Hormones and Behavior **31,** 65–74 (1997)
Article No. HB971363

Turning Bias in Humans Is Influenced by Phase of the Menstrual Cycle

Larissa A. Mead and Elizabeth Hampson[1]

Department of Psychology, University of Western Ontario, London, Ontario, Canada N6A 5C2

Previous studies have provided evidence that humans demonstrate subtle, but measurable, turning biases when tested in the absence of environmental constraints. Preferences for leftward or rightward rotation have been repeatedly demonstrated in rodents and appear to be modulated to a significant degree by ovarian hormones, particularly estrogen. In the present study, we examined the turning biases of adult women at the midluteal and menstrual phases of the menstrual cycle, associated with high and low levels of estradiol and progesterone, respectively. Saliva samples were collected during each test session, and salivary concentrations of estradiol and progesterone were measured using radioimmunoassays. Overall, a rightward-turning bias was evident; however, a minority of the women displayed consistent leftward biases. Among right-turning subjects, turning biases were significantly weaker at the midluteal phase than at the menstrual phase. These results suggest that the mechanisms underlying human turning biases are subject to modulation by ovarian hormones.

Although the rotational behavior of rats has been studied extensively since the early 1970s, it is only recently that attention has turned to the study of human turning biases, or the tendency to turn preferentially in a given direction in the absence of environmental constraints. With the exception of the work of Schaeffer (1928), who reported spontaneous ''spiral movement'' among forward-moving blindfolded subjects, most studies of human rotational behavior have been performed within the past several years by Bracha and his colleagues (Bracha, 1987; Bracha, Lyden, and Khansarinia, 1989; Bracha, Seitz, Otemaa, and Glick, 1987a; Bracha, Shultz, Glick, and Kleinman, 1987b; Gordon, Busdiecker, and Bracha, 1992), who found that humans, like rodents, display detectable biases in turning direction. These studies were carried out using an instrument called the ''human rotometer,'' an automated device designed to detect and measure spontaneous rotational movement as part of a subject's natural behavioral repertoire.

Previous research with animals provides a natural backdrop against which to compare studies of turning bias in humans. For example, animal studies have shown that rotational behavior in rats—particularly female rats—is associated with an asymmetry in dopamine (DA) concentrations between the left and right striata, such that greater DA concentrations on one side will result in circling in the contralateral direction (Robinson, Becker, and Ramirez, 1980; Shapiro, Glick, and Hough, 1986; Zimmerberg, Glick, and Jerussi, 1974; see review by Carlson and Glick, 1989). This dopaminergic asymmetry is found endogenously (Zimmerberg *et al.*, 1974), but surgical or pharmacological manipulations may increase, decrease, or reverse the existing disparity, resulting in alterations in the strength and / or direction of turning (e.g., Glick and Cox, 1978; Glick, Jerussi, Waters, and Green, 1974; Jerussi and Glick, 1975; Robinson and Becker, 1983). A study by Bracha *et al.* (1987b) has raised the possibility that rotational tendencies in humans may be governed through similar mechanisms. A small group of patients was tested who each displayed highly lateralized Parkinsonian symptoms. Symptoms manifested in this fashion have previously been associated with unequal concentrations of DA in the left and right nigrostriatal regions, with motor signs first appearing on the side opposite to the more deteriorated nigrostriatal region (Pycock, 1983). During a testing period of 8–12 hr, each of these hemi-Parkinsonian patients turned preferentially in the direction contralateral to the more intact striatum. This behavior occurred

[1] To whom correspondence should be addressed at Dept. of Psychology, University of Western Ontario, London, Ontario, Canada N6A 5C2. Fax: (519) 661-3213. E-mail: ehampson@uwovax.uwo.ca.

0018-506X/97 $25.00

without conscious awareness on the part of the patients, in the absence of any clinically apparent inability to move in either direction, and at a rate (i.e., total turns per hour) equivalent to that of healthy controls.

In the rat, clear sex differences in circling behavior are also found, with female rats demonstrating significantly stronger rotational biases than males. This has been found for both spontaneous (Glick, Schonfeld, and Strumpf, 1980) and amphetamine-induced rotation (Robinson *et al.*, 1980; Brass and Glick, 1981; Becker, Robinson, and Lorenz, 1982). Studies of human rotation have also shown stronger turning preferences among women than among men (Bracha *et al.*, 1987a; Mead and Hampson, 1996a), although this is not always detected (Seltzer, Forsythe, and Ward, 1990). Bracha *et al.* (1987a) found a leftward bias in spontaneous rotation for females and no bias for males. However, Mead and Hampson (1996a) used a behavioral task designed to elicit 180° turns and found rightward turning biases for both males and females, with the female bias being significantly stronger than the male bias.

The fact that sex differences are commonly found in the strength of rotational biases has been interpreted as suggesting a hormonal influence on this behavior. Accordingly, a number of studies have examined the influence of ovarian hormones on rodent circling using variations in endogenous steroids over the estrous cycle as a natural paradigm. These studies have shown that female rats tested during estrus, shortly following the peak in estradiol (E_2) and progesterone (P_4) levels, display stronger induced rotational biases than rats tested during diestrus 1, when hormone levels are low (Becker *et al.*, 1982; Robinson, Camp, Jacknow, and Becker, 1982). Joyce and Van Hartesveldt (1984) also showed that rotational bias peaked at the estrus phase, although in that study, the weakest rotational bias was found during proestrus.

