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Review

Sex differences and reproductive hormone influences on human odor perception

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ABSTRACT

The question of whether men and women differ in their ability to smell has been the topic of scientific investigation for over a hundred years. Although conflicting findings abound, most studies suggest that, for at least some odorants, women outperform men on tests of odor detection, identification, discrimination, and memory. Most functional imaging and electrophysiological studies similarly imply that, when sex differences are present, they favor women. In this review we examine what is known about sex-related alterations in human smell function, including influences of the menstrual cycle, pregnancy, gonadectomy, and hormone replacement therapy on a range of olfactory measures. We conclude that the relationship between reproductive hormones and human olfactory function is complex and that simple associations between circulating levels of gonadal hormones and measures of olfactory function are rarely present.

Contents

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1. Introduction

The question of sex differences in human perceptual and cognitive abilities has been the subject of scientific inquiry since the proclamation by 19th Century social Darwinists that men are more intelligent than women [1,2]. Aside from the well-documented sex differences in verbal, spatial, and perceptual motor tasks [3–6], sex differences and menstrual cycle-related changes in basic measures of human sensory function have been reported for every major sensory system, including audition [7–9], vision [10–14], olfaction (this review), gustation [15–19], and the skin senses [20–22]. Such effects, when present, are usually not large, raising the question as to what biological purpose they may serve.

In this review we examine what is known about sex-related alterations in human smell function, including the influences of the menstrual cycle, pregnancy, gonadectomy, and hormone replacement therapy on a range of olfactory measures. Recent electrophysiological and functional imaging studies are included. Although major studies in which olfaction-related sex differences have been reported are highlighted, this review is not inclusive and the reader is referred elsewhere for additional information on this general topic, including the large literature on the sexually dimorphic accessory (vomeronasal) olfactory system of non-human species [23–32].

2. Sex differences

2.1. Odor detection

With rare exception [33,34], published investigations of sex differences in olfactory threshold sensitivity have reported either greater female sensitivity or no sex differences in sensitivity, depending upon the odorant. In the first of a series of four studies published in 1899, Toulouse and Vaschide [35] found women to be more sensitive than men to the odor of camphor. For men, the minimum perceptible concentration in water was 9 parts per 100,000, whereas for women this value was 1 part per 100,000. A half-century later, Le Magnen [36] found lower female than male thresholds for the odors of the artificial musk Exaltolide and the steroid testosterone. Because no sex differences were evident for the odors of safrole, guiacol, amyl salicylate, and eucalyptus, he suggested that sex differences in olfactory sensitivity likely occur primarily for sex hormones or closely related substances. However, his hypothesis has not been borne out, since more recent workers have reported, in addition to Exaltolide [37], greater female threshold sensitivity to a wide range of compounds, including acetone, 1-butanol, 2-methyl,3-mercapto-butanol, citral, ethanol, 1-hexanol, hydrogen sulfide, 1-octanol, pentyl acetate, phenyl ethanol, pyridine, and m-xylene [38–44,46]. Sex differences for some of these compounds, as well as a number of steroids, have been noted in children before the age of puberty, implying a lack of dependence on concurrent gonadal hormones [38,41,47]. Such a lack of dependence also has been observed in some non-human species for opposite-sex conspecific odors [48,49].

Among investigators reporting no sex differences in odor sensitivity are Amoore and Venstrom [50], who found "no convincing differences in thresholds" between men and women for 21 odorants, including the musk Thibetolide (see also [51]) and Punter [52], who examined 58 compounds but noted (p. 233), "The data do suggest that females are more sensitive (although not statistically significant)." Negative findings have been reported for the odors of hydrogen cyanide, n-butanol, safrol, pyridine, and phenyl ethanol [38,44,45,53–58]. Although Griffith and Patterson [59] reported finding no sex differences in olfactory thresholds to the steroid 5a-androst-16-en-3-one, subjects unable to detect this substance were eliminated from consideration, which amounted to 44.4% of the men and 7.6% of the women he evaluated. Had these subjects been included in the threshold test, the conclusion of greater female than male sensitivity would have been supported.

A reasonable assessment of the aforementioned literature suggests that women, on average, are more sensitive than men to some odorants, although the sex differences are not large. The reasons for the discrepant findings likely reflect procedural factors, including the reliability of the test measures, the number and ages of the subjects examined, and the frequency of specific anosmics within the male and female groups. Experience with odorants may also be involved, given that sensitivity to some odorants is increased as a result of repeated exposure [60–62], an effect that is stronger in women than in men [63,64]. Unfortunately, specifics of the procedures used for determining sensitivity are not always provided and it is frequently unclear if recognition or detection is being measured. Furthermore, sampling biases and other confounding factors, such as differences in smoking habits of men and women, may be present. It is worth noting that women are more likely to volunteer for experiments around mid-cycle [65]. If they are more sensitive to odorants at this time (see next major section of this review), then some comparisons may be between men and mostly mid-cycle or near-mid-cycle women, rather than between men and women who represent all phases of the menstrual cycle. The sex of the experimenter may also be a factor in some instances, in light of evidence that this can influence the motivation of subjects. For example, Stevenson and Allen [66] conducted a motor performance task in male and female college students in which half the experimenters were male and half female. The experimenters complimented the subjects as they performed the task. Higher levels of performance occurred when the compliments came from the experimenter of the opposite sex.

2.2. Odor identification

Many studies report superior female performance on tests of odor identification [35,57,67–72]. For example, Cain [70] tested 22 men and 24 women for their ability to identify 80 common odors (from the actual objects, such as cigarette butts, mothballs, tuna, crayons, etc.) and found that the women outperformed men in the identification of 74 of the stimuli (92.5%). Odors believed by subjects to be stereotypically male, such as beer, cigar butts, machine oil, and varnish, were identified better by the women than by the men. Similar results were found in a study of 455 men and 742 women asked to identify each of 50 odors being evaluated for inclusion in a standardized smell identification test [71]. Women outperformed men on 45 of the 50 stimuli (90%). In general, those odorants that were most poorly identified by the group as a whole were the ones for which the sex difference was largest (Fig. 1). This sex difference was present across a wide age range (Fig. 2) and spanned the time of puberty (Fig. 3).

Analogous female superiority has been reported in studies employing human body odor. In a cross-cultural study, Schleidt et al. [73] found German, Italian, and Japanese women outperformed their male counterparts in correctly assigning axillary odors to gender categories. Wallace [74] demonstrated that women were superior to men in discriminating between the smell of hands of two men, of two women, and of a man and a woman. Doty et al. [75,76] found women to be more accurate than men in correctly assigning both axillary odors and breath odors to male and female gender categories. However, like assignments made from body weight, stronger odors were assigned to the male category and weaker odors to the female category, regardless of the sex of the donor, suggesting that qualitative differences in male and female odors was not the basis for this discrimination. Recently, Platek et al. [77], using gauze pads that had been taped in the axillae, found that over half (59.4%) of 32 women they tested were able to identify their own odor from such pads, whereas only one of the 18 (5.6%) men they tested was able to do so, implying a sex difference in odor-based recognition of individuality.

2.3. Ratings of suprathreshold attributes of odorants

Sex differences also have been reported for tasks where odors are rated on psychological attributes such as intensity, pleasantness,

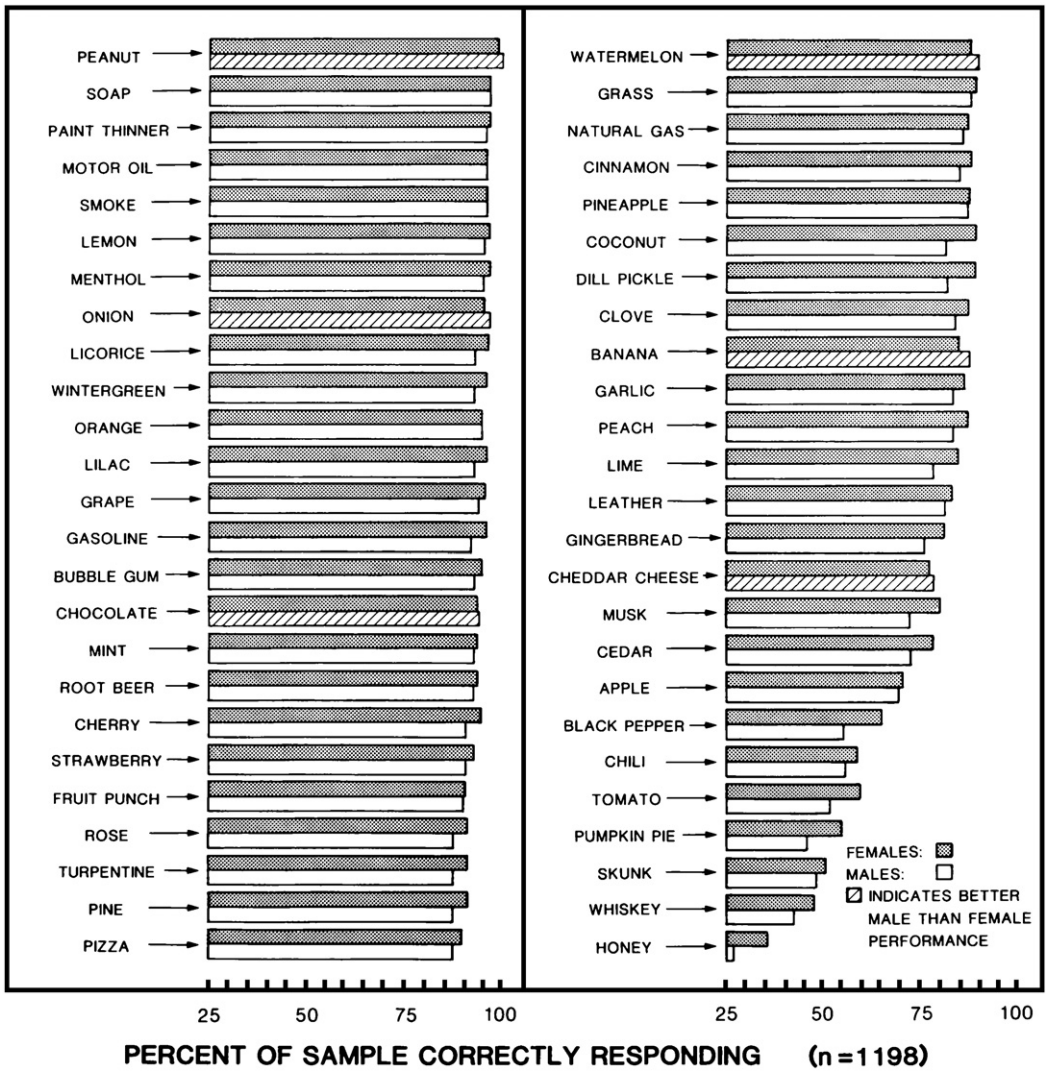

Fig. 1. Percent of men and women correctly identifying, in a forced-choice four-alternative multiple-choice situation, 50 microencapsulated fragrances. From [71] with permission.

