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Menstrual effects on asymmetrical olfactory acuity

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Abstract

Gender specific discrepancies on psychometric examination are often interpreted to reflect static differences in cerebral hemisphere specialization, but dynamic alterations relating to circulating gonadal hormones may also be relevant after puberty. The often cited inference of a right hemisphere advantage in males and left hemisphere advantage in females derived from small but reliable differences on spatial tasks and verbal tasks, for example, may to some extent relate to gender-specific differences in circulating gonadal hormones. Performance fluctuations on other higher order cognitive tasks through the menstrual cycle tend to support a temporal association between alterations in cerebral laterality and hormone fluctuations. A potential left hemisphere advantage after menstruation when estrogen and progesterone levels are high in contrast to a right hemisphere advantage at menstruation when estrogen and progesterone levels are low has also received support from shifts in visual field perception. The present investigation continues this line of work by measurement of prospective changes in unirhinal olfactory acuity in the menstrual, ovulatory, and midluteal phases of the menstrual cycle in 11 healthy women who agreed to blood assays of estradiol and progesterone prior to completing a modified version of the Connecticut Chemosensory Perception Exam (CCPE). The CCPE detection of n-butanol showed a clear pattern of changes over the menstrual cycle marked by an asymmetry favoring the right nostril during menstruation when estradiol and progesterone levels were low, an asymmetry favoring the left nostril during ovulation when estradiol levels were high and progresterone levels were low, and an absence of asymmetry during the midluteal phase when estradiol levels decreased and progesterone levels increased. Preliminary correlation analyses revealed a potential competitive influence of estradiol and progesterone on this apparent shift in cerebral laterality. There is thus sufficient evidence to conclude that dynamic changes in relative cerebral hemisphere advantages have a temporal relation to fluctuations in circulating gonadal hormones and to suggest the value of additional investigation of more specific causal relations. (*JINS*, 2001, *7*, 703–709.)

Keywords: Menstruation, Olfaction, Asymmetry, Estrogen

INTRODUCTION

A number of interesting discrepancies have been noted between the anatomical structure of the male and female brain but the implications of the differences to emotion, cognition, and behavior have not been clearly articulated. For example, there is no clear cerebral basis for the popularized dissociation suggesting a relative male advantage on visual spatial and mathematical tasks and a relative female advantage on verbal tasks (MacCoby & Jacklin, 1974). The differences are small in magnitude but they are reliable after puberty and have suggested a possible gender-specific difference in cerebral specialization favoring the left hemisphere in women and the right hemisphere in men (McGlone, 1980; Wisniewski, 1998). The difference was often attributed to a neurodevelopmental sex differentiation, perhaps linked to the effects of circulating gonadal hormones during critical states of cerebral development (Juraska, 1986; Wisniewski, 1998), but this view tends to neglect dynamic interhemispheric changes that may result from transient post-puberty contributions from gender-specific circulating gonadal hormones. The latter possibility was suggested in a seminal review of psychometric gender differences (e.g., MacCoby & Jacklin, 1974) and it has been supported by variability in cognitive skills through the menstrual cycle of normal healthy women (Hampson, 1990; Hampson & Kimura, 1988). Motor coordination speed was better in the midluteal phase when estradiol and progesterone were at