These results suggest that high endogenous concentrations of ovarian hormones are associated with an increased striatal dopaminergic asymmetry, which magnifies any existing rotational bias. Further behavioral evidence supporting this possibility is provided by studies showing that ovariectomy leads to a decrease in rotational asymmetry compared to castrated males (Robinson *et al.*, 1982) and compared to intact females (Becker and Beer, 1986). In addition, the administration of E_2 to ovariectomized females serves to reinstate the previous rotational bias (Becker and Beer, 1986; Roy, Buyer, and Licari, 1990), indicating that elevated levels of E_2 alone are sufficient to increase rotation. To our knowledge, there have been no studies of rotation following treatment with P_4 alone. However, one biochemical study (Becker and Ramirez, 1981) demonstrated that amphetamine-stimulated DA release in the striatum was significantly greater in ovariectomized rats administered both E_2 and P_4 than in animals treated with only one of these hormones. Therefore, progesterone and estrogen may act in concert to produce an increased rotational bias.

Although hormonal effects on turning behaviors have not yet been examined in humans, findings reported by Mead and Hampson (1996a) were suggestive of such influences. Specifically, it was shown that the consistency between two test sessions (1–2 weeks apart) in the direction and degree of turning bias was significantly greater for males and for females using oral contraceptives than for females experiencing natural menstrual cycles. Only the latter group would be potentially subject to large fluctuations in ovarian hormones. Therefore, it is possible that some proportion of the naturally cycling group was tested during phases associated with widely discrepant hormone concentrations, which may have resulted in the reduced turning consistency evident among these women.

To test this possibility, the present study used the rotation task described by Mead and Hampson (1996a) to examine whether hormonal fluctuations across the menstrual cycle affect the turning preferences of women to a measurable degree. The rotation task was performed by subjects twice, once during the menstrual phase when both E_2 and P_4 levels are low and once during the midluteal phase when these hormones are at high concentrations. Radioimmunoassays were used to quantify salivary E_2 and P_4 concentrations from saliva samples collected during each test session.

METHODS

Subjects

Subjects were recruited by means of advertisements placed around the University of Western Ontario campus and in the campus newspaper. Prior to participation in the study, all volunteers completed a detailed screening questionnaire to ensure their eligibility. Subjects selected for participation were right-handed, as determined by a 16-item modified version of the Waterloo Handedness Questionnaire (Steenhuis, Bryden, Schwartz, and Lawson, 1990), and ranged in age from 20 to 40 years (mean age 24.0 years). No subjects had taken oral contraceptives during the previous 4 months

nor were any currently taking any medication which might affect their hormone status or motor abilities. All selected participants reported regular menstrual cycles, normal or corrected-to-normal vision and hearing, and no deficits in the motor abilities of their lower extremities. Eligible subjects also denied any recent ear infections or neurological problems which may conceivably have influenced motor equilibrium.

A total of 48 subjects were tested twice during cycle days selected to coincide with the menstrual and midluteal phases (see definitions below). An additional 20 subjects completed only the first testing session on a day-of-cycle consistent with either the menstrual or midluteal phase. The final subject group was determined solely on the basis of the salivary E_2 values obtained for each subject at each phase. Two saliva samples were collected at each session, and the inclusion criteria required that the E_2 values for both midluteal samples be greater than the values for both menstrual samples. Subjects who did not meet this criterion were excluded, day of cycle notwithstanding. Among the subjects who met this criterion, obtained values for salivary E_2 were 4.88 (SEM = 0.26) pg / mL at the menstrual phase and 9.22 (0.40) pg / mL at the midluteal phase. In general, subjects tested only once were included if their E_2 values fell within one standard deviation of the mean for their ostensible day of cycle, although subjects whose E_2 values fell below this range were included if they were tested during the menstrual phase ($N = 2$) and subjects whose E_2 values fell above this range were included if they were tested during days consistent with the midluteal phase ($N = 2$). Progesterone values for the latter two subjects were also indicative of midluteal status. On this basis, the final sample consisted of 31 women tested twice and 11 additional subjects tested only once. Salivary P_4 values for this final sample group were 18.83 (1.93) pg / mL at the menstrual phase and 88.59 (10.59) pg / mL at the midluteal phase. These values are well within acceptable published ranges for ovulatory cycles (Ellison, 1993).

Procedure

Behavioral testing was conducted once during the menstrual phase and once during the immediately preceding or subsequent midluteal phase, with order of testing counterbalanced. The timing of menstrual sessions was fixed to the onset of menses (Day 1), with test sessions occurring on Days 3–5. In order to optimize the likelihood of testing subjects during peak concentrations of E_2 and P_4, midluteal test sessions were targeted for Days -5 to -10, and these days were confirmed retrospectively by having the subjects contact the experimenter at the onset of menses. However, inspection of the salivary E_2 concentrations at the conclusion of behavioral testing revealed that midluteal-range values were sometimes evident 1–2 days outside of this 6-day window. In these instances, as our primary interest was the effects of elevated levels of E_2, the data were included in the analyses.

