in menstrual cycle phase, when combining all studies and across a wide range of odorants used in testing. Analysis 2 confirms that this variation holds when restricting studies to those that explicitly compare fertile and non-fertile cycle phases. Sensitivity to odorants is higher during the fertile phase than non-fertile

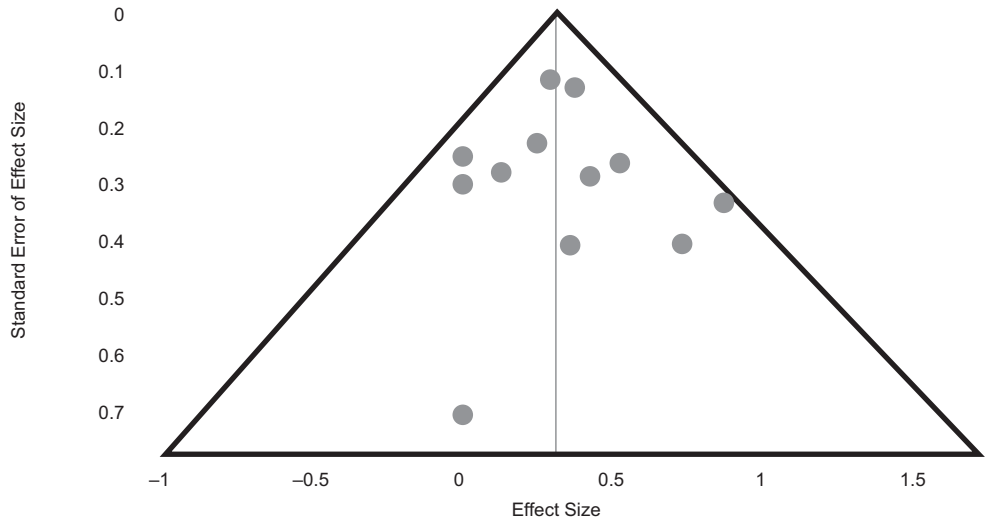

Fig. 1. Funnel plot for Analysis 1. Straight lines (inverted funnel) define a region within which 95% of points might lie in the absence of both heterogeneity and publication bias

Table 2. Summary of results of the individual meta-analyses
Mean ES ± SE denotes mean effect size estimate ± standard error, 95% CI is the 95% confidence interval for the mean ES, Z and p are the associated mean Fisher Z and its p-value, Q and critical Q refer to estimated between-study heterogeneity and its referential critical value, which should not be exceeded if variability across effect sizes is not to exceed what would be expected based on sampling error

Meta-analysis	Studies	N	Mean ES±SE	95% CI	Z	p	Q	Critical Q
1) Threshold change	1–13	13	0.316±0.07	0.188/0.444	4.84	<0.001	7.95	26.21
2) Fertile/non-fertile	2, 4–12	10	0.301±0.08	0.142/0.459	3.72	<0.001	6.45	21.67
3) Food	2, 7–10, 12	6	0.290±0.10	0.098/0.482	2.96	<0.01	4.28	15.09
4a) Musky including androstenes	1, 2, 4–7, 11–13	9	0.511±0.07	0.370/0.652	7.12	<0.001	18.64	20.09
4b) Musky excluding androstenes	1, 2, 4, 7, 13	5	0.582±0.09	0.414±0.750	6.79	<0.001	14.69	13.28
5) PEA	5, 6, 12	3	0.041±0.15	–0.248/0.330	0.28	<0.390	.11	5.99
6) Androstenes	5, 6, 11, 12	4	0.369±0.13	0.112/0.627	2.81	<.01	1.98	11.35

phases. We calculated Rosenthal's fail-safe *N* for these two analyses as 111.85 and 54.59, and by applying Rosenthal's criterion of $5k+10$, we have tolerances of 75 and 60. This suggests that the findings of the first analysis are robust to possible file-drawer bias, while the second may not be. Fig. 1 shows a funnel plot for Analysis 1, which, however, suggests publication bias towards studies with smaller standard errors (greater sample sizes) and particularly those showing greater effect sizes.