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high levels relative to menses when estradiol and progesterone levels were low. In contrast, perceptual–spatial skills were lower in the midluteal phase relative to menses. The functional integrity of the left cerebral hemisphere has been associated with the speed of motor coordination (Kimura, 1977; Liepmann, 1908), whereas the right cerebral hemisphere has been implicated in perceptual–spatial skills (Jackson, 1915; Zangwill, 1960). The variation in motor skill and spatial skill through the menstrual cycle may thus implicate left cerebral hemisphere advantages when estradiol and/or progesterone levels are high in contrast to right cerebral hemisphere advantages when estradiol and progesterone levels are low. This interpretation was further supported by a face-matching left visual field (i.e., right cerebral hemisphere) advantage during menses in normal healthy women that shifted to a right visual field (i.e., left cerebral hemisphere) advantage in the premenstrual phase when estrogen and progesterone levels were high (Heister et al., 1989). Also, the induction of female hormone release by administration of luteinizing hormone releasing hormone (LHRH) to young healthy males resulted in verbal fluency enhancement and spatial orientation decrements that also implicated asymmetrical effects of circulating gonadal hormones favoring the left over the right cerebral hemisphere (Gordon et al., 1986). In a more recent experiment that included radioimmunoassay of gonadal hormones, normal healthy women showed a prominent left relative to right visual field advantage on a figure matching task during menstruation that was not apparent in the luteal phase (Rode et al., 1995), though this investigation also replicated an earlier absence of a similar shift on a lexical decision task (Heister et al., 1989).

There is thus sufficient evidence to warrant caution in the generalization of neurodevelopmental explanations for the apparent differential gender-specific advantages on psychometric instruments and to encourage more direct assessment of transient fluctuations of gonadal hormones that may relate to cerebral laterality. Also, although this work has implicated a general association between female hormones and hemisphere asymmetries, it has not delineated between the relative importance of a general hormone increase (e.g., LHRH), a more specific increase in either estrogen or progesterone, or central nervous system alterations that establish a temporal but not a causal relation between cerebral laterality and the menstrual cycle. In one of the few studies to monitor estrogen and progesterone levels directly, no visual field asymmetry was observed when both estrogen and progesterone were high but a prominent asymmetry was apparent when both estrogen and progesterone levels were low (Rode et al., 1995). No direct correlation between the shift in asymmetry and changes in estrogen or progesterone was observed. It is thus possible that estrogen and progesterone exert competitive effects that obviate a direct association (e.g., Le Magnen, 1952) or it is possible that another biological alteration through the menstrual cycle is responsible for alterations in cerebral asymmetry without a direct association with gonadal hormones (e.g., Rode et al., 1995).

The olfactory system may provide a useful method for the psychometric quantification of cerebral alterations related to neuroendocrine fluctuations with sufficient sensitivity to assist the delineation of the relative importance of different hormones. The olfactory system is sensitive to natural, surgically induced, or genetically determined deficiencies in circulating gonadal hormones, and may also be sensitive to fluctuations in circulating gonadal hormones over the course of the menstrual cycle. Women show a particular sensitivity to the odor of the synthetic musk Exaltolide during ovulation that is more acute relative to men or relative to women during menstruation or pregnancy, or relative to women after menopause or removal of the ovaries (Le Magnen, 1952). Postmenopausal or therapeutic ovariectomized hypogonadal women have impairment of olfactory acuity that is exacerbated by testosterone supplements and improved with estrogen replacements (Schneider et al., 1958). Similarly, women with primary amenorrhea and abnormal menstrual function are frequently hyposmic (Marshall & Henkin, 1971). Moreover, women showing hypogonadotropic hypogonadism with anosmia similar to that of Kallmann's syndrome, a genetic disorder resulting in hypothalamic dysregulation of gonadotropin release, also show olfactory acuity impairment that is further exacerbated by testosterone supplements (Males et al., 1973). A number of prospective investigations of olfactory thresholds through the menstrual cycle have demonstrated a decrease in sensitivity during menstruation (Park & Schoppe, 1997; Schneider & Wolf, 1955; Vierling & Rock, 1967) and greater sensitivity during ovulation (Doty et al., 1982; Mair et al., 1978; Schneider, 1974) or during the second half of menses, midcycle, and midluteally (Doty et al., 1981; Good et al., 1976). Exceptions have been noted (e.g., Hummel et al., 1991) and the enhanced olfactory sensitivity in phases of the cycle with elevated estrogen and/or progesterone levels may have stimulus specificity (Mair et al., 1978). However, the work to date is in general agreement with the results of the hypogonadal studies as well as with the reduced latency of N1, P2, and P3-2 components of chemosensory (olfactory) event-related potentials in the ovulatory phase relative to the follicular (preovulatory) phase of menstruation in normal healthy women (Pause et al., 1996). Although the relative importance of estrogen and progesterone has rarely been directly examined in the studies of olfaction, the alterations in olfaction between menstruation and ovulation may be interpreted in relation to a more prominent role for estrogen because the increased release of progesterone occurs in the postovulatory phase. This remains speculative, however, because similar fluctuations in olfactory sensitivity have been reported in 3 women receiving oral contraceptives resulting in suppression of both estrogen and progesterone (Doty et al., 1981).