Saliva samples were produced by the subjects at the outset and at the conclusion of each test session, an interval of about 40 minutes. Samples of approximately 6 mL were collected in polystyrene test tubes pretreated with sodium azide, a bacteriocide. Sugarless gum, previously shown to be inert in the radioimmunoassay procedure, was used to stimulate salivation. While producing the first saliva sample, subjects completed the Profile of Mood States (POMS) (McNair, Lorr, and Droppleman, 1971), a self-report inventory of six mood states (Tension, Depression, Anger, Vigor, Fatigue, and Confusion). The turning preference task (''rotation task'') was then performed, followed by a measure of finger tapping speed. Tapping speed has previously been shown to be sensitive to fluctuations in hormone levels across the menstrual cycle (e.g., Becker, Creutzfeldt, Schwibbe, and Wuttke, 1982; Hampson, 1990a,b; Hampson and Kimura, 1988; Mead and Hampson, 1996b). Finger tapping data were collected for two 10-sec intervals for each hand, alternating between the left and right index fingers.

Rotation Task

The testing area was defined by four tables surrounding a square open area. One tape recorder was placed in the center of each table, facing inward, such that opposing tape players were 3 m across from each other. Approximately every 5 sec, one of the tape players emitted a 1-sec tone. Subjects were instructed to begin each session in the center of the area and to walk directly toward the tape recorder each time they heard a tone. Upon arriving at the appropriate tape recorder, subjects ensured that their toes were aligned with markings on the floor and placed a checkmark on a response sheet located on the table in front of the tape recorder. Subjects remained facing this direction until the next tone was heard. The tones were played in a pseudorandom order; in half of the trials the tone came from directly behind the subject, and in half of the trials, the tone came from either the left or the right of the subject. The entire test consisted of 160 trials. Thus, 80 of these

were critical trials in which the tone came from directly behind the subject. The direction the subject turned on each trial was recorded by the experimenter. A previous study (Mead and Hampson, 1996a) showed that foot preference is not related to turning preference. Likewise, turning bias was not found to differ between subjects asked to use their left or right hands to mark the response sheet.

The position of the experimenter during the rotation task was counterbalanced to avoid any potential bias due to experimenter location. Four possible seating positions at each corner of the testing area were systematically varied between subjects. Moreover, the position of the experimenter at each subject's second testing session was diametrically opposed to the location at the first testing session. Turning biases were determined by subtracting the number of critical trial left turns from the number of critical trial right turns and dividing this value by the total number of critical trials. Thus, 0 represents an equal number of left and right turns, a positive value represents a right-turning bias, and a negative value represents a left-turning bias.

Radioimmunoassays

Upon completion of behavioral testing, salivary estradiol and progesterone concentrations were determined by a technician specializing in salivary RIA techniques. Saliva specimens were stored at −20°C until this time. Prior to the estradiol assay, specimens were centrifuged and submitted to a double ether extraction. A tritium label (New England Nuclear, Boston MA) and specific estradiol antiserum (Animal Reproduction and Biotechnology Laboratory, Colorado State University) were employed in the estradiol assay. Sensitivity of the assay was less than 2 pg/mL, and the intra-assay coefficient of variation averaged 15%. Progesterone was assayed without extraction using an ^{125}I Coat-A-Count progesterone kit (Diagnostic Products, Los Angeles CA), modified for use with saliva. The sensitivity of the assay was 5 pg/mL and the intra-assay coefficient of variation averaged below 7%.

RESULTS

The design of the present study allowed for the examination of both within- and between-subjects experimental effects. Within-subjects analyses were performed for the group of 31 women tested at both phases of interest. Between-subjects analyses were performed on the data collected in the first session only, during which 20 women were at the menstrual phase and 22 women were at the midluteal phase.

Overall Turning Bias

Consistent with our earlier findings (Mead and Hampson, 1996a), a significant rightward turning bias was evident overall. Among the group of women tested twice, for example, of 80 possible turns per session, the average number of turns to the right was 49.89, whereas the average number of turns to the left was 30.11 [$t(30) = -3.21$, $P = .003$], producing an average turning ratio of 0.247 overall. A rightward bias was apparent during both menstrual and midluteal test sessions, in the within-subjects analyses as well as in the Session 1 analyses ($P < .02$ in all cases). The consistency in turning bias between the two sessions was moderately high [$r(29) = 0.738$, $P < .001$]. This value is virtually identical to the correlation obtained in a prior study of the turning preferences of a mixed group of males and females (Mead and Hampson, 1996a).

Effects of Phase on Turning Bias

To examine any effects of phase on turning bias, a mixed analysis of variance using SPSS/PC+ MANOVA (Norusis, 1988) was performed on the within-subjects turning ratios, with phase of cycle as the within-subjects factor and order of testing as the between-subjects factor. A main effect of phase reached the level of a trend, but was not significant [$F(1,29) = 2.83$, $P = .10$]. Turning bias at the menstrual phase averaged 0.299 (SEM = 0.08) and at the midluteal phase averaged 0.195 (0.08).

Because individual subjects displayed overall biases toward either the left or the right, subjects were classified according to the direction of their turning preference. Classification was performed by reference to the turning preference demonstrated at the menstrual phase, as any influence of gonadal hormones on the turning bias was presumably minimal at this time. Subjects whose turning bias at the menstrual phase was less than 0 were classified as left-turners; those whose turning bias was greater than 0 were considered right-turners. This subdivision resulted in the categorization of 7 subjects as left-turners and 24 as right-turners.