Analyses 3 and 4 concerned thresholds for odors found in foodstuffs and musky odors, respectively. In both cases, thresholds are found to be lower during the fertile than non-fertile phases. A similar result was found for studies using androstenes (analysis 6), but there appeared to be no evidence for cycle-correlated variation in sensitivity to PEA (analysis 5).

Homogeneity analyses showed that values of *Q* generally fell below the critical value, indicating that variability observed across effect sizes did not exceed what might be expected based on sampling error. An exception was analysis 4b (musky odors without the androstenes), where heterogeneity in effect sizes across studies suggested the presence of additional moderator variables.

Discussion

We employed a meta-analytic approach to summarise the research literature addressing the effects of the menstrual cycle on human olfactory threshold. The results, taking into account the thirteen studies investigating olfactory threshold across the menstrual cycle, support the view that there is significant cycle-correlated variation. Thresholds are in general significantly lower in the fertile than the non-fertile phases, with effect sizes consistently in this direction (even for the one involving PEA). This same conclusion applies to both 'food' and 'musky' odorants, despite their different evolutionary significance, and to the androgen steroids (androstadienone, androstenone, and androsterone) which

are putative human semiochemicals influencing behavior (Saxton et al. 2008), but could not be applied to PEA, at least based on existing evidence.

Although, on the whole, variability observed across effect sizes did not exceed what might be expected based on sampling error for most analyses, an analysis of musky odors that are not found in human body odor (4b) did reveal heterogeneity in effect sizes across studies that suggests the presence of additional moderator variables. Since it did not pertain to musky odorants including the androstenes (4a) or the androstenes alone (6), this heterogeneity can be ascribed to various discrepancies in methodology employed to test pentadecalactone (Exaltolide) and/or musk-ketone thresholds. Potential sources include, for instance, the use of different types of psychophysical paradigms (staircase vs. signal detection procedures). Most importantly, considerable variation stems from the use of single ascending or descending series (e.g. Amoore et al. 1975; Vierling and Rock 1967), which is highly unreliable as the thresholds tend to fluctuate rather wildly on repeated measures (e.g. Stevens et al. 1988). Further, large step sizes in odorant concentration could have obscured small, but consistent, changes. Manipulations that are clearly inconsistent with best practice include threshold testing on up to 3 successive days around ovulation until a clear increase in sensitivity could be observed (Mair et al. 1978) and pooling the data of normally cycling women and those who used hormonal contraceptives (Amoore et al. 1975).

If cycle-related change in odor processing appears domain-general, why then is there so much variability in findings across studies? Some variation undoubtedly lies in the above-mentioned diversity of olfactory measurement techniques employed (Doty et al. 1986; Doty et al. 1995). The manner in which the individual menstrual cycle phases are defined and data combined across cycle phases also plays a major role (Doty 1979). Namely, in few studies the circulating hormone levels have actually been measured, which is more accurate in comparison to, for example, counting methods. Further, in some studies the olfactory measures might have been taken too sparsely to detect any patterns of change. Differences in sensitivity in either nostril may also account for some of the variability observed (Purdon et al. 2001). Also, Sueda et al. (2003) discuss the exclusion of individuals who have a particularly poor sense of smell. They initially found no significant differences in olfactory threshold for androstenone, but were able to detect cyclic changes only when they took into account individual variation in absolute threshold levels. It is conceivable that had other studies applied a similar criterion to restrict analyses to normosmic subjects within a sample, more pronounced or consistent effects may have been observed. A further explanation for the apparent lack of congruency in results relates to the absence of cyclic variation in the studies using the odorant PEA. These null findings cannot be simply explained by methodological inadequacies, since in two of the studies using PEA the researchers did find significant effects for other odorants (androstadienone: Lundström et al. 2005; androstenone: Sueda et al. 2003). It could be then suggested that PEA is among the more volatile of the odorants that have been tested to date. This, however, is clearly not the case (see Table 1) and the odorant cannot even be