The predominantly ipsilateral projections of the olfactory system and the sensitivity of olfactory acuity to variations in circulating hormones may be conducive to the investigation of dynamic alterations in cerebral laterality related to gender-specific neuroendocrinological changes.

Although there are contralateral pathways in the olfactory system as well, they do not appear to confound the detection of laterality differences in olfactory acuity (Purdon & Flor-Henry, 2000). Olfactory acuity appears to show predictable variation with fluctuations in circulating gonadal hormones and thus may provide an effective tool for the quantification of variation in cerebral hemisphere advantages. Olfactory acuity is most sensitive when estrogen levels are increased by ovulation or supplements, and least sensitive when estrogen levels are lower during menses or the follicular phase or through natural, surgical, or genetically determined hypogonadism. The present investigation was undertaken to quantify unirhinal fluctuations in olfactory acuity over the course of the menstrual cycle in normal healthy women. The right hemisphere advantages presumed related to low estrogen levels were anticipated to be manifest in asymmetrical olfactory acuity favoring the right nostril during menstruation. The left hemisphere advantages presumed related to high estrogen levels were anticipated to manifest in asymmetrical olfactory acuity favoring the left nostril during ovulation. As the estrogen level declined in the postluteal phase we anticipated no clear asymmetry as the system moved from a relative left advantage post ovulation to a relative right advantage during menses. In the unlikely event that progesterone was important to this association, the olfactory changes from the menstrual phase would be anticipated in the midluteal rather than the ovulatory phase.

METHODS

Research Participants

Eleven healthy women were recruited from the staff at Alberta Hospital Edmonton and received a small monetary compensation for completing all aspects of this study. Women were included if they were right-handed nonsmokers and experienced regular menstrual cycles between 28 and 32 days in length. Women were excluded if they had any history of olfactory disorder, head injury with loss of consciousness, or recreational inhalation of glue or gas. Women were also excluded if they had any current medical complaints, were receiving any medication or oral contraceptives, or were averse to providing a blood sample. The sample ranged in age from 25 to 47 years ($M = 36.45$, $SD = 7.16$) and their estimated general intelligence (PPVT–R; Dunn & Dunn, 1981) was average ($M = 103.82$, $SD = 10.12$).

Procedure

After receiving informed consent, the stage of the current menstrual cycle was estimated from the days elapsed since onset of the last menstrual period. Three testing sessions were scheduled over the next month to capture the menstrual phase (Day 4.5 ± 1.5 days), the ovulatory phase (Day 13 ± 1 day), and the midluteal phase (Day 21 ± 1 day). The study began for 9 women in the menstrual phase, 1 woman in the ovulatory phase, and 1 woman in the midluteal phase. At the first session all participants completed the Annett's Handedness Inventory (AHI; Annett, 1975) and the Peabody Picture Vocabulary Test–Revised (PPVT–R; Dunn & Dunn, 1981) to provide a confirmation of subjectively reported handedness and to establish an estimate of baseline intelligence. Blood was drawn for estradiol assay at all three sessions at which time participants also completed the University of Pennsylvania Smell Identification Test (UPSIT; Doty, 1983) and the Connecticut Chemosensory Perception Exam (CCPE; Martinez et al., 1993). The UPSIT entails 40 items with four written-alternative forced-choice identifications of a birhinal olfactory stimulus after abrasion of a microencapsulated odor. The Martinez et al. (1993) version of the CCPE has established reliability and validity for the assessment of olfactory acuity thresholds. It involves a series of two-choice discriminations of deionized water from up to 10 ascending concentrations of n-butanol diluted in deionized water. The active stimulant was renewed every 7 days from an initial 4% solution (4 ml n-butanol in 96 ml deionized water, designated solution Number 1) diluted down by three-fold steps to solution number 10. The task began with the lowest concentration (Solution #10) and participants occluded one nostril while propelling the vaporous solution into the opposing nostril. Five correct discriminations at a given concentration terminated the task and established the acuity threshold for the nostril under investigation. Nostril of initiation was determined by a random number table for the first visit and alternated on subsequent visits. Order of presentation of the stimulus or foil within any given series of five was determined from a random number table.