Inclusion of turning direction as a factor in the ANOVA proved quite interesting. Besides the expected main effect of direction [$F(1,27) = 44.05$, $P < .001$], a significant interaction was obtained between direction of turning and phase of cycle [$F(1,27) = 4.31$, $P < .05$].

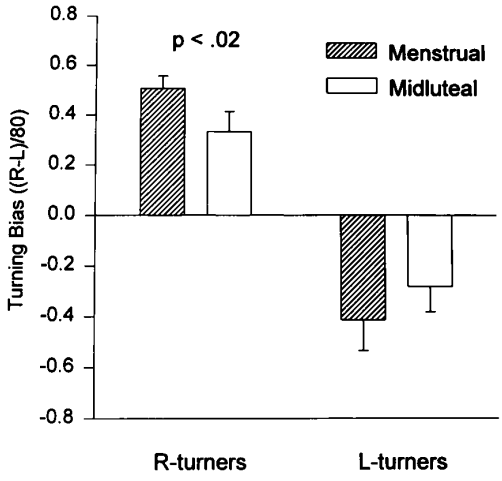

FIG. 1. A significant interaction between phase and preferred turning direction on turning bias. Right-turning subjects ($N = 24$) demonstrated a significantly decreased turning bias at the midluteal phase. Left-turning subjects ($N = 7$) showed a pattern which is similar, but did not reach significance. Bars represent the means and standard errors for each condition.

This interaction is displayed graphically in Fig. 1, and clearly suggests that right-turning subjects displayed a lesser rightward bias at the midluteal phase, whereas left-turning subjects displayed a lesser *left*ward bias at the midluteal phase. Indeed, analysis of simple main effects revealed a significant effect of phase in the right-turning group. These subjects demonstrated a stronger rightward bias during the menstrual phase than during the midluteal phase [$F(1,22) = 6.83$, $P = .016$]. Among the left-turning group, a stronger leftward bias appeared to be present at the menstrual phase compared to the midluteal phase; however, presumably due to the small sample size ($N = 7$), this difference did not reach significance ($F < 1$). Examination of the between-subjects data did not reveal a main effect of phase, nor effects related to the direction of turning.

Further evidence for an increased rightward bias at the menstrual phase came from a frequency count of the number of subjects who demonstrated left- or right-turning biases during each phase. Among all the subjects tested at the menstrual phase ($N = 34$), 26 showed rightward biases and only 8 showed leftward biases ($\chi^2 = 9.53$, $P = .002$). However, among all the subjects tested at the midluteal phase ($N = 39$), 22 demonstrated rightward biases and 17 demonstrated leftward biases ($P =$ ns). The difference between these distributions just missed a conventional level of significance ($\chi^2 = 3.25$, $P = .07$). Furthermore, although there was a high degree of consistency in the preferred direction of turning between the two sessions (among the 31 subjects tested twice, 17 retained a rightward bias and 7 retained a leftward bias), the 7 subjects who showed an inconsistency between sessions all turned to the right during the menstrual phase and to the left during the midluteal phase.

An additional analysis of the rotation data was based on an informal impression during testing that the turning behavior of some subjects appeared to change across the 80 critical trials. Thus, the test sessions were divided into four quarters, each consisting of 20 critical trials, to examine this possibility more objectively. Analysis of the between-subjects data indicated a significant effect of quarter [$F(3,120) = 4.47$, $P = .005$], revealing a pattern of increasing rightward bias as the test progressed. This effect interacted with phase of cycle in the within-subjects data [$F(3,87) = 2.63$, $P = .05$] and was also marginally significant in the between-subjects data [$F(3,120) = 2.50$, $P = .06$]. Inspection of the within-subjects interaction revealed that an increased rightward bias at the menstrual phase compared to the midluteal phase was evident during quarters 1, 3, and 4, but not during the second quarter of the session (see Fig. 2). The significance of this phase by quarter interaction is not clear; it may simply reflect sampling fluctuation.

Correlations with Hormonal Values

To help elucidate the source of the fluctuation in turning bias reported here for right-turning subjects, Pear-

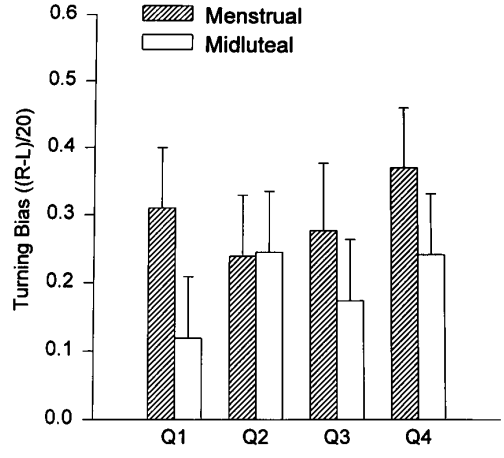

FIG. 2. A significant interaction between phase and quarter of the test session in the within-subjects sample ($N = 31$). Although the phase effects evident in quarters 1, 3, and 4 did not differ from each other, the second quarter differed significantly from Q1 ($P = .001$), and tended to differ from Q3 ($P < .07$) and Q4 ($P < .12$).