simply characterized as volatile based on the criterion outlined by Vo and Morris (2014). Mair et al. (1978) suggested that the patterns of threshold changes across different odorants might be due to different volatility. Volatility is caused by the evaporation or rapid sublimation of an odorant and is proportional to the vapor pressure of the substance and inversely proportional to its molecular weight. Mair et al. (1978) noted that involatile esters (e.g. pentadecalactone, coumarin, and cinnamyl butyrate) might be strongly retarded by nasal mucus (which alters across the cycle), while the volatile ester amyl acetate might escape this effect and thus exhibit relatively stable threshold levels. However, recent work by Vo and Morris (2014) makes such a clear-cut distinction problematic. While odorants with a vapor pressure greater than 0.1 mm Hg at 25°C are volatile, those with smaller values may fall under all three categories: non-volatile, volatile, or semi-volatile, making the suggestion raised by Mair et al. (1978) more difficult to test than previously assumed.

The lack of odor specificity in relation to their biological relevance might seem surprising in light of studies that have demonstrated cyclic changes in preferences for odors potentially involved in mate choice. The results indicate that olfactory sensitivity may be linked to general physiological fluctuations or differences in neural processing experienced across the cycle to a broad spectrum of odorants in the same way as they appear to be for visual, gustatory, and other stimuli (Becker et al. 1982; Dye 1992; Kuga et al. 1999). Our results are therefore consistent with the suggestion that changes in sensitivity may be linked to a general effect in odor processing, whose mechanism has been proposed in a review by Doty and Cameron (2009) (for details see Introduction). Another possibility is that, as already noted above, the cyclic changes in hydration of nasal mucus may influence chemicals depending on their volatility (Mair et al. 1978). However, it should be noted that the individual mechanisms may not be mutually exclusive and may in fact work in concert.

Researchers in this area have not neglected the possibility that changes in odor perception of biologically relevant odors across the cycle could potentially mediate changes in preferences. For instance, Gangestad and Thornhill (1998) explicitly discussed this possibility in their article reporting changes in women's preferences for the body odor of symmetrical men. They assessed women's ratings of intensity (not to be equated with threshold measurements) of men's body odor as well as of its pleasantness and sexiness. Mean intensity ratings did tend to be greater among fertile than non-fertile women or women using hormonal birth control (though this contrast was only marginally significant if a one-tailed test is applied), a pattern expected if fertile women are more sensitive to odors and consistent with this meta-analysis. However, intensity scores tended to be negatively associated with pleasantness scores, the correlation between women's mean intensity ratings and their preference for symmetry was near-zero and controlling for mean intensity ratings left the association between fertility risk and preference for the scent of symmetry completely unchanged. Havlicek et al. (2005) found a preference for odors of dominant men when rated by women in their fertile phase, but not by women in the non-fertile phase. Similarly to the above-reviewed study, the association was not mediated by intensity

ratings. To sum up, women's olfactory preferences for cues of male quality (e.g. symmetry) shown in the fertile period cannot simply be attributed to cyclical changes in perceived intensity. Conversely, Hummel et al. (1991) reported menstrual cycle-related variation in hedonic ratings for the odorous steroid androstenone but not for other odors, while thresholds did not vary.

The results of the present meta-analysis of thirteen studies that investigated olfactory thresholds across the menstrual cycle point in the direction of significant cycle-related, general shifts in olfactory sensitivity to a number of odors, including those with different evolutionary significance. In the future, further integration of studies on cyclic variation in olfactory sensitivity as a continuing process is encouraged, expanding research questions to, for instance, the occurrence and relative magnitude of similar fluctuations in hormonal contraceptive users. This might contribute to a more profound understanding of the underlying mechanisms involved in the cyclic changes in odor thresholds and shed more light on whether such changes can be viewed as a general phenomenon. Finally, a similar meta-analytic approach, employed here for cyclic changes in olfactory threshold, should also be applied to studies on cyclic fluctuations in olfactory preferences.

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Authors' Contributions

Conceived and designed the meta-analysis: SCR, JH, and LMN. Conducted the search for references: SCR and LMN. Analyzed the data: SCR and LMN. Wrote the manuscript: SCR, JH, and LMN.