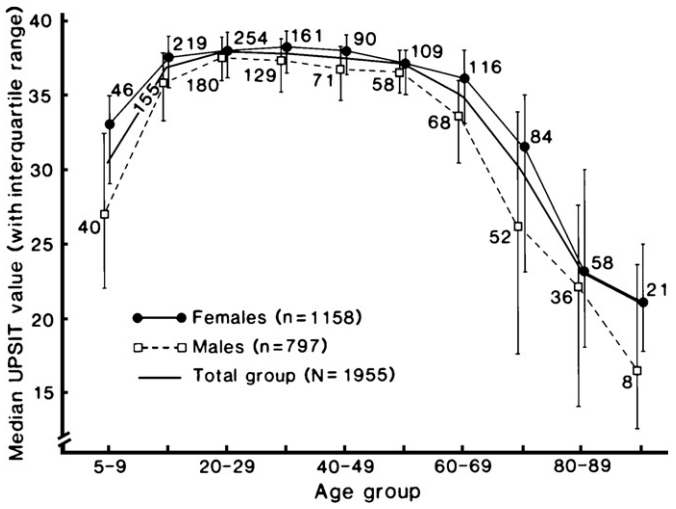

Fig. 2. Median (interquartile range) scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of sex and age. Note that females outperform males at all ages, despite a ceiling effect of the test in the younger years. From [194] with permission. Copyright © 1984 American Association for the Advancement of Science.

coolness/warmth, irritation, and familiarity. In a 1927 study, Kenneth [78] found camphor, menthol, citronella, and ferric valerian to be rated as more pleasant by women than by men, whereas the opposite occurred for cedarwood oil, pine oil, musk, and tonka beans. In the

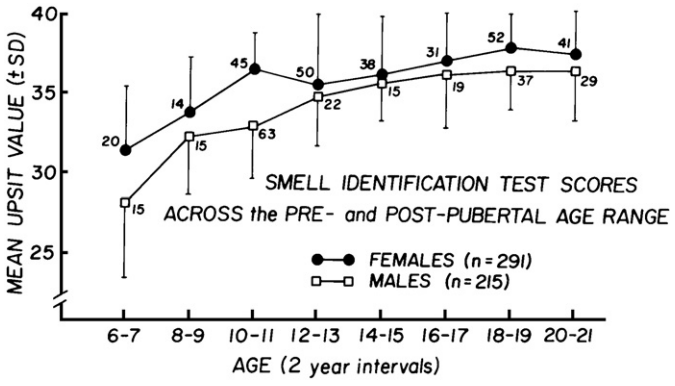

Fig. 3. Mean (SD) scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of sex across the prepubertal, adolescent, and early adult years. From [79] with permission. Copyright © 1986, Macmillan Publishing Company, a division of Macmillan, Inc.

late 1950s, Le Magnen [36] obtained intensity ratings of the odor of crystalline Exaltolide from adult men, adult women, prepubescent boys, and prepubescent girls. Most of the men, girls, and boys rated the stimulus as very weak or absent, whereas adult women rated it as strong or extremely strong. This led Le Magnen to suggest that sensitivity to Exaltolide is likely dependent upon ovarian hormones, since the sex difference did not appear to be present in the prepubescent subjects. However, close examination of his data suggests that the prepubescent girls tended to rate the odor stronger than the prepubescent boys ($p<0.10$) [79].

In the early 1970s, Griffith and Patterson [59] had over 300 men and women rate the pleasantness of a suprathreshold concentration of the steroid, 5α-androst-16-en-3-one. As noted in the early study by Kenneth for the odors of cedarwood oil, pine oil, musk, and tonka beans [78], the odor was rated as less pleasant by the women than by the men. For both sexes, the lower a subject's threshold for the odor, the greater was his or her dislike of the odor. More recently, Doty et al. [71] asked 26 men and 26 women to rate, on visual analogue scales, the intensity, pleasantness, irritation, familiarity, and coolness/warmth of 50 microencapsulated odors. Most were perceived as more intense and less pleasant by the women than by the men. In addition, women rated some odors as less cool, less irritating, and more familiar. The few odorants viewed as more familiar by the men (e.g., coconut, root beer, tomato, honey) did not fall into a class that could be conceived of as stereotypically "male." Similar heterogeneity of responses was noted in a massive 'scratch & sniff' odor survey of the readers of National Geographic magazine, termed the National Geographic Smell Survey (NGSS), where amyl acetate (banana) and mercaptan (skunk) were rated as more pleasant by men than by women, and rose and eugenol (clove) as more pleasant by women than by men [80].

Sex differences are also observed in the ratings of the intensity and pleasantness of body odors. For example, in a study of human vaginal odors, women, on average, assigned larger intensity and smaller pleasantness magnitude estimates to the odors than men [81]. A similar phenomenon was found in ratings of the intensity and pleasantness of both human axillary and breath odors [75,76]. Recently, Platek et al. [77] reported that women, relative to men, rated their own axillary odors as less pleasant, although there was no difference in pleasantness ratings between those who could and could not identify their own odor from that of others.

2.4. Odor memory

Assessing odor memory is not straightforward (for reviews, see [82,83]). Thus, a typical memory task requires stimulus encoding, retention, and recall, all of which can be independently altered by factors such as sex, age, and basic smell function. Moreover, when one smells an odor, such as lemon, and is asked to pick this odor from foils after some delay period, what is held in memory is not the odor of lemon, per se, which has been previously encoded in long term memory, but the remembrance of having smelled the lemon odor. Such remembrance is often aided by semantically labeling the odor that was smelled, allowing recall of the label at the time of the recall period.

To overcome this problem, odors that are unfamiliar and difficult to semantically label have been used, although even unfamiliar odors can be so labeled. In one type of 'incidental' memory paradigm, a weak background odor seemingly unnoticed by the subject is present while the subject completes some task, such as a discrimination task using other odorants [84]. Later, in a second phase of the study, the subject is presented with an array of odors, including the one that was covertly presented, and asked to identify which odors were previously smelled.

Superior female performance has been noted in the few studies of odor memory where sex differences have been assessed [57,85–87]. An example of the sex difference in a match-to-sample paradigm with 10-, 30- and 60-second delay intervals is shown in Fig. 4 [87]. In this case, no delay interval effects were present so that the data were collapsed across delay intervals. The authors suggested that the sex difference was likely due to a greater female reliance on semantic cues, even though backwards counting was instituted during the delay intervals in an effort to minimize semantic rehearsal. This hypothesis was supported by the finding of a correlation between the test scores and scores on an odor identification test in women, but not in men. Others have found similar sex differences in odor memory tasks that appear to be associated with semantic processes. For example, Oberg et al. [57] found women outperformed men on an odor memory task only when familiar, but not unfamiliar, odorants were employed. When they controlled for odor naming ability, this sex difference disappeared. A similar disappearance was noted by Larsson et al. [85] after controlling for verbal proficiency in a study of recollective odor experience.

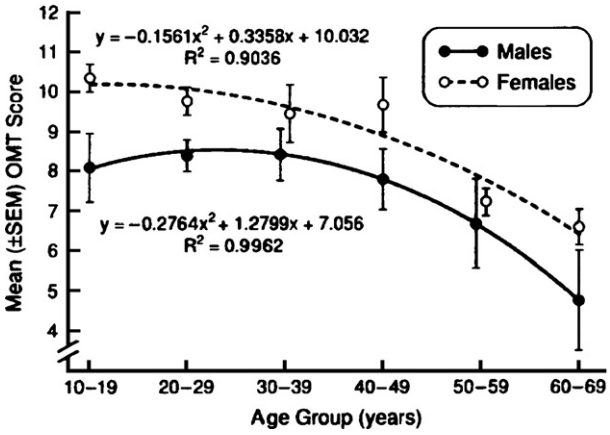

Fig. 4. Odor Memory Test Scores as a function of sex and age. Curves represent quadratic functions fitted by least squares. From [87] with permission. Copyright © 2003 Oxford University Press.

2.5. Electrophysiological measures

Odor-induced electrical potentials can be measured from electrodes placed on the surface of the human olfactory epithelium (the electro-olfactogram), as well as from the scalp (odor event-related potentials or OERPs). The latter potentials represent minute temporal changes in electrical fields generated by large populations of central nervous system neurons in response to chemical stimuli. The measured components of these changes are named P1, N1, P2, and N2, reflecting voltage changes in positive (P) and negative (N) directions.

Becker et al. [88] were the first to report a sex difference in OERPs. In this study of normal and psychosis-prone individuals, P1/N1 and P2/N1 amplitude differences were consistently larger in women than in men for the two odorants that were presented (vanillin and hydrogen sulfide), regardless of the subject group. Subsequently, Evans et al. [89] noted larger female than male P1/N1 amplitudes for pentyl acetate, and Olofsson and Nordin [90] found early OERP components (P1,N1) to be more identifiable in women than in men in response to pyridine. The late P2/P3 positive components displayed larger amplitudes at all electrode sites and shorter latencies at electrode placements at the center of the scalp (Cz) in women than in men. Stuck et al. [91] found larger P2 amplitudes in women than in men in response to the odor of hydrogen sulfide. Interestingly, stimuli presented to right nostril of the women resulted in larger P2 amplitudes than stimuli presented to the left nostril. The opposite was the case for men. Recently Chopra et al [41] reported that P1, N1, and P2 latencies are prolonged in pubescent boys for androstadienone and 2-methyl,3-mercapto-butanol.