RESULTS

Estradiol levels showed the anticipated fluctuation from very low levels during menstruation ($M = 99.73$ pmol/L, $SD = 87.82$) to very high levels at ovulation ($M = 475.09$, $SD = 310.24$) and intermediate levels in the midluteal phase ($M = 394.36$, $SD = 110.31$; see Figure 1). Progesterone levels showed the anticipated fluctuation from very low levels in the menstrual ($M = 2.57$ nmol/L, $SD = 1.46$) and ovulatory ($M = 4.16$, $SD = 3.90$) phases to relatively high levels in the midluteal phase ($M = 26.88$, $SD = 18.99$).

The smell identification test (UPSIT) gave no suggestion of impairment relative to published norms or any remarkable change across the menstrual ($M = 34.27$, $SD = 3.10$), ovulatory ($M = 33.64$, $SD = 2.91$), or midluteal ($M = 34.26$, $SD = 2.50$) phases of the cycle. After combing the observations of change between menstruation and ovulation with the changes between ovulation and the midluteal phase, there were no significant correlations in the amount of change in the UPSIT and the changes in either estradiol ($r = -.23$) or progesterone ($r = .00$).

Analysis of variance with nostril (right *vs.* left) and phase (menstrual, ovulatory, mid-luteal) as within-subject variables showed no effect of nostril [$F(1,10) = 2.02$, $p = .186$]

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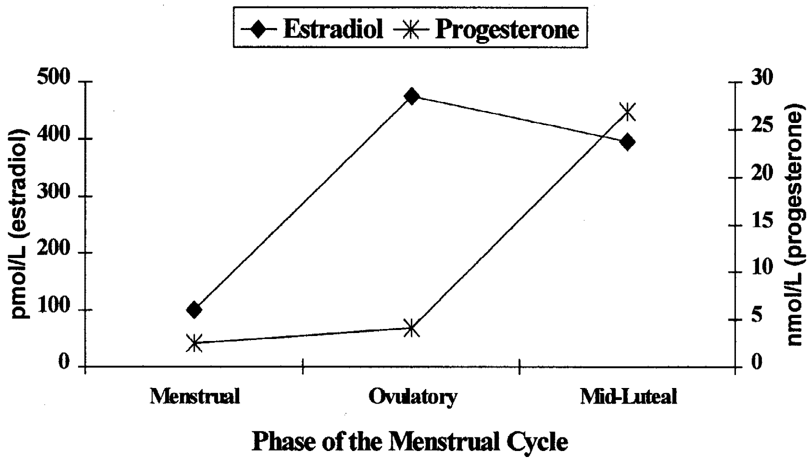

Fig. 1. Estradiol and progesterone levels across the menstrual cycle.