Conflict of interest

The Authors declare that there is no Conflict of interest.

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References

Amoore JE, Popplewell JR, Whissell-Buechy D. 1975. Sensitivity of women to musk odor: no menstrual variation. J Chem Ecol 1(3):291–97.

Arctander S. 1969. Perfume and Flavor Chemicals: (aroma Chemicals). Montclair, NJ: TheAuthor.

Becker D, Creutzfeldt OD, Schwibbe M, Wuttke W. 1982. Changes in physiological, EEG and psychological parameters in women during the spontaneous menstrual-cycle and following oral-contraceptives. Psychoneuroendocrinology 7(1):75–90.

Bedoukian. Safety Data Sheet [Internet]. Danbury, CT: Bedoukian Research.

Bedoukian PZ. 1986. Perfumery and flavoring synthetics. Wheaton, IL: Allured Publishing Corp.

Bremner EA, Mainland JD, Khan RM, Sobel N. 2003. The prevalence of androstenone anosmia. Chem Senses 28(5):423–32.

Burdock GA. 2009. Fenaroli's Handbook of Flavor Ingredients, Sixth Edition. Boca Raton: Taylor & Francis.

Caruso S, Grillo C, Agnello C, Maiolino L, Intelisano G, Serra A. 2001. A prospective study evidencing rhinomanometric and olfactometric outcomes in women taking oral contraceptives. Hum Reprod 16(11):2288–94.

De Rovira D. 2008. Dictionary of Flavors. Ames, IA: John Wiley & Sons.

Doty RL. 1979. Procedure for combining menstrual cycle data. J Clin Endocr Metab 48(6):912–18.

Doty RL, Cameron EL. 2009. Sex differences and reproductive hormone influences on human odor perception. Physiol Behav 97(2):213–28.

Doty RL, Gregor TP, Settle RG. 1986. Influence of Intertrial Interval and Sniff-Bottle Volume on Phenyl Ethyl-Alcohol Odor Detection Thresholds. Chem Senses 11(2):259–64.

Doty RL, Hall JW, Flickinger GL, Sondheimer SJ. 1982. Cyclic changes in olfactory and auditory sensitivity during the menstrual cycle: no attenuation by oral contraceptive medication. In: W Breipohl, editor. Olfaction and endocrine regulation. London: IRL Press. 35–42.

Doty RL, McKeown DA, Lee WW, Shaman P. 1995. A study of the test-retest reliability of ten olfactory tests. Chem Senses 20(6):645–56.

Doty RL, Snyder PJ, Huggins GR, Lowry LD. 1981. Endocrine, cardiovascular, and psychological correlated of olfactory sensitivity changes during the human menstrual cycle. J Comp Physiol Psych 95(1):45–60.

Dye L. 1992. Visual information processing and the menstrual cycle. In: JTE Richardson, editor. Cognition and the menstrual cycle. New York: Springer Verlag. 67–97.

Gangestad SW, Thornhill R. 1998. Menstrual cycle variation in women's preferences for the scent of symmetrical men. Proc R Soc B 265(1399):927–33.

Gangestad SW, Thornhill R. 2008. Human oestrus. Proc R Soc B 275(1638):991–1000.

Good PR, Geary N, Engen T. 1976. The effect of estrogen on odor detection. Chem Senses 2(1):45–50.

Gower DB, Nixon A, Mallet AI. 1998. The significance of odorous steroids in axillary odour. In: S Van Toller and Dodd GH, editors. Perfumery. London: Chapman & Hall. 47–75.

Grillo C, La Mantia I, Triolo C, Scollo A, La Boria A, Intelisano G, Caruso S. 2001. Rhinomanometric and olfactometric variations throughout the menstrual cycle. Ann Oto Rhinol Laryn 110(8):785–89.

Havlícek J, Roberts SC, Flegr J. 2005. Women's preference for dominant male odour: effects of menstrual cycle and relationship status. Biology Letters 1(3):256–59.

Hedges LV, Olkin I. 1985. Statistical methods for meta-analysis New York: Academic Press.