2.6. Functional imaging

Sex differences in odor-induced brain activation have been reported, as measured by functional imaging. The results of such studies, however, have not been uniform. Levy et al. [92] obtained functional magnetic resonance imaging (fMRI) scans on 9 men and 8 women while they were smelling cotton pledgets saturated with pyridine, menthone, or pentyl acetate. Brain activation was consistently *lower* in women than in men for all three stimuli in the three coronal brain sections that were assessed. Similar findings were observed for banana and peppermint odors in another study by this same group [93]. Interestingly, simply imagining odors in the absence of odor stimulation also induced activation in the assessed brain regions, with less activation occurring in women than in men [93]. The ratio of brain activation by imagination of banana to activation by actual banana odor was about twice as high in women as in men.

Using an air-dilution olfactometer to present stimuli in a pulsed fashion without creating somatosensory artifacts, Yousem et al. [94] compared fMRI activation maps obtained from eight right-handed women to those obtained from 8 right-handed men for eugenol, phenyl ethanol, and phenyl ethanol alternating with hydrogen sulfide. The odorants were delivered to both nostrils for 1 s every 4 s during a 30 second 'on-period.' During the 30 second 'off-period,' room air was presented at the same flow rate. In contrast to the Levy et al. work, more women showed activation than men. The left and right inferior frontal regions showed a statistically significant increase in activation in the women, who exhibited up to eight times more activated voxels than the men within the frontal and perisylvian regions.

No odor-related sex differences were observed in a positron emission tomography (PET) study by Bengtsson et al. [95]. These investigators evaluated activation in 11 men and 12 women during the smelling of vanillin, cedar oil, lavender oil, eugenol, and butenol. Activation occurred bilaterally in the amygdala, piriform and insular cortices of both sexes, irrespective of odor. Neither the pattern nor the subjective perception of the odors differed between the men and women, suggesting to the authors that "the reported female superiority in assessing olfactory information including odor identification is probably an effect of a difference at a cognitive, rather than perceptive level of olfactory processing."

It is of interest that Garcia-Falgueras et al. [96], using voxel-based morphometry, concluded that the human olfactory system is a sexually dimorphic network. In this study, they found women to have a higher concentration of gray matter in the orbitofrontal cortex (Brodmann areas 10, 11 and 25) and temporomedial cortex (bilateral hippocampus and right amygdala), as well as in their left basal insular cortex. In contrast, men were found to have relatively more gray matter concentration in the left entorhinal cortex (Brodmann's area 28), right ventral pallidum, left dorsal insular cortex and a region of the orbitofrontal cortex (Brodmann's area 25).

3. Menstrual cycle influences on olfactory sensitivity

Le Magnen [36] was the first to systematically examine the influences of the menstrual cycle on human olfactory sensitivity. In one experiment, he tested thresholds for Exaltolide across ten menstrual cycles of five women. Measurements were made every two or three days. Although an increase in sensitivity was noted in all cycles on the days following the menses, considerable variability in the onset, offset, and rate of change of this increase was present. In some cases the sensitivity peaked soon after the menses, whereas in others it occurred much later. In three of nine cases, a second peak in sensitivity occurred during the late luteal phase. Exaltolide-like fluctuations in sensitivity to other odorants (safrole, guiacol, amyl salicylate, pyridine) were not observed in a smaller number of subjects that were tested, with the exception of a cholesterol–testosterone mixture, supporting Le Magnen's belief that urinoid smelling odorants such as musks and some hormones may have special biological meaning to humans.

Using a signal detection paradigm, Mair et al. [97] longitudinally tested normally cycling women for their sensitivity to Exaltolide, coumarin, cinnamyl butrate, and pentyl acetate. Better performance was found mid-cycle than during menses for all odors except pentyl acetate, in seeming contradiction to Le Magnen's hypothesis. Also in disaccord with his hypothesis are results from other laboratories showing menstrual cycle-related fluctuations for not only Exaltolide [37,98], but for ammonia, anise, eugenol (clove), furfural, m-xylene, phenyl ethanol, and pyridine [60,99–103]. In contrast to Mair et al.'s study, one laboratory reported menstrual cycle-related fluctuations to pentyl acetate [104]. Some investigators have reported no menstrual cycle-related fluctuations in sensitivity to phenyl ethanol, androstenone, nicotine, and citral [105,106].

In the most extensive menstrual cycle-olfactory investigation to date, a signal detection paradigm was used to evaluate odor detection performance to furfural every other day across 17 menstrual cycles of

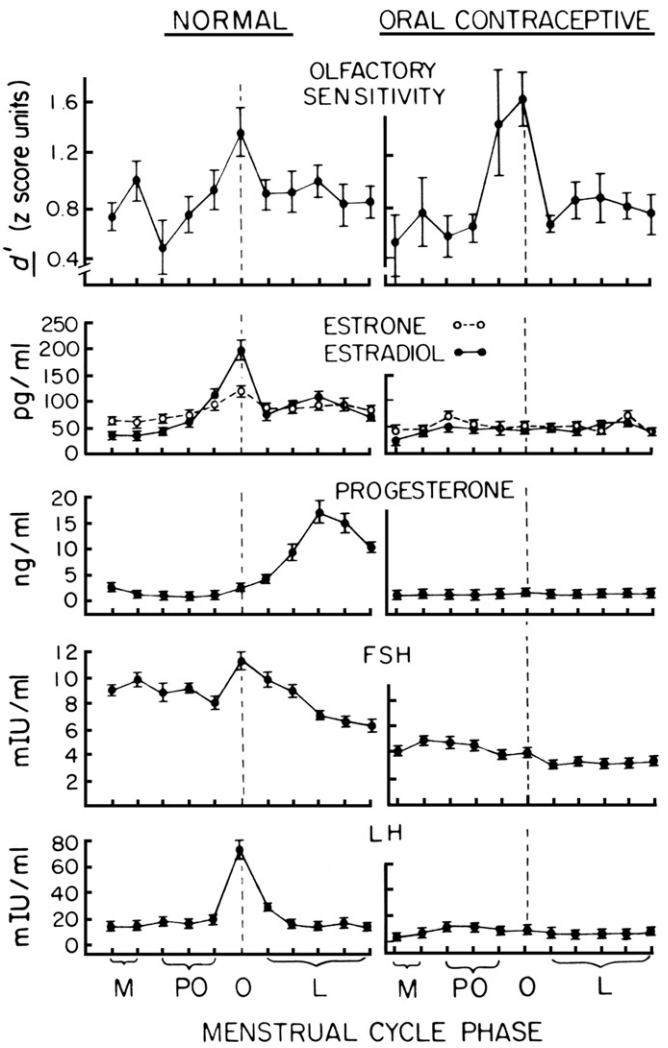

Fig. 5. Patterns of changes in signal detection measures of olfactory sensitivity and plasma levels of five reproductive hormones across cycle phases of women taking and women not taking oral contraceptives. Data are normalized and assigned to cycle phases using the Doty [108] procedure. M = menstrual phases 1 and 2; PO = preovulatory phases 1–3; 0 = ovulatory phase (day of LH surge or day before LH surge in normally cycling group, day 13 or 14 in oral contraceptive group, where day 1 = 1st day of menses); L = luteal phases 1–5. Note clear fluctuation in olfactory sensitivity in both groups and the lack of correlation between these changes and circulating levels of pituitary and gonadal hormones in the oral contraceptive group. From [103] with permission. Copyright © 1982 IRL Press.

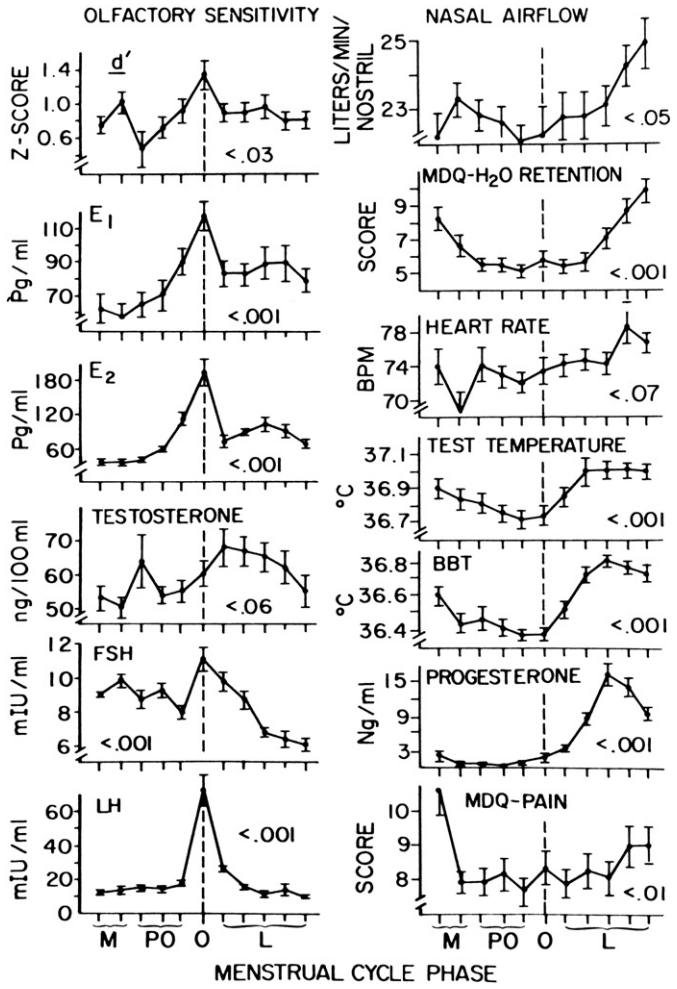

Fig. 6. Mean (SEM) changes in 13 variables as a function of menstrual cycle phase in normally cycling women. E_1 = estrone; E_2 = estradiol; FSH = follicle stimulating hormone; LH = luteinizing hormone; MDQ = Moods Menstrual Distress Questionnaire; BBT = basal body temperature; M = menstrual phase; O = ovulatory phase (day of LH surge or day before); PO = preovulatory phase; L = luteal phases. Phase designation establish by Doty's procedure [108]. The *p* values refer to the cycle phase factor in one-way analyses of variance. Reprinted from [60] with permission. Copyright © 1981, American Psychological Association.