son product–moment correlations were calculated between estrogen and progesterone values and turning ratios obtained at the first test session. Data from every right-turning woman tested ($N = 46$) were included in this analysis, regardless of day of cycle, in order to maximize the potential range of the hormonal values. A significant negative correlation was obtained between estrogen concentrations and turning bias [$r(44) = -.348$, $P = .017$]. Progesterone was not significantly associated with turning bias [$r(44) = -.105$, $P = .506$]. A stepwise multiple regression using forward entry was also performed, with estrogen and progesterone concentrations as predictors of turning bias. This analysis supported the predominant role of estrogen in our findings: estrogen was the first and only variable entered into the equation, producing a multiple R of .348 [$F(1,44) = 6.06$, $P < .02$]. Progesterone did not meet the minimum criteria for entry [$t(44) = 0.24$, $P = .814$]. When progesterone was forced into the equation, the obtained multiple R was raised only from .348 to .350, again suggesting that this hormone did not contribute significantly to the turning behavior of subjects in this study.

Effects of Phase on Other Measures

Examination of the finger tapping means showed that tapping rate was somewhat faster at the midluteal phase than the menstrual phase, as expected; however, this difference failed to reach significance ($F < 1$). Phase effects were not evident for any of the six mood states tapped by the Profile of Mood States.

DISCUSSION

In the present study, women were tested for the strength and direction of their turning biases during two phases of the menstrual cycle associated with high and low circulating levels of ovarian hormones, the midluteal and menstrual phases, respectively. On average, the subjects displayed a strong rightward bias, consistent with the findings of a previous study using an unselected group of normal females (Mead and Hampson, 1996a). Of most interest was the discovery that, among right-turning subjects, the strength of this turning bias was decreased at the midluteal phase, when both E_2 and P_4 levels were demonstrably high, compared to the menstrual phase, when hormone levels were low. The smaller group of left-turning subjects showed a similar, though nonsignificant, tendency toward a decreased leftward bias at the midluteal phase. Furthermore, the distribution of subjects demonstrating leftward or rightward biases tended to differ between the phases, with an increased number of subjects in this study demonstrating a rightward bias at the menstrual phase compared to the midluteal phase.

Although direct evidence has not yet been obtained, the underlying basis for turning biases in humans is presumed to be an endogenous asymmetry in DA levels between the left and the right striatum (Bracha *et al.*, 1987b), as is the case for other animals in which this phenomenon has been studied. As such, variations in the behavioral index are thought to reflect variations in the underlying DA asymmetry. Thus, female rodents generally display stronger rotational biases than males (Glick *et al.*, 1980; Robinson *et al.*, 1980; Brass and Glick, 1981; Becker *et al.*, 1982) and also show an enhanced striatal DA asymmetry (Dark, Ellman, Peeke, Galin, and Reus, 1984; Drew, Lyon, Titeler, and Glick, 1986; Glick *et al.*, 1980; Robinson *et al.*, 1980). Using the same logic, evidence collected in the present study and in several previous animal studies (Becker *et al.*, 1982; Joyce and Van Hartesveldt, 1984; Robinson *et al.*, 1982) suggests that endogenously cycling ovarian hormones are capable of exerting a measurable effect on the underlying striatal DA asymmetry, as manifested through alterations in strength of turning bias.

Animal studies have generally found an increase in the net rotations (i.e., strength of the turning bias) on the day of estrus, relative to rotational behavior occurring on diestrus 1 or proestrus. The estrus phase itself is associated with very low concentrations of E_2 and P_4 (Butcher, Collins, and Fugo, 1974), as is the menstrual phase in women. It is thus tempting to conclude that an hormonal effect has been shown here in humans analogous to that seen in rats. However, the extremely rapid hormonal changes that take place across the estrous cycle make direct comparisons to the menstrual cycle inadvisable. That is, it is not uncommon for hormonal effects on behavior to appear following a temporal lag, which in the rat may coincide with an entirely different hormonal milieu. For example, Joyce and Van Hartesveldt (1984) reported that when rats were given intrastriatal injections of either DA or amphetamine (AMPH) at various times throughout the days of proestrus and estrus, an increased rotational bias was not seen until the morning of estrus, although the surge in serum concentration of E_2 is over by the afternoon of proestrus (Butcher *et al.*, 1974). Direct neurochemical evidence for such temporal lags has also been described. For example, when rats were killed 4 hr after lights on during each phase of the estrous cycle, Becker

and Ramirez (1981) found that amphetamine-stimulated striatal DA release was depressed on proestrus, and elevated on estrus and diestrus 1. However, if the rats were killed at 4 hours after lights off (i.e. approximately 12 hours later), DA release was significantly higher on estrus than during diestrus 1 (Becker *et al.*, 1982). This result is thus compatible with behavioral data showing increased rotation at the estrus phase, compared to diestrus 1, when tested during lights off (Becker *et al.*, 1982). It is noteworthy in this context that Morissette, Lévesque, Bélanger, and Di Paolo (1990) reported that plasma estradiol levels are accurate reflections of striatal concentrations as a function of time. Therefore, delays in behavioral or neurochemical measures are not due to a slow hormonal ''buildup'' in the striatum.