or phase [$F(2,20) = .967$, $p = .397$], but a significant interaction was apparent between nostril and phase [$F(2,20) = 5.24$, $p = .015$]. Although there was no main effect of cycle phase in our analysis, there was a slight trend towards lower olfactory sensitivity during menstruation ($M = 6.45$, $SD = 1.47$) compared to the ovulatory ($M = 7.32$, $SD = 1.95$) and midluteal ($M = 7.45$, $SD = 1.71$) phases. The source of the interaction is readily apparent in the right and left nostril acuity scores of the menstrual, ovulatory, and midluteal phases of the menstrual cycle (see Figure 2). In the menstrual phase when estrogen levels were low there was a significant advantage of the right nostril ($M = 7.64$, $SD = 1.86$) over the left nostril [$M = 6.27$, $SD = 1.56$; $t(10) = 2.59$, $p = .027$]. In the ovulatory phase when estrogen levels were high there was a significant advantage of the left nostril ($M = 7.64$, $SD = 2.29$) over the right nostril [$M = 7.00$, $SD = 1.67$; $t(10) = 2.28$, $p = .046$]. In the midluteal phase when estrogen levels began to subside after ovulation there was no significant asymmetry [right: $M = 7.64$, $SD = 1.80$; left: $M = 7.27$, $SD = 1.95$; $t(10) = 0.77$, $p = .459$]. The interaction is also apparent in an asymmetry index derived by subtraction of left nostril acuity from right nostril acuity (see Figure 3). As anticipated the asymmetry index showed a substantial change from a right nostril advantage to a left advantage between menstruation and ovulation [$t(10) = 3.24$, $p = .009$]. There was no significant change between ovulation and the midluteal phase. The most remarkable shift in asymmetry occurred between menstruation and ovulation when estradiol levels increased substantially but progesterone levels showed only minor change. The remarkable changes in cerebral laterality between menstruation and ovulation were not entirely specific to changes in a single nostril but showed a trend towards a right nostril decline [$t(10) = 1.21$, $p = .255$], and a significant improvement in the left nostril [$t(10) = 3.16$, $p = .010$]. The attenuation of the shift to the left nostril advantage in the midluteal phase corresponded with a small reduction of estradiol and a substantial increase in progesterone.

After combining change scores between menstruation and ovulation with change scores between ovulation and the

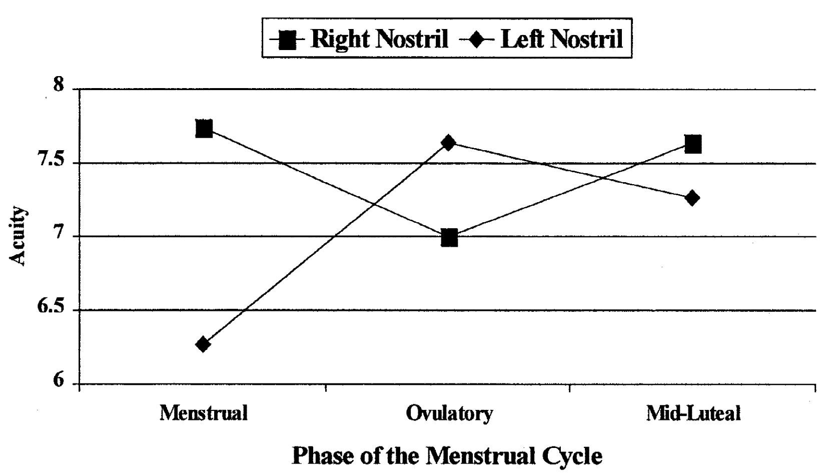

Fig. 2. Nostril acuity across the menstrual cycle.