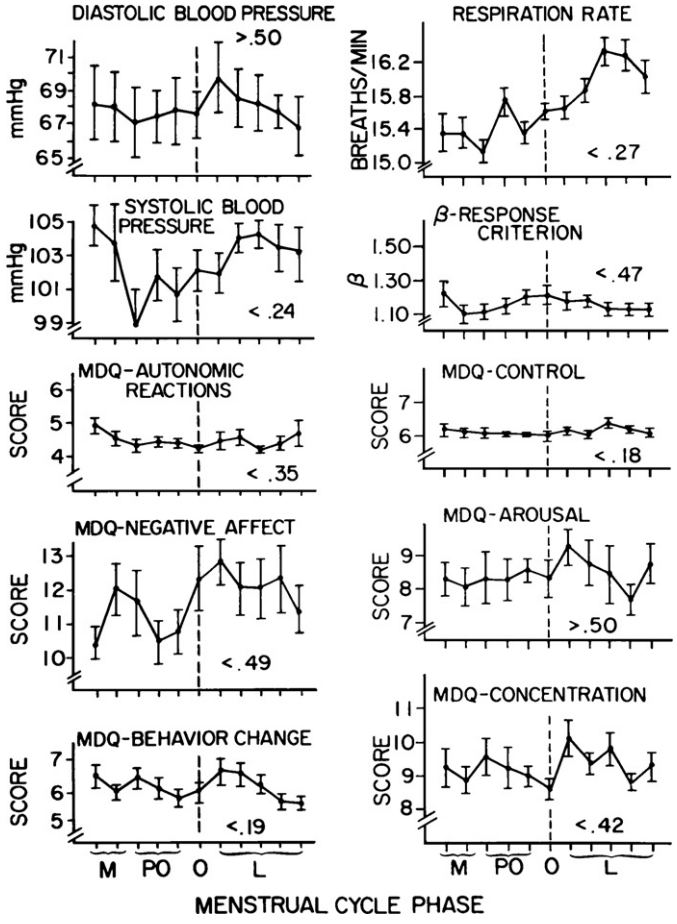

Fig. 7. Mean (SEM) changes in 10 additional variables (see Fig. 6) as a function of menstrual cycle phase in normally cycling women. MDQ = Moos Menstrual Distress Questionnaire. From [79] with permission. Copyright © 1986, Macmillan Publishing Company, a division of Macmillan, Inc.

women not taking oral contraceptives and 6 menstrual cycles of women taking oral contraceptives [60]. Concomitant measures of blood pressure, heart rate, body temperature, nasal airflow, and respiration rate were taken, along with circulating levels of follicle stimulating hormone (FSH), estrone (E_1), estradiol (E_2), progesterone (P), testosterone (T), and luteinizing hormone (LH). LH was also measured on a daily basis from day 10 to day 20 of the projected cycle to establish the day of the LH surge. The Moos Menstrual Distress Questionnaire (MDQ) [107] was administered on each test occasion.

Using a normalization and cycle phase categorization procedure that overcame a number of the problems of averaging data across cycles of different lengths and different temporal hormone profiles [108], peaks in average sensitivity were observed mid-cycle, midluteally, and during the second half of menses in both women taking and not taking oral contraceptives (Fig. 5). A serendipitous finding of systematic changes in the detection performances of the women taking oral contraceptives suggested the possibility that the sensory fluctuations observed in normally cycling women may not be directly dependent upon circulating levels of gonadal hormones or hypophyseal gonadotropins, despite being correlated with them. The fluctuations observed in the variables of this study for the women not taking oral contraceptives are shown in Figs. 6 and 7.

To establish whether statistical relationships existed among the 23 variables within the normally cycling women, correlations were computed across the means of the 11 cycle phases of these subjects.

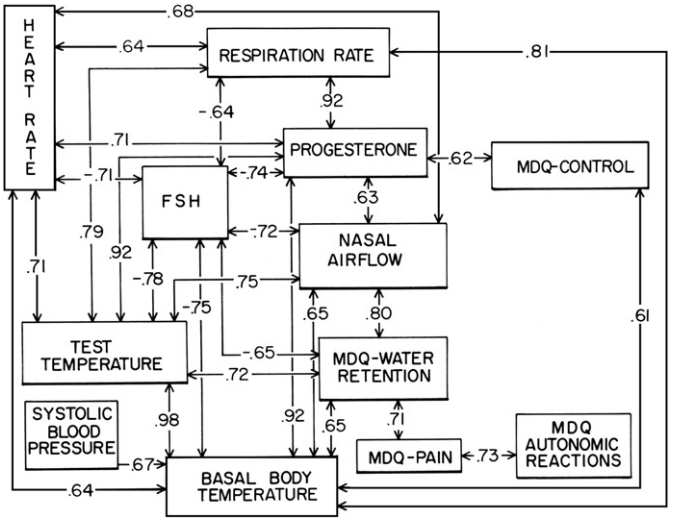

Fig. 8. Cluster of primary correlations among variables that most strongly loaded on Factor 1 of the principal components analysis of the data from the normally cycling women. FSH = follicle stimulating hormone. MDQ = Moos' Menstrual Distress Questionnaire. From [79] with permission. Copyright © 1986, Macmillan Publishing Company, a division of Macmillan, Inc.

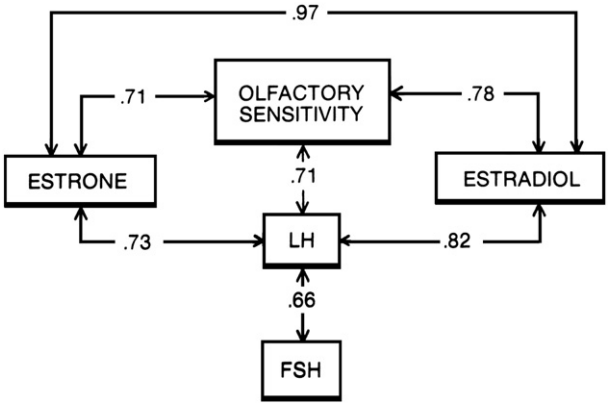

Fig. 9. Cluster of primary correlations among variables that most strongly loaded on Factor 2 of the principal components analysis of the data from the normally cycling women. LH = luteinizing hormone; FSH = follicle stimulating hormone. From [79] with permission. Copyright © 1986, Macmillan Publishing Company, a division of Macmillan, Inc.

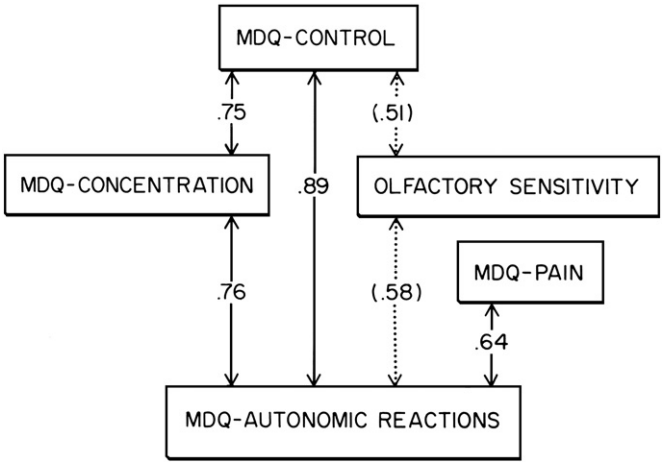

Fig. 11. Cluster of primary correlations among variables that most strongly loaded on Factor 2 of the principal components analysis of the data from the women of the oral contraceptive group. Correlation coefficients in parentheses not significant. From [79] with permission. Copyright © 1986, Macmillan Publishing Company, a division of Macmillan, Inc.

The resulting correlations were then subjected to principal component analysis to help define the nature of the patterns of the underlying relations. The intercorrelations of those variables which loaded most strongly on Factor 1, which accounted for most of the explained variance, are shown in Fig. 8. This set of measures could be termed a "progesterone-cardiovascular" factor. The only variable with a strong negative loading on this factor was FSH, possibly reflecting the higher levels of this hormone in the preovulatory phase of the cycle. Variables loading on Factor 2 are shown in Fig. 9 and largely reflect measures that tended to peak mid-cycle, including that of olfactory sensitivity. This set of variables appears to reflect an "estrogen-LH-olfactory sensitivity" factor.

A similar analysis of the data from the women taking oral contraceptives revealed a primary factor with a negative loading by FSH and positive loadings by body temperature during testing, systolic blood pressure, and heart rate (Fig. 10). These loadings were similar to those observed for Factor 1 of the normally cycling group, although progesterone, respiration rate, and the MDQ water retention symptom scale did not load strongly on this factor, conceivably reflecting the absence of cyclic ovarian progesterone in this group. In addition, nasal airflow loaded negatively on this factor. As in the normally cycling group, olfactory sensitivity (d') loaded positively on a second factor of the oral contraceptive group, although the strong positive loadings of E_1, E_2, and LH were absent (Fig. 11). In addition, the MDQ symptom scales of concentration, autonomic reactions, and control were positively loaded on this factor.

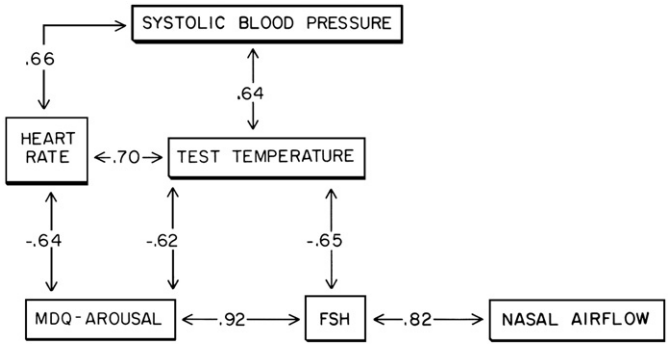

Fig. 10. Cluster of primary correlations among variables that most strongly loaded on Factor 1 of the principal components analysis of the data from the women of the oral contraceptive group. FSH = follicle stimulating hormone. From [79] with permission. Copyright © 1986, Macmillan Publishing Company, a division of Macmillan, Inc.

A subsequent study sought to determine whether the shifts in olfactory sensitivity observed in pill cycles for furfural were also present for another compound, phenyl ethanol, as well as whether auditory measures exhibit fluctuations during the cycle [103]. In this experiment, the following measures were taken at bidaily intervals across two complete menstrual cycles in a 24-year-old woman taking oral contraceptives: olfactory sensitivity (d'), pure-tone auditory thresholds, acoustic impedance, brain stem auditory evoked potentials, body temperature, heart rate, plasma LH, plasma FSH, plasma total estrogens, and plasma progesterone. A close correspondence was present between several of these variables (Fig. 12), although slight differences in the times of their maxima and minima were noted. Because these data are from only one individual and because each point represents a moving average with equal weights attached to three adjacent time points, some of the lack of correspondence may reflect noise. It is also possible that some of these rhythms are relatively independent of one another, as has been noted in human activity and temperature rhythms when major Zeitgeibers are absent (i.e., in the free-running state).