In relation to the estrous cycle, the hormonal variations evident across the human menstrual cycle occur at a much slower rate. With the possible exception of the rapid preovulatory E_2 surge, hormone concentrations generally rise and fall over a period of days rather than hours; thus, behavioral testing can be taken to be reflective of the current hormonal milieu. Since in this case we cannot legitimately compare evidence derived from studies of the menstrual cycle to evidence from the estrous cycle, it is necessary to interpret the present results in light of our limited knowledge of the effects of estrogen on the human striatum. Currently, our primary source of information in this regard is the medical literature on the effects of estrogen on various extrapyramidal disorders, including neuroleptic-induced Parkinsonian symptoms, neuroleptic-induced tardive dyskinesia, dyskinetic episodes induced by L-DOPA during treatment of Parkinson's disease, and choreiform disorders.

Reviews by Van Hartesveldt and Joyce (1986) and Di Paolo (1994) indicate a complex pattern of effects of estrogen on the pathologic dopaminergic systems underlying each of these disorders. Treatment with estrogen appears to ameliorate symptoms associated with dopaminergic supersensitivity such as occurs in tardive and L-DOPA-induced dyskinesias (Bédard *et al.*, 1979; Bédard, Langelier, and Villeneuve, 1977; Glazer, Naftolin, Morgenstern, Barnea, MacLusky, and Brenner, 1985; Koller, Barr, and Biary, 1982; Villeneuve, Cazejust, and Coté, 1980; Villeneuve, Langelier, and Bédard, 1978) and to increase the prevalence and severity of Parkinsonian symptoms induced by neuroleptics (Villeneuve *et al.*, 1978). These treatment effects suggest a suppressive effect of estrogen on DA functioning. Quinn and Marsden (1986) have also reported a worsening of Parkinsonian symptoms among a group of premenopausal women during the late luteal phase of the menstrual cycle. A similar case was described by Giladi and Honigman (1995), in which the Parkinsonian symptoms of one woman increased so markedly during the week prior to menses that she required nearly twice her normal dosage of levodopa to remain functional during that time.

On the other hand, pregnancy (Donaldson, 1978) and the ingestion of oral contraceptives (Bickerstaff, 1975; Gamboa, Isaacs, and Harter, 1971; Nausieda, Koller, Weiner, and Klawans, 1979)—conditions involving prolonged exposure to high levels of estrogen—have each been associated with chorea, a disorder thought to involve excessive DA activity. It is notable, however, that both pregnancy and the earlier formulations of oral contraceptives are also characterized by high concentrations of progesterone. Therefore, the apparent upregulation of DA activity associated with these conditions could be attributable to opposing actions of progesterone on the nigrostriatal system (Van Hartesfeldt and Joyce, 1986).

Although the evidence available to date suggests that estrogen may have a suppressant effect on human striatal DA function, it is not clear that reference to pathological conditions is useful when the action of interest occurs in the normal, intact brain. There are virtually no studies, to our knowledge, addressing this issue. A single report by Wong *et al.* (1988) indicated that the binding rate constant (k_3) of D_2 DA receptors in the caudate nucleus fluctuated with the menstrual cycle in healthy human subjects, as assessed by PET. Specifically, k_3 tended to be lower during the follicular phase, when E_2 and P_4 concentrations are relatively reduced, and higher during the periovulatory and luteal phases, associated with higher levels of ovarian hormones. Since k_3 reflects both the density and the affinity of D_2 DA receptors, this finding may point to an hormonally mediated increase in postsynaptic DA activity in the healthy striatum. An increased DA binding rate at phases associated with higher levels of ovarian hormones is suggestive of *reduced* concentrations of DA in the striatum prior to or during those phases.

It is obvious that further study is necessary in order to clarify the actions of ovarian hormones on the human striatal dopaminergic system. The present findings contribute to this inquiry in suggesting that higher estrogen levels are associated with a reduction in the asymmetry of striatal DA activity. This effect could be produced through one of two mechanisms: (a) there may be a truly asymmetrical effect of estro-

gen on the left and right striatal systems, such that the more active DA system is disproportionately suppressed, relative to the less active system, thereby reducing the original asymmetry, or (b) the activity of both left and right striatal DA systems may be increased by a constant measure, thereby decreasing the relative disparity between the two sides. Other mechanisms may be ruled out on the basis that they would not produce a decreased dopaminergic asymmetry. For example, assuming an initial disparity in the DA activity of the left and right striata, suppression of both sides by an equivalent amount would result in an increased disparity. A proportionate increase or decrease in DA functioning on the two sides may also be ruled out as these actions would not alter the initial asymmetry. Although either of the two proposed mechanisms is theoretically possible, the available evidence suggests a suppressive effect of estrogen on the system in question (Van Hartesveldt and Joyce, 1986); therefore, the first mechanism outlined—involving a disproportionate suppression of the more active DA system—appears to be the more plausible alternative. The effect may be similar in concept, although opposite in direction, to that exhibited by amphetamine, which effectively increases the DA asymmetry in rats by facilitating DA release from the more active nigrostriatal pathway (Glick, Jerussi, and Zimmerberg, 1977).