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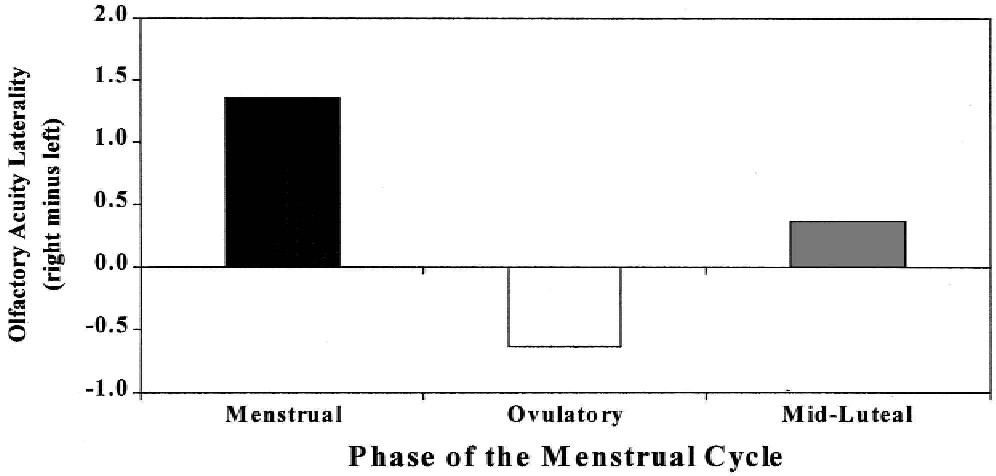

Fig. 3. Asymmetry of nostril acuity across the menstrual cycle.

mid-luteal phase, the shift in the asymmetry index showed a substantial negative correlation with the change in estradiol levels ($r = -.638$, $p = .001$], and a trend towards a positive correlation with the change in progesterone [$r = .407$, $p = .060$], implicating a significant reduction of the relative right nostril advantage with increased estradiol and a trend toward an increase in the relative right nostril advantage with increased progesterone. Analysis of correlations between the changes in estradiol or progesterone and each nostril suggested that the asymmetry shift related to estradiol resulted from a significant inverse association with the right nostril [$r = -.47$, $p = .028$] combined with a negligible direct association with the left nostril [$r = .26$, $p = .24$], in contrast to the trend towards an inverse negative association between progesterone levels and the left nostril [$r = -.40$, $p = .065$] and a negligible direct association with the right nostril [$r = .17$, $p = .46$].

DISCUSSION

Olfactory acuity demonstrated a relative advantage of the right nostril during menstruation that shifted to a left nostril advantage at ovulation and no discernable difference between nostrils in the midluteal phase. The alterations share a temporal association with the low estradiol levels during menstruation that increased at ovulation and then subsided in the midluteal phase, but not with the low progesterone levels at menstruation and ovulation that increased at the midluteal phase. Although the sample size was relatively small, the anticipated shift in olfactory asymmetry between the menstrual and the ovulatory phase occurred in 8 of the 11 women examined, with 2 women showing no shift and 1 woman showing a slight shift towards a greater right over left nostril advantage in the ovulatory phase. There were no differences in olfactory identification or acuity through the menstrual cycle, though the latter showed a trend towards less sensitivity at menstruation compared to the ovulatory or midluteal phases. The absence of a change in olfactory identification through the menstrual cycle is consistent with a prior report (Kopala et al., 1995) and the presence of a nonsignificant trend towards changes in olfactory acuity is also consistent with observations of unirhinal citral thresholds through the menstrual cycle (Pause et al., 1996). The absence of a general change in olfactory sensitivity through the menstrual cycle is somewhat discordant with prior demonstrations of birhinal alterations in sensitivity (e.g., Doty et al., 1981; Vierling & Rock, 1967), a discrepancy that may relate to the limited statistical power of the present study or the use of a unirhinal procedure with an n-butanol stimulant.