A striking positive correlation can be observed in Fig. 12 between body temperature during testing and olfactory sensitivity, as well as negative relations between pulse rate and olfactory sensitivity (note that pulse rate is inversely plotted). Pure-tone thresholds appear to be more closely related to basal body temperature than to the other measures, as would be expected from the literature [109], although several points of correspondence are clearly present across all the non-hormonal measures. These data raise the possibility that the sensory shifts noted in women taking oral contraceptives are not specific to olfaction, but occur in audition as well. Whether they reflect the same or different underlying physiological processes is not clear, but it is interesting that both seem to be closely associated with fluctuations in body temperature.

Given the inconsistencies across menstrual cycle studies, four methodological issues are worthy of mention. *First*, the type of odorant employed seems to play a role. However, clear associations with physiochemical parameters have not been found and some of the stimuli that have been employed likely activate both olfactory and intranasal trigeminal afferents, complicating the interpretation of the findings [110]. *Second*, different types of psychophysical paradigms have been used to measure threshold-level sensitivity. Some of these paradigms, such as single ascending or descending series, are highly unreliable. A number of studies failing to find significant effects have used large step sizes in their odorant concentration series which may obscure small, but consistent, changes. Signal detection paradigms,

which do not depend upon concentration steps as such, likely provide a more sensitive measure. *Third*, the manner in which cycle phase is defined varies among studies. Although many have used basal body temperature to establish the general time of ovulation, few have measured circulating hormones, which is much more accurate. *Fourth*, in some studies the sensory measures are collected too infrequently to allow for an understanding of the underlying fluctuations. *Fifth*, the classification scheme used to combine data across cycle phases can greatly affect the findings, as shown in Fig. 13 [108], where the signal detection measure of olfactory sensitivity, *d′*, was categorized into menstrual cycle phases using eight different techniques found in the literature (see figure caption for specifics). The left column depicts categorization of raw data points and the right column categorization

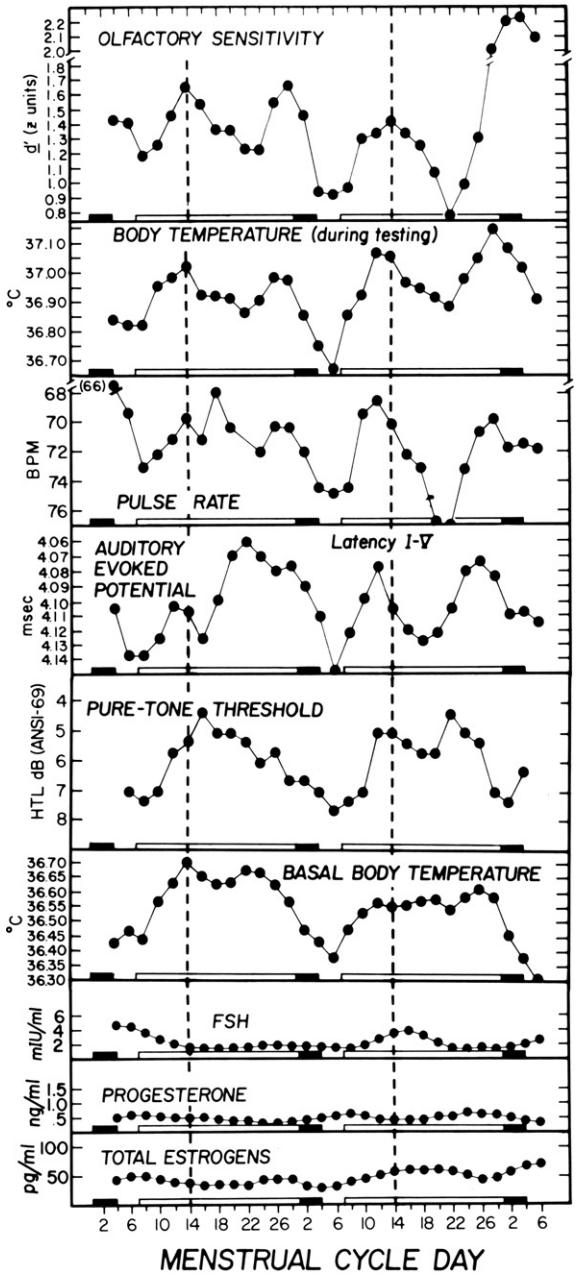

Fig. 12. Changes in nine variables across two consecutive menstrual cycles of a subject taking oral contraceptive medication. To diminish noise, a moving average with equal weights attached to three adjacent time points was applied to each series. Dark rectangles on the abscissae signify periods of menstrual bleeding; open rectangles, days during which the oral contraceptive medication was taken. Testing took place from 9:30 AM to noon each day. Pure-tone thresholds were averaged across a range of frequencies. From [103] with permission. Copyright © 1982 IRL Press, Ltd.

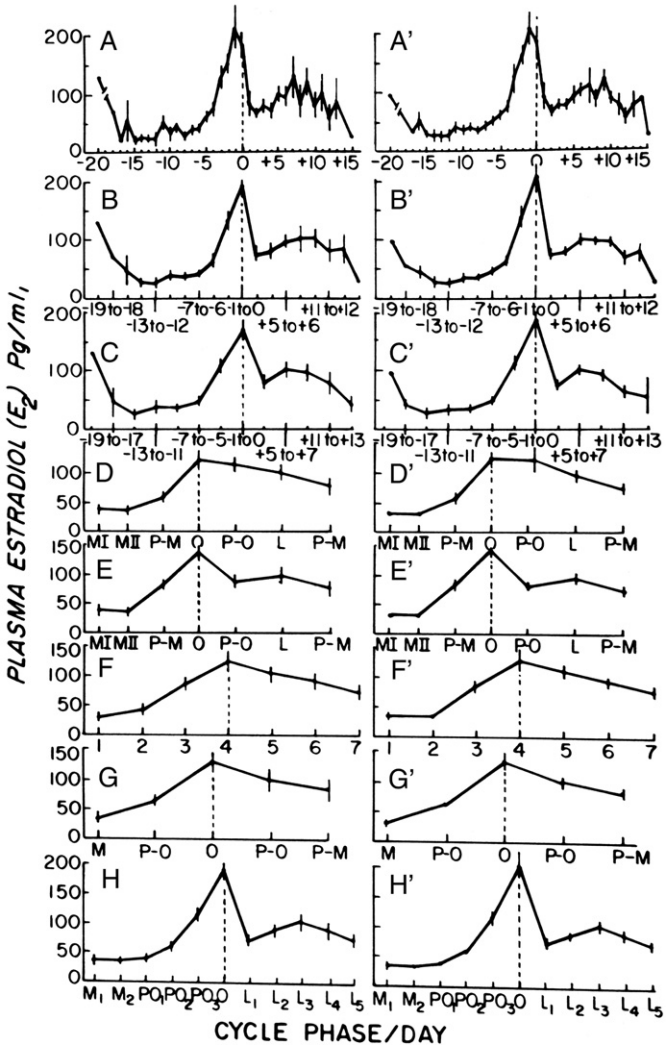

Fig. 13. Mean (±SEM) plasma levels of 17β-estradiol for eight women across 14 cycles categorized by eight techniques. Raw (i.e., non-normalize) data are represented on the left, and normalized data on the right. Normalization consisted of multiplying each daily measure from a given cycle by a factor that equated the arithmetic mean of all of the daily measure of that cycle to the grand arithmetic mean of the entire cycle day/cycle matrix. A, A′: Data plotted daily from LH surge; B, B′: data plotted in two-day intervals from LH surge. C, C′: Data plotted in three-day intervals from LH surge. D, D′: Data categorized by the Spitz et al. [187] procedure. E, E′: Data categorized by a modified Spitz et al. [187] procedure. F, F′: Data categorized into successive sevenths of the cycle. G, G′: Data categorized by the Doty and Silverthorne [65] procedure. H, H′: Data categorized by the Doty [108] procedure. From [186] with permission. Copyright © 1979 by The Endocrine Society.

of data points after between-cycle variation is minimized using a data matrix normalization procedure. This figure shows that some categorization procedures lead to erroneous conclusions. For example, procedures A, B, and C suggest the presence of three or more sensitivity peaks, whereas procedures F and G imply few peaks are present. The preferred procedure, shown in H′, assigns data to a set of discrete cycle phases using a weighted-average technique that allows for grouping data from cycles of different lengths and different times of LH surges on the same figure. The traditional LH-centering technique results in combining of heterogenous sectors of individual cycles as distance from the mid-cycle LH surge increases, a problem illustrated in Fig. 14 for basal body temperature. These problems are discussed in detail elsewhere [108].

4. Odor perception during pregnancy

Many women report experiencing enhanced sensitivity or other alterations in their ability to smell while pregnant, as evidenced by

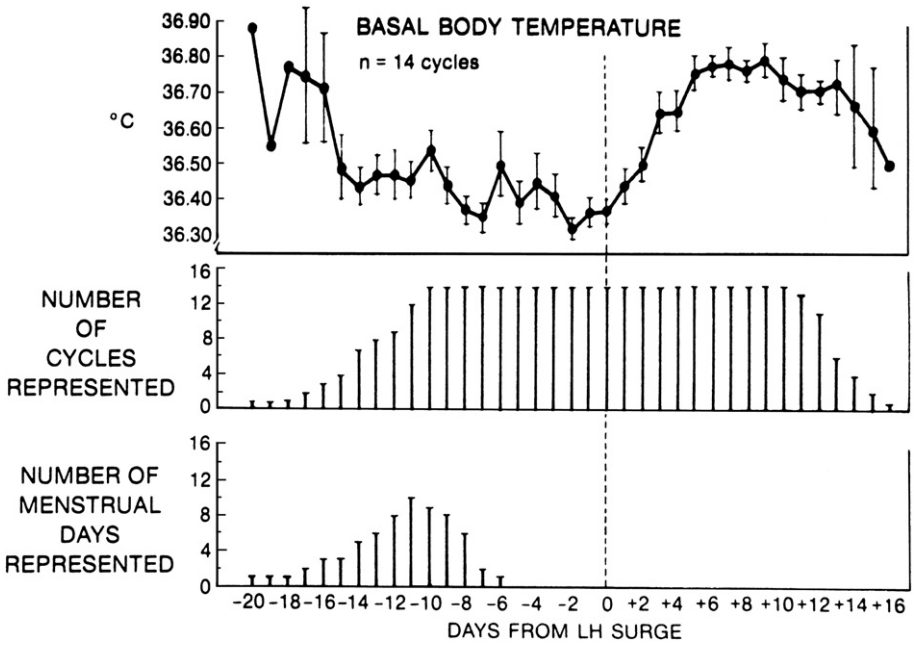

Fig. 14. Basal body temperature (BBT) means (SD) plotted by day from the major LH surge. Based on 14 menstrual cycles of 8 health women ranging in age from 18 to 33 years [mean (SD) = 24.9 (4.8)]. Average cycle length = 27.4 days (range 23–33 days); mean duration of menses = 5.0 days (range: 3–7 days). The day of the major LH surge occurred, on average, 14.9 days (range: 11–21) from the onset of menstrual bleeding. Note the decrease in the number of cycles represented as the distance form the LH surge increases and the additional of menstrual cycle days as one moves from day −6 outward. From [79] with permission. Copyright © 1986, Macmillan Publishing Company, a division of Macmillan, Inc.