The present investigation provides the first systematic evidence that the human turning bias is subject to modulation by endogenous ovarian hormones. Similar effects have been demonstrated repeatedly in experimental animals, lending further credence to a fundamental similarity in the mechanism underlying mammalian turning biases. Although the reduction in turning bias seen here at the midluteal phase suggests a functional reduction of an underlying striatal DA asymmetry, the mode of this action is as yet unknown. However, evidence from the medical literature (see for review Van Hartesveldt and Joyce, 1986) and from the present study suggests that estrogen, and not progesterone, is the critical hormone mediating this effect.

The results of the present study are also relevant to the question of the therapeutic usefulness of estrogen in the treatment of extrapyramidal disorders. For example, if certain phases of the menstrual cycle are associated with a suppression of striatal DA function, one may tailor medication regimens to the cycles of premenopausal women in order to optimize functioning (Giladi and Honigman, 1995). Postmenopausal women suffering from conditions related to dopaminergic supersensitivity may benefit from exogenous estrogen treatment (e.g., Glazer *et al.*, 1985), whereas such treatment appears to be inadvisable for patients whose striatal DA systems are already compromised, as in Parkinson's disease. The apparently asymmetrical action of estrogen on the striata suggested by the present findings implies that patients for whom symptoms are lateralized and related to overactivity of the DA system (e.g., unilateral neuroleptic-induced dyskinesias) may be especially suited for estrogen treatment. It is of interest that Waziri (1980) has reported an increased likelihood of dyskinetic activity in the right extremities following treatment with neuroleptics, a finding which points to an increased vulnerability of the left basal ganglia to neuroleptic activity. Since the majority of women in the present study displayed rightward-turning biases—presumably due to greater DA activity in the left basal ganglia—the midluteal reduction of the rightward bias shown here may also reflect an increased susceptibility of the left basal ganglia to the effects of estrogen.

ACKNOWLEDGMENTS

We thank Kay Noh for excellent technical assistance in performing the radioimmunoassays and Scott Moffat for assistance in the development of the rotation task. Larissa Mead was the recipient of a postgraduate studentship provided by the Medical Research Council of Canada. Elizabeth Hampson was the recipient of a New Faculty Research Fellowship from the Ontario Mental Health Foundation. This research was also partially supported by a grant to Elizabeth Hampson from the Natural Sciences and Engineering Research Council of Canada.

REFERENCES

Becker, J. B., and Beer, M. E. (1986). The influence of estrogen on nigrostriatal dopamine activity: Behavioral and neurochemical evidence for both pre- and postsynaptic components. *Behav. Brain Res.* **19,** 27–33.

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

Becker, J. B., and Ramirez, V. D. (1981). Sex differences in the amphetamine stimulated release of catecholamines from rat striatal tissue in vitro. *Brain Res.* **204,** 361–372.

Becker, J. B., Robinson, T. E., and Lorenz, K. A. (1982). Sex differences and estrous cycle variations in amphetamine-elicited rotational behavior. *Eur. J. Pharmacol.* **80,** 65–72.

Bédard, P. J., Langelier, P., Dankova, J., Villeneuve, A., Di Paolo, T., Barden, N., Labrie, F., Boissier, J. R., and Euvrard, C. (1979). Estrogens, progesterone, and the extrapyramidal system. *Adv. Neurol.* **24,** 411–422.

Bédard, P., Langelier, P., and Villeneuve, A. (1977). Oestrogens and extrapyramidal system. *Lancet* **2,** 1367–1368.

Bickerstaff, E. R. (1975). *Neurological Complications of Oral Contraceptives.* Clarendon Press, Oxford.

Bracha, H. S. (1987). Asymmetric rotational (circling) behavior, a dopamine-related asymmetry: Preliminary findings in unmedicated and never-medicated schizophrenic patients. *Biol. Psychiatry* **22,** 995–1003.

Bracha, H. S., Lyden, P. D., and Khansarinia, S. (1989). Delayed emergence of striatal dopaminergic hyperactivity after anterolateral ischemic cortical lesions in humans; Evidence from turning behavior. *Biol. Psychiatry* **25,** 265–274.

Bracha, H. S., Seitz, D. J., Otemaa, J., and Glick, S. D. (1987). Rotational movement (circling) in normal humans: Sex difference and relationship to hand, foot and eye preference. *Brain Res.* **411,** 231–235.

Bracha, H. S., Shults, C., Glick, S. D., and Kleinman, J. E. (1987). Spontaneous asymmetric circling behavior in hemi-Parkinsonism: A human equivalent of the lesioned-circling rodent behavior. *Life Sci.* **40,** 1127–1130.

Brass, C. A., and Glick, S. D. (1981). Sex differences in drug-induced rotation in two strains of rats. *Brain Res.* **223,** 229–234.

Butcher, R. L., Collins, W. E., and Fugo, N. W. (1974). Plasma concentrations of LH, FSH, prolactin, progesterone, and estradiol-17-β throughout the 4 day estrous cycle of the rat. *Endocrinology* **94,** 1704–1708.

Camp, D. M., Becker, J. B., and Robinson, T. E. (1986). Sex differences in the effects of gonadectomy on amphetamine-induced rotational behavior in rats. *Behav. Neural Biol.* **46,** 491–495.

Carlson, J. N., and Glick, S. D. (1989). Cerebral lateralization as a source of interindividual differences in behavior. *Experientia* **45,** 788–798.