Hummel T, Gollisch R, Wildt G, Kobal G. 1991. Changes in olfactory perception during the menstrual cycle. Experientia 47(7):712–15.

Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 1997. 'Sniffin' Sticks': Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 22(1):39–52.

Jacob TJC, Wang LW, Jaffer S, McPhee S. 2006. Changes in the odor quality of androstadienone during exposure-induced sensitization. Chem Senses 31(1):3–8.

Keller A, Vosshall LB. 2004. Human olfactory psychophysics. Curr Biol 14(20):R875-R878.

Kuga M, Ikeda M, Suzuki K. 1999. Gustatory changes associated with the menstrual cycle. Physiol Behav 66(2):317–22.

Le Magnen J. 1952. Les phénoménes olfacto-sexuels chez l'homme. Archives des Sciences Physiologiques 6:125–60.

Lundström JN, McClintock MK, Olsson MJ. 2005. Effects of reproductive state on olfactory sensitivity suggest odor specificity. Biol Psychol 71(3):244–47.

Mair RG, Bouffard JA, Engen T, Morton TH. 1978. Olfactory sensitivity during the menstrual cycle. Sensory Processes 2(2):90–98.

McNeil J, Cameron JD, Finlayson G, Blundell JE, Doucet E. 2013. Greater overall olfactory performance, explicit wanting for high fat foods and lipid intake during the mid-luteal phase of the menstrual cycle. Physiol Behav 112:84–89.

Navarrete-Palacios E, Hudson R, Reyes-Guerrero G, Guevara-Guzmán R. 2003. Lower olfactory threshold during the ovulatory phase of the menstrual cycle. Biol Psychol 63(3):269–79.

NCBI. 2014. PubChem. 2004 ed. Bethesda, MD: National Center for Biotechnology Information.

Pause BM, Sojka B, Krauel K, Fehm Wolfsdorf G, Ferstl R. 1996. Olfactory information processing during the course of the menstrual cycle. Biol Psychol 44(1):31–54.

Purdon SE, Klein S, Flor-Henry P. 2001. Menstrual effects on asymmetrical olfactory acuity. J Int Neuropsych Soc 7(6):703-09.

Raghava GPS. 2011. DrugPedia: A Wikipedia for Drug Discovery. Chandigarh, India.

Renfro KJ, Hoffmann H. 2013. The relationship between oral contraceptive use and sensitivity to olfactory stimuli. Horm Behav 63(3):491–96.

Rosenthal R. 1991. Meta-analytical procedures for social research. London: Sage.

Rosenthal R, DiMatteo MR. 2001. Meta-analysis: Recent developments in quantitative methods for literature reviews. Annu Rev Psychol 52:59–82.

Rusak B, Zucker I. 1979. Neural regulation of circadian rhythms. Physiol Rev 59(3):449–526.

Saxton TK, Lyndon A, Little AC, Roberts SC. 2008. Evidence that androstadienone, a putative human chemosignal, modulates women's attributions of men's attractiveness. Horm Behav 54(5):597–601.

Schmidt H. 1990. Methods of meta-analysis. London: Sage.

Stevens JC, Cain WS, Burke RJ. 1988. Variability of olfactory thresholds. Chemi Senses 13(4):643–53.

Sueda K, Arao Y, Nishida N. 2003. Changes in olfactory perception for androstenone during the menstrual cycle. Aroma Research 4:51–55.

Vierling J, Rock J. 1967. Variations in olfactory sensitivity to exaltolide during the menstrual cycle. J Appl Physiol 22(2):311–15.

Vo UUT, Morris MP. 2014. Nonvolatile, semivolatile, or volatile: Redefining volatile for volatile organic compounds. J Air Waste Manage 64(6):661–69.

Whissell-Buechy D, Amoore JE. 1973. Odour-blindness to musk: simple recessive inheritance. Nature 242(5395):271–73.

Wolf FM. 1986. Meta-analysis quantitative methods for research synthesis London: Sage.

Wysocki CJ, Beauchamp GK. 1984. Ability to smell androstenone is genetically determined PNAS Biol Sci 81(15):4899–902.