anecdotal reports and numerous surveys. For example, Nordin et al. [111] administered an extensive smell and taste questionnaire to 187 pregnant and 80 non-pregnant women at various time points during pregnancy, postpartum, or the equivalent time periods, inquiring about self-perception of olfactory sensitivity and experiences of distortion and phantom smell sensations. Over two-thirds (67%) of the pregnant women reported experiencing an increase in smell sensitivity at some point during pregnancy. Qualitative smell distortions were noted by 17%, and phantom smells by 14%. Such experiences occurred more frequently during early pregnancy.

Despite such reports, the data on changes in olfactory function during pregnancy do not reveal a clear picture, and it is unknown whether measurable sensory changes accompany the cravings and aversions that are commonly experienced [112,113]. Only rarely has smell and taste perception been tested repeatedly across the trimesters of pregnancy, and signal detection measures that would aid in differentiating between response biases and actual sensitivity have not been performed (for summaries of the early non-English literature on olfactory changes in pregnancy, see [114–116]).

4.1. Olfactory sensitivity

Some of the earliest studies, which assessed recognition thresholds, reported decreased odor sensitivity in late pregnancy. For example, Hansen and Glass [115] measured thresholds for rose oil, nitrobenzene, and rubber using a Zwaardemaker apparatus [117] in 22 women during the last weeks of pregnancy and on postpartum days 2–3 and postpartum weeks 6 to 8. A 30 to 45% decrease in sensitivity was noted during late pregnancy for all substances (compared to two postpartum measures, which did not differ from one another). Noferi and Giudizi [116], using a blast-injection procedure, found higher recognition thresholds (hyposmia) for lemon odor in 15 women during the last two months of pregnancy relative to measures obtained from 15 non-pregnant women and 15 postpartum women. Likewise, Luvara and Murizi [114] found, in 47 women, a progressive hyposmia during the second and third trimesters to the odors of carnation, anise, and musk, although hyperosmia was present in early pregnancy.

Conflicting findings are present in more recent studies. In contrast to the aforementioned work, Laska et al. [118] found, in a study of 20 pregnant and 20 non-pregnant women, *hyposmia* in early pregnancy and *hyperosmia* in late pregnancy for the odorant n-butanol. Hyperosmia for n-butanol was also reported in late pregnancy by Ochsenbein-Kölble et al. [119] in 38 pregnant women. Decreased pyridine thresholds were noted by Broman et al. [120] in 30 2nd-trimester women compared to 30 non-pregnant women. Kölble et al. [121] found no pregnancy-related influences on n-butanol thresholds in 53 pregnant women (first trimester only) relative to 59 non-pregnant controls.

4.2. Odor identification

No study has found pregnancy-related *general* enhancement in the ability to identify odors. Gilbert and Wysocki [122] examined odor identification data from 13,610 pregnant and 277,228 non-pregnant women who responded to the NGSS. No differences between pregnant and non-pregnant respondees were found for 5 of the 6 odors; pregnant women did identify eugenol (clove) correctly more often than non-pregnant women. Laska et al. [118] similarly found, relative to non-pregnant controls, a pregnancy-related enhancement in the ability to identify eugenol presented in squeeze bottles. However, their pregnant subjects were less able than controls to identify the remaining 11 odors. Ochsenbein-Kölble et al. [119] found no differences between pregnant and non-pregnant women in their ability to identify 16 odors in a 4-alternataive forced-choice test. In a similar study of 40 odorants, Cameron [123] found that 20 pregnant women tested in each trimester of pregnancy were superior to 20 non-pregnant women and 20 postpartum women in their ability to identify only one odor, that of watermelon. Unlike the earlier studies, no superiority was found for the odor of clove (eugenol).

4.3. Hedonics

It has been consistently reported that pregnancy affects hedonic ratings, primarily by decreasing the pleasantness of odors. This phenomenon seems stimulus dependent. For example, in a

retrospective study of 500 women who had successfully completed at least one pregnancy [124], approximately three-quarters of the women reported that there were odors that smelled less pleasant during pregnancy (e.g., cigarettes, coffee, meat, food in general, diesel exhaust, sweat). Less than a quarter reported that there were odors that smelled more pleasant (fruits, flowers, woodlands, perfume).

A similar phenomenon has been noted when odorants were actually sampled by pregnant women. For example, in the NGSS, of the 6 presented odors, half were rated as less pleasant by pregnant than by non-pregnant women (Galaxolide, eugenol, and mercaptan) and one (androstenone) was rated as more pleasant [122]. Laska et al. [118] reported a complex odor-dependent relationship between trimester of pregnancy and hedonic ratings. Although some odors were rated less pleasant on certain test sessions (peanut, aniseed and banana), some were rated as more pleasant (clove, musk and perfume). In the Kölble et al. [121] study, pregnant women rated the pleasantness of most odors no differently than controls, although three odors (rum, cigarettes and coffee) were reported to be more aversive. Recently, Cameron [123] found that, compared to non-pregnant controls, women in the first trimester of pregnancy tended to rate the majority of 40 UPSIT odorants as less pleasant. However, statistical significance was achieved for only three; namely, orange, grape and natural gas. Interestingly, fruit punch was rated as significantly more pleasant.

4.4. Olfaction and nausea

The idea of a causal link between enhanced olfactory sensitivity during pregnancy and nausea and vomiting is compelling. Thus, Cantoni et al. [124] reported that 58% of women reported that there were odors that caused nausea during pregnancy and Heinrichs [125] reported a substantial decrease in reports of nausea and vomiting in pregnant women with congenital anosmia. However, Hummel et al. [126] found no correlation between self-reported nausea and performance on measures of odor threshold, discrimination, and identification, suggesting that such effects may not be strongly tied to basic olfactory function.

Clearly the literature on olfaction and pregnancy is inconclusive. It appears that many changes that occur in smell function during this time are idiosyncratic and specific to only some odorants. Further research, employing large numbers of odorants, is needed to better understand the nature of the influences of pregnancy on olfactory function. A key to such understanding may rest on the chemicals chosen for evaluation and an examination of cognitive factors that are influenced by pregnancy.

5. Influences of administration of gonadal steroids on olfactory function

Only a handful of studies have examined the effects of oophorectomy, orchidectomy, or hormonal replacement therapy (HRT) on human olfactory function. Most of these studies suffer from small sample sizes, lack double-blind or placebo control procedures, and confound test order with hormone treatments.

In the early 1950s, Le Magnen [36] self-injected large doses of testosterone and estradiol and reported that (1) estradiol increased his sensitivity to trimethylamine and pyridine and decreased his sensitivity to safrol and (2) testosterone decreased his sensitivity to most of the odors he evaluated, including Exaltolide. He also assessed Exaltolide detection thresholds in seven ovariectomized women and found them to be elevated. After estrogen treatment of five of these women, thresholds dropped by factors greater than two log units in two subjects and by less than a log unit in two others. No change was noted in the thresholds of the fifth subject.

Following up on this work, Schneider et al. [127] tested thresholds to the odorant citral in two hypogonadal women (age 84 and 30 years) once a week over 28- and 43-week time periods. Daily injections of either placebo or Equilin SO_4, Premarin, or estradiol were interspersed in 1- to 2-week-long treatment intervals within the test period. Similar assessment of the influences of testosterone was made in a 69-year-old woman. Estrogen injections lowered the thresholds and testosterone injections raised them, although the effects were small and considerable day-to-day overlap in the threshold values was present.

In a third positive study, Good et al. [128] reported, using a signal detection procedure, an increase in sensitivity to Exaltolide following the administration of estrogen (dosage and type of estrogen not reported) in a woman who was initially anosmic to Exaltolide. The woman was evaluated two days before and on each of nine days during a series of the hormone treatments. The percentage of hits and false alarms were both zero on the two pretreatment days, implying that detection was not reported on any trial. During the initial treatment days the percentage of hits and false alarms rose to about the same level, whereas during the later days the percentage of hits rose even higher, with a decrease occurring in the false alarm rate.

In contrast, a number of studies have reported finding no influence of hormone administration on measures of olfactory function. In a well-controlled study, Hughes et al. [129] administered tests of odor detection, intensity, discrimination, quality discrimination, and two measures of quality recognition to 62 post-menopausal women. No differences in performance on any of these tests were found between women receiving and women not receiving hormone replacement therapy (HRT). Robinson et al. [130] reported that olfactory thresholds to phenyl ethanol, mercaptan, glacial acetic acid, and eucalyptol were not influenced by *in vitro* fertilization procedures designed to enhance ovarian production of estradiol. In this paradigm, down-regulation of FSH and LH receptors is first induced by Suprecur injections, resulting in low circulating 17β-estradiol levels. Up to 12 subsequent daily injections of FSH are then used to stimulate ovarian production of 17β-estradiol. Comparison of the olfactory threshold values for 6 women under low and high 17β-estradiol conditions revealed no effects on the threshold measures. A comparison of data sets collected on seven subjects prior to and after the steepest rise in 17β-estradiol levels also failed to show any meaningful influence of estrogen on the threshold measures.