The shift in olfactory acuity from a right nostril advantage at menstruation to a left nostril advantage at ovulation suggests a dynamic alteration of cerebral hemisphere activity that converges on earlier observations from studies of speeded motor coordination, visual field perception of figures, spatial perception, and verbal fluency (Gordon et al., 1986; Hampson, 1990; Hampson & Kimura, 1988; Heister et al., 1989; Rode et al., 1995). The prior studies demonstrated a relative right hemisphere advantage during menstruation when estrogen and progesterone were low that shifted to a relative left hemisphere advantage in the ovulatory or postovulatory phases of the menstrual cycle when estrogen and progesterone were high. The shift in asymmetrical olfactory acuity occurred between menstruation and ovulation when estrogen was elevated, and no additional asymmetry was apparent at the midluteal phase when progesterone was also high, implicating a more prominent temporal association of the shifts in cerebral asymmetry with estradiol than with progesterone. A similar prior discussion of asymmetrical visual field differences suggested a more prominent role of progesterone over estrogen (Heister et al., 1989), a divergence from the present interpretation that may relate to the different phases of the cycle under investigation and the absence of quantified hormone levels in the prior study. Also, preliminary evidence of opposing influences of estradiol and progesterone were apparent in the shifts of olfactory asymmetry and in the relative changes in each nostril. The divergent effects of estradiol and progesterone were not anticipated and will require replication for verification, but the different effects may offer a *post-hoc* explanation for the absence of a significant correlation between estrogen or progesterone and shifts in laterality from a prior investigation (Rode et al., 1995). The previous study compared the menstrual phase of the cycle, when estrogen and progesterone are low, to the luteal phase of the cycle when estrogen and progesterone are high. Competitive effect may thus have obscured direct associations between changes in these hormones and shifts in cerebral laterality that might have been apparent in comparisons of the menstrual, ovulatory, and midluteal phases. The particular sensitivity of the right nostril to changes in estradiol observed in the present study may also provide a *post-hoc* account of the visual field shifts apparent on a figure matching task presumed sensitive to changes in the right cerebral hemisphere and not on a lexical decision task presumed sensitive to changes in the left cerebral hemisphere (Heister et al., 1989; Rode et al., 1995).

There is a considerable body of evidence to implicate hormonal effects on asymmetrical neurodevelopment of cerebral structure (see review by Wisniewski, 1998) and, if replicated, the shift in asymmetrical olfactory acuity can be added to the small but expanding literature implicating dynamic changes in functional cerebral laterality as well. Much of the research implicating dynamic change has been derived from inferences regarding the relative predominance of the left or right cerebral hemisphere in the performance of higher cognitive tasks (e.g., Hampson, 1990; Hampson & Kimura, 1988). There have been fewer investigations of sensory systems that might allow greater precision in detecting differential effects of circulating hormones on the left or right cerebral hemisphere (e.g., Heister et al., 1989; Rode et al., 1995) but the evidence to date is remarkably consistent. Again, if replicated, the olfactory acuity procedure may provide a sensitive measure of asymmetrical shifts that is capable of differentiations between the temporal associations of different hormone fluctuations. This is a novel area of investigation worthy of additional scrutiny but it does not as yet establish a direct causal link between fluctuations in circulating gonadal hormones and asymmetrical shifts in cerebral laterality, nor does it establish a direct causal link between fluctuations in circulating gonadal hormones and olfactory sensitivity. Thus, although asymmetrical structural alterations of the central nervous system have been linked to neurodevelopmental differences in circulating hormones (e.g. Wisniewski, 1998), there is little direct evidence to support a direct effect of circulating hormones on dynamic alterations of asymmetry. The temporal association is important but it must be considered within the context of known associations between estrogen and progesterone and a wide range of neurotransmitters and neuropeptides including dopamine, catecholamine, and NMDA receptors (see review by Rode et al., 1995). It would thus be premature to rule out an indirect contribution from circulating gonadal hormones to shifts in cerebral laterality through other neurochemical systems. Previous investigators of differences in olfactory acuity thresholds through the menstrual cycle have noted similar complex associations between circulating gonadal hormones and other neurotransmitters in drawing the inference that these changes are likely related to central nervous system changes (e.g., Doty et al., 1981), rather than alterations in peripheral epithelium or mucosa (e.g., Mair et al., 1978; Schneider & Wolf, 1955). A shift in nostril acuity through the menstrual cycle may offer an important novel parameter to this discussion that would tend to underscore a central rather than a peripheral explanation with implications to cerebral pathology and pharmacology (Purdon & Flor-Henry, in press).

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