Recently, Doty administered a standardized 12-item odor memory/discrimination test [131] to each side of the nose of 14 post-menopausal women receiving estrogen replacement therapy (ERT) and 48 post-menopasual women receiving no such therapy [132]. Although no influence of ERT was observed on the overall test scores, those receiving ERT performed better in the left nostril, and poorer in the right nostril, a phenomenon absent in those not receiving ERT. This effect was independent of handedness, age, detection threshold sensitivity to phenyl ethanol, and left:right differences in nasal volume or cross-sectional area, as measured by acoustic rhinometry. These data suggest that ERT may differentially influence the left and right sides of the brain, since olfactory projections are largely ipsilateral from the bulb to the structures that make up the primary olfactory cortex.

As in the case of the pregnancy studies, a wider range of stimuli need to be assessed in well-designed double-blind placebo controlled studies before confidence can be placed in the notion that gonadal hormones meaningfully influence human olfactory sensitivity. If positive effects are found, exploration of dose–response relations should be instigated to more definitively link the behavior to the hormone treatment.

6. Discussion: causal mechanisms producing sex differences and reproductive state-related changes in olfactory perception

For a number of years a straightforward reproductive hormone-based explanation for the phenomena described in the previous sections was generally accepted; i.e., that the relative levels of circulating gonadal hormones, particularly the androgens and estrogens, were responsible for differences seen in olfactory performance

measures between the sexes and across the stages of the reproductive cycle (including pregnancy). While one cannot discount the potential involvement of such hormones on the olfactory pathways, a critical examination of previous literature and the results of a number of experiments throw into question the validity of this enticing explanation, at least for the data on sex differences. Instead, it would appear that complex relationships exist between the functional properties of the olfactory system and a range of interacting neuroendocrine factors during early brain development and at later stages of life. This perspective is discussed in the following sections.

6.1. Sex differences

Many sex differences arise from the influence of gonadal hormones on the central nervous system during early, largely prenatal, periods of brain development. Such influence provides a substrate upon which hormones have their effects later in life, e.g., during and following puberty. Sexually dimorphic behavioral traits can generally be classified into three types [133,134]:

Type 1 — those that require, for full expression, relevant hormones both during an early critical stage and during a later life period (e.g., male rat copulatory behaviors).
Type 2 — those that require relevant hormones only at a later life stage (e.g., the testosterone-induced yawning behavior of rhesus monkeys).
Type 3 — those that require only relevant hormones during an early critical period (e.g., the micturition patterns of dogs).

Obviously, a number of human sex differences in behavior are learned and depend on cultural factors. However, many others arise from hormonal influences. While most authors reporting sex differences in odor perception would not exclude cultural factors from their list of potential explanations, endocrine differences have received the most attention in their theorizing [36,44]. Furthermore, implicit in much of this literature is Type 2 above; namely, a rather direct dependence of the dependent measure upon circulating levels of hormones present at the time of assessment without much concern for the sex (and thus early critical-period endocrine influences) of the experimental subject.

How well do the sex difference data from human olfactory studies fit these three types of hormonal influences? If Type 1 or 2 is correct, and if the notion that androgens depress and estrogens enhance olfactory performance is also correct [36,98,127], several predictions should be supported. *First*, one would expect prepubertal subjects to exhibit no marked sex difference in the measure of interest, since clear-cut sex differences in circulating levels of the primary reproductive hormones are not present at this time [135,136]. *Second*, the observed sex difference should occur around the time of puberty (when clear-cut sex differences in such reproductive hormones appear) and continue into middle adulthood. *Third*, assuming that the endocrine effect is of a magnitude sufficient to overcome the detrimental effects of aging which, for the most part, occur after the age of 60, a rather marked decline in olfactory sensitivity might be expected in women at menopause, since their estrogen levels decrease dramatically at that time [137]. *Fourth*, one might expect older men to be more sensitive than younger ones, since they exhibit reduced circulating levels of testosterone and elevated circulating levels of estrogen [138].

Although the data in this field are sparse, they are consistent in providing little support for any of these predictions. Thus, as indicated earlier, prepubescent girls outperform prepubescent boys in a number of threshold and odor identification tasks, and the degree of this sex difference does not appear to change at puberty. Furthermore, no marked decline in either of these measures is seen at the time of the female menopause (although a gradual decline does occur across the later years), and older men do not outperform younger men. If concurrent gonadal hormones contribute to the olfactory perception of the elderly, the degree to which they do so must be fairly minor.

Despite the temptation to conclude from the aforementioned information that reproductive hormone Types 1 and 2 do not explain the sex differences in the literature, it is still possible that some other endocrine substance is present before puberty and in adulthood that produces the sex difference in odor detection or recognition performance. For example, sex differences are present in the circulating levels of several steroids from the adrenal gland before puberty, such as dehydroepiandrosterone (DHEA), perhaps the most abundant steroid in humans [139]. More work is obviously needed to determine whether this or other steroids that are precursors to the main ovarian and testicular hormones influence human olfactory sensitivity in any substantial manner.

Assuming that concurrent reproductive hormones are not primarily responsible for producing the sex differences noted in olfactory perception, Category 3 would appear to be the most likely endocrine-based explanation for these differences. However, just how early endocrine factors influence neural circuits in producing these changes is not clear. A large body of literature indicates that rather gross morphologic differences exist between male and female brains. For example, a sex difference exists in the shape and area of the human corpus callosum and the anterior commissure, and sex differences exist in the numbers of dendritic branches and interconnections in certain areas of the hypothalamus and cortex of a number of species [140–147].

6.2. Menstrual cycle

Although the olfactory sensitivity fluctuations observed in normally cycling women may well reflect fluctuations in ovarian steroids, the finding that such fluctuations continue to occur in women taking oral contraceptives opens the door to the possibility that ovarian hormones may not be the primary cause for the cyclic changes in olfactory sensitivity. If ovarian hormones or pituitary gonadotropins are not the direct cause of these fluctuations in women taking oral contraceptives, what are the possible responsible mechanisms? Four possibilities, outlined below, come to mind.

The first possibility is that the fluctuations observed in women taking oral contraceptives simply reflect the influence of the exogenous synthetic steroids of the oral contraceptives on either the olfactory system proper or some related process that might alter olfactory function, such as body temperature. It is known that that oral contraceptives raise the body temperature in women [148,149] and that some measures of sensory function, such as auditory thresholds and auditory event-related brainstem responses, are positively correlated with body temperature [109]. Certainly the pattern of olfactory sensitivity and body temperature is highly correlated in the data presented in Fig. 12. In this scenario, there would be no strong evidence against the idea that the fluctuations observed in normally cycling women are due to fluctuations in ovarian hormones, although multiple determinants cannot be ruled out.

A second possibility is that cyclic changes in the oral contraceptive users reflect fluctuations in hormones other than the primary ovarian steroids. Prime candidates would include agents from the adrenal gland. In an early study, Bourne and Zuckerman [150] demonstrated recurrent vaginal estrus in gonadectomized females given a low daily dose of estrone. The periodicity of this phenomenon was indistinguishable from that of estrous cycles in non-ovariectomized females. Although the cyclicity was not markedly altered by hypophysectomy, it was eliminated or greatly affected by adrenalectomy. In another series of experiments, these authors noted a 4- to 5-day rhythm in adrenal weight and volume of ovariectomized female rats given an appropriate noncyclic daily dosage of estrone [151]. This rhythm was due mainly to hypertrophy of cells within the zona fasciculate of the cortex, although adrenal medullary cells increased in size as a result of the daily

estrogenic stimulation. Tangential support for the possible involvement of the CRH–ACTH–adrenal axis comes from reports that patients with Addison's disease have lowered thresholds to odors and sounds [152,153]. Administration of the glucocorticoid prednisolone (which returns the heightened ACTH levels to normal) also reportedly returns the olfactory sensitivity to normal, whereas the administration of the mineralocorticoid desoxycorticosterone acetate (which has little or no effect on ACTH levels) has no influence [152]. Enhanced odor detection performance following adrenalectomy was found in one rat study [154], although a more recent study did not see such enhancement [155].

A third possibility is that the origin of these fluctuations lies within the central nervous system proper, being controlled by centers or networks similar to those implicated in the control of a wide variety of other behavioral rhythms [156]. For example, these fluctuations could reflect either specific or nonspecific influences of neurotransmitters or other neuroactive substances that oscillate with a 25 to 30 day periodicity which become unmasked once ovarian cyclicity is attenuated. In light of the work by Bourne and Zuckerman [151], it is possible that estrogens may serve a permissive role in the expression of some hypothalamic rhythms that, in turn, influence olfactory function. Terasawa and Timiras [157], for example, noted that estrous-related cyclic changes in electrically-induced seizure thresholds in the hippocampus and amygdala, although eliminated by ovariectomy, were briefly restored, in dampened fashion, following a single injection of estradiol. That this phenomenon may be influenced by some type of early hormonal organizational process is suggested by their finding that such restoration was most marked in rats ovariectomized in early adulthood and was not present in rats ovariectomized in infancy.

6.3. Pregnancy

As with sex differences and menstrual cycle-related fluctuations, the basis for changes reported in chemosensory function during pregnancy are poorly understood and no physiological basis for such changes has been convincingly demonstrated. Profet [158] has argued that enhanced olfactory sensitivity is an adaptive mechanism designed to protect the developing fetus by altering the food intake patterns of pregnant women, particularly in the first trimester. Although empirical evidence has not universally supported this concept [159], a number of studies have lent at least some support. Thus, heightened levels of disgust for foods have been reported in the first trimester of pregnancy, which correlates with a period of immunosuppression [160]. Reports of heightened sensitivity to odors during pregnancy largely point to noxious agents that may provide a threat to the fetus, rather than to the intolerance of environmental stimuli in general [161,162].

Kölble et al. [121], who found that pregnant women reported coffee, rum and cigarettes to be aversive, suggested that "changes in cognitive odor information processing occur in the first trimester and may be adaptive in terms of fetal survival" (p. 182). A role for central cognitive processing changes in pregnancy is indirectly supported by research performed by Olofsson et al. [163] who obtained OERPs from 15 pregnant (weeks 21–23) and 15 non-pregnant women. Although the sensory OERP components (N1 and P1) showed no modulation due to pregnancy during the presentation of three concentrations of pyridine, the so-called cognitive component (P3) showed a larger amplitude and shorter latency response during pregnancy. Thus, the olfactory alterations experienced by some women during pregnancy conceivably arise from psychological changes during this time, possibly explaining the largely negative sensory sensitivity test results. Signal detection measures that differentiate between sensory sensitivity and response biases might aid in establishing whether this is, in fact, the case.

6.4. Injection or oral administration of reproductive hormones

A detailed discussion of mechanisms responsible for changes in human olfactory sensitivity or function brought about by the administration of hormones is difficult in light of the paucity of data and the complexity of this topic. The few rodent studies in which olfactory sensitivity has been measured after hormone injections are limited in scope and provide findings discrepant from one another and from those reported in humans. For example, Pietras and Moulton [164] found a statistically significant *increase* in odor detection performances of adult female rats to cyclopentanone following ovariectomy (which would not be expected from a pure estrogen-based notion of olfactory modulation), although such an increase was not present in a nearly identical study by Phillips and Vallowe [165]. Unlike the claims of some human studies, Pietras and Moulton found that supraphysiologic doses of testosterone actually improved odor detection performance in ovariectomized female rats. Whether this was due to aromatization of testosterone to estrogens is not clear. Male castration does not alter sensitivity of male rats to either female estrous urine [166] or ethyl acetate [167], although it does mitigate the improvement in ethyl acetate detection performance observed in sham castrates as a result of repeated testing [167]. It should be pointed out that even studies examining the influences of estrus on rodent olfactory sensitivity are discordant. Thus, Pietras and Moulton [164] reported that optimal performance during the rat estrous cycle for detecting the odors of cyclopentanone, eugenol, α-ionone, and Exaltolide occurs on the day of vaginal estrus, with relatively poor performance occurring during proestrus. In contrast, Schmidt and Schmidt [168] reported that, in housemice, optimal performance for detecting geraniol occurs during proestrus, not estrus.

If gonadal hormones influence olfactory sensitivity, they may do so through a number of mechanisms. Assuming that their major effect is not upon nasal patency, airflow, or alterations in the permeability of the olfactory mucus to odorants, three primary – non-mutually exclusive – means include (1) an influence on nonspecific brain arousal systems, such as the reticular activating system, (2) a direct influence on CNS olfactory transduction pathways, and (3) an indirect influence on CNS olfactory pathways via other endocrine systems. An example of the latter is the well known influence of gonadal hormone injections on pituitary ACTH and adrenal corticosterone levels [169].

A potential means by which reproduction-related and other hormones might influence olfactory sensitivity is via their effects on the neurotransmitter γ-aminobutyric acid (GABA). GABA is intimately involved in damping general brain excitability, and is inhibited by estradiol and facilitated by progesterone [170,171]. Estradiol potentiates glutamatergic neural transmission (glutamate is a neurotransmitter for both first and second order olfactory projection neurons) and promotes kindling and seizure activity, whereas metabolites of progesterone suppress kindling and seizure activity [172]. Seizure frequency is positively correlated with the serum estradiol/progesterone ratio [173], which is highest just prior to menses and just prior to ovulation — times when two of the three peaks in olfactory sensitivity occur during the menstrual cycle (Fig. 6). It is well established that a major component of the primary olfactory cortex, namely the piriform cortex, plays a significant role in seizure activity, including the development of amygdala kindling and the amplification and distribution of seizure activity from amygdala foci to other limbic brain regions [174].

In accord with the concept of GABAergic modulation of olfactory sensitivity by hormones is the observation that the same hormonal manipulations similarly influence olfactory and electrically-induced seizure thresholds (see [175] for a review of the seizure literature). This correspondence, shown in Table 1, suggests the hypothesis that both thresholds for odor detection and experimentally induced seizures may be modulated by similar mechanisms. Since hormonal influences on GABAergic systems are quite general, one might predict that the administration of exogenous hormones similarly influences more than one sensory system. Olfactory system specificity is also possible, depending upon the type of GABA receptor, given GABA's role via granule cells in postsynaptic inhibition on olfactory bulb

mitral cells (for review, see [176]). Most centrifugal fibers from higher brain centers project to GABA-containing granule cells and not to the mitral cells themselves, providing a direct means of GABAergic inhibition of mitral cell activity. For example, Dahlstrom et al. [177] demonstrated that norepinephrine-containing centrifugal fibers synapse primarily within the granule cell layer, and Salmoiraghi et al. [178] found that electrophoretically applied norepinephrine decreases the firing of mitral cells. Nicoll [179] has described the depression of mitral cell activity by locally applied GABA and the antagonism both of this action and of the lateral tract inhibition of mitral cells by intravenous administration of picrotoxin.

That being said, it is prudent to recognize that the relationship between gonadal hormones, neural excitability, and sensory function is fraught with complexities [180]. For example, pretreatment of rats with low doses (<10 μg) of β-estradiol delays kainic acid-induced clonic seizures [181], whereas such treatment with 20 μg of this steroid has no influence. Higher doses (e.g., 40 μg) are proconvulsant. As reviewed by Veliskova [180], the influences of estrogens on neural excitability often are region-specific. Thus, β-estradiol administration facilitates kindling from the dorsal, but not the ventral, hippocampus. Moreover, estrogen interacts with neurotransmitter systems involved in the generation of seizures. For example, pretreatment of ovariectomized rats with a low dose of β-estradiol (10 μg) increases high-affinity muscimol binding in the hippocampus, suggesting enhancement of sensitivity of these neurons to GABA.

Recent research has shown that the subunit composition of $GABA_A$ receptors – receptors which are common in the olfactory bulb inhibitory circuits and in the olfactory cortex – dynamically changes over the course of the estrous cycle in mice [172]. For example, elevations in progesterone levels are associated with increased expression of $\delta GABA_A$ receptors and decreased expression of $\gamma 2GABA_A$ receptors. Up-regulation of $\delta GABA_A$ receptors is correlated with decreased seizure susceptibility, whereas up-regulation of $\gamma 2GABA_A$ receptors is correlated with increased seizure susceptibility. Macquire and Mody have shown that both ovarian and stress-related hormones can change the ratio of such receptor subtypes and, thereby, moderate their efficacy [182]. Whether the fluctuations observed in olfactory sensitivity across the phases of the menstrual cycle reflect such processes is unknown.

In summary, there is circumstantial evidence that GABAergic systems may be a common denominator in producing similarities between olfactory sensitivity and seizure thresholds, and that endocrine manipulations that influence this transmitter substrate could influence olfactory sensitivity. However, at the present time this notion is highly speculative, and systematic manipulation of numerous neurotransmitters in addition to GABA is needed. For example, there are a number of reports which indicate that drugs that nonselectively lower total brain levels or activity of norepinephrine, dopamine, and serotonin facilitate seizure activity induced by toxins or electric current (e.g., reserpine [183]). Conversely, drugs which increase total levels or the availability of these amines reduce the susceptibility to seizure activity (e.g., drugs that inhibit monoamine oxidase and catechol-O-methyl transferase or drugs that block uptake, such as imipramine [184,185]). Studies more specifically aimed at factoring out the relative roles of norepinephrine, dopamine, and serotonin suggest that norepinephrine and serotonin may be more important than dopamine in regulating minimum electroshock seizure susceptibility [185,186]. It is possible, however, that these monoamine effects are mediated through GABAergic systems, making GABA the final common denominator.

7. Conclusion

It is apparent from this review that complex relations exist between the functional properties of the human olfactory system and neuroendocrine factors. Previous notions of simple relations between olfactory function and circulating concurrent levels of gonadal hormones are likely oversimplifications of how the endocrine system influences smell function. In addition to understanding the influences of an array of neuroactive agents on the adult olfactory system of both sexes, a concerted effort is needed to understand the possible organizing role of early hormones on sectors of the brain responsible for mediating sex differences and other endocrine-related events in olfactory function. At a more general level, a number of rather straightforward questions regarding human olfactory function have yet to be answered. For example, does olfactory sensitivity, as discerned using signal detection analysis, change systematically during pregnancy and, if so, are such changes odor-specific and related to nutritional needs, food intake, cravings, and aversions? Are the fluctuations in olfactory sensitivity noted across the reproductive cycle closely coupled with fluctuations in other sensory systems? If so, which ones? Are fluctuations in olfactory sensitivity present in prepubescent girls whose brains have not yet experienced cyclic changes in levels of reproductive hormones from the ovary? Are sex differences or endocrine-related changes in olfactory sensitivity specific to only some types of odors? If so, what are the physiochemical parameters most closely related to these changes? In a double-blind situation, what influences, if any, do exogenously administered hormones have on olfactory function? If injections of reproductive hormones influence olfactory sensitivity, by what means do they exert their influence?

An important question yet to be addressed is whether the olfactory sex differences observed in humans serve any biological role. This would seem to be the case, if it is assumed that such differences are specific to context, bodily states, and emotional factors. Given that a number of toxins can be transferred from the pregnant female's circulatory system to the fetus, as well as from her milk to the nursing newborn, the chemical senses likely play a role in warning a mother of foodstuffs and ambient air conditions potentially dangerous to her born or yet-to-be-born offspring. Along these lines, it is noteworthy that women are generally much more selective in food choices than men, although cognitive and societal factors, such as weight consciousness, likely play a role in such choices. Examples of foods reportedly disliked more by women than by men are brains, kidneys, buttermilk, beer, and potato soup [192]. More attune with animal studies, sex differences in the perception of odors may also play a significant role in mate selection and sexual relationships. Despite lacking a functioning vomeronasal system (a system critical for the social and sexual behaviors of many mammals), women are much more smell-oriented than men in a variety of social and sexual contexts. For example, when asked about factors critical for choosing someone as a potential lover, women are more concerned about

Table 1

Endocrine manipulation	Rat sensitivity to electrically-induced seizures	Olfactory sensitivity
Prepubertal male castration	Increased [187]	Increased (ns trend) [166]
Mature female ovariectomy	No influence [187]	No influence, [165] increased [164]
Mature female ovariectomy + estradiol replacement	Increased [187]	Increased [165]
Mature female ovariectomy + progesterone replacement	Decreased [187]	Decreased [164]
Testosterone injection	Increased [187,188]	Increased [164]
Adrenalectomy	Increased [189,190]	Increased [154]
Adrenalectomy + glucocorticoid injection	Decreased [190]	Decreased [154]
Deoxycorticosterone injections	Decreased [190]	No data
Estrous cycle		
Diestrus	No influence [191]	No influence [164]
Proestrus	Some increase [191]	Some increase [164]
Estrus	Marked increase [191]	Marked increase [164]

smells than about looks, whereas the opposite is true of men [193]. That being said, one can still question whether many of the sex differences observed on olfactory tests are, in fact, epiphenomena not directly associated with any specific biologic function.

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