Dark, K. A., Ellman, G., Peeke, H. V. S., Galin, D., and Reus, V. I. (1984). Sex differences and asymmetries of catecholamines: Relation to turning preferences. *Pharmacol. Biochem. Behav.* **20,** 327–330.

Di Paolo, T. (1994). Modulation of brain dopamine transmission by sex steroids. *Rev. Neurosci.* **5,** 27–42.

Donaldson, J. O. (1978). *Neurology of Pregnancy*. Saunders, Philadelphia.

Drew, K. L., Lyon, R. A., Titeler, M., and Glick, S. D. (1986). Asymmetry in D-2 binding in female rat striata. *Brain Res.* **363,** 192–195.

Ellison, P. T. (1993). Measurements of salivary progesterone. *Ann. N.Y. Acad. Sci.* **694,** 161–176.

Gamboa, E. T., Isaacs, G., and Harter, D. (1971). Chorea associated with oral contraceptive therapy. *Arch. Neurol.* **25,** 112–114.

Giladi, N., and Honigman, S. (1995). Hormones and Parkinson's disease. *Neurology* **45,** 1028.

Glazer, W. M., Naftolin, F., Morgenstern, H., Barnea, E. R., MacLusky, N. J., and Brenner, L. M. (1985). Estrogen replacement and tardive dyskinesia. *Psychoneuroendocrinology* **10,** 345–350.

Glick, S. D., and Cox, R. D. (1978). Nocturnal rotation in normal rats: correlation with amphetamine-induced rotation and effects of nigrostriatal lesions. *Brain Res.* **150,** 149–161.

Glick, S. D., Jerussi, T. P., Waters, D. H., and Green, J. P. (1974). Amphetamine-induced changes in striatal dopamine and acetylcholine levels and relationship to rotation (circling behavior) in rats. *Biochem. Pharmacol.* **23,** 3223–3225.

Glick, S. D., Jerussi, T. P., and Zimmerberg, B. (1977). Behavioral and neuropharmacological correlates of nigro-striatal asymmetry in rats. *In* S. Harnad (Ed.), *Lateralization in the Nervous System,* pp. 213–249. Academic Press, New York.

Glick, S. D., Schonfeld, A. R., and Strumpf, A. J. (1980). Sex differences in brain asymmetry of the rodent. *Behav. Brain Sci.* **3,** 236.

Gordon, H. W., Busdiecker, E. C., and Bracha, H. S. (1992). The relationship between leftward turning bias and visuospatial ability in humans. *Int. J. Neurosci.* **65,** 29–36.

Hampson, E. (1990a). Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cogn.* **14,** 26–43.

Hampson, E. (1990b). Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology* **15,** 97–111.

Hampson, E., and Kimura, D. (1988). Reciprocal effects of hormonal fluctuations on human motor and perceptual-spatial skills. *Behav. Neurosci.* **102,** 456–459.

Jerussi, T. P., and Glick, S. D. (1975). Apomorphine-induced rotation in normal rats and interaction with unilateral caudate lesions. *Psychopharmacology* **40,** 329–334.

Joyce, J. N., and Van Hartesveldt, C. (1984). Behaviors induced by intrastriatal dopamine vary independently across the estrous cycle. *Pharmacol. Biochem. Behav.* **20,** 551–557.

Koller, W. C., Barr, A., and Biary, N. (1982). Estrogen treatment of dyskinetic disorders. *Neurology* **32,** 547–550.

McNair, D. M., Lorr, M., and Droppleman, L. F. (1971). *Profile of Mood States.* EdITS, San Diego.

Mead, L. A., and Hampson, E. (1996a). A sex difference in turning bias in humans. *Behav. Brain Res.* **78,** 73–79.

Mead, L. A., and Hampson, E. (1996b). Asymmetric effects of ovarian hormones on hemispheric activity: Evidence from dichotic and tachistoscopic tests. *Neuropsychology* **10,** 578–587.

Morissette, M., Lévesque, D., Bélanger, A., and Di Paolo, T. (1990). A physiological dose of estradiol with progesterone affects striatum biogenic amines. *Can. J. Physiol. Pharmacol.* **68,** 1520–1526.

Nausieda, P. A., Koller, W. C., Weiner, W. J., and Klawans, H. L. (1979). Chorea induced by oral contraceptives. *Neurology* **29,** 1605–1609.

Norusis, M. J. (1988). *SPSS/PC+ V2.0 Base Manual.* SPSS Inc., Chicago.

Pycock, C. J. (1983). Experimental model of hemi-Parkinsonism. *In* M. S. Myslobodsky (Ed.), *Hemisyndromes: Psychobiology, Neurology, Psychiatry,* pp. 69–90. Academic Press, New York.

Quinn, N. P., and Marsden, C. D. (1986). Menstrual-related fluctuations in Parkinson's disease. *Mov. Disord.* **1,** 85–87.

Robinson, T. E., and Becker, J. B. (1983). The rotational behavior model: asymmetry in the effects of unilateral 6-OHDA lesions of the substantia nigra in rats. *Brain Res.* **264,** 127–131.

Robinson, T. E., Becker, J. B., and Ramirez, V. D. (1980). Sex differences in amphetamine-elicited rotational behavior and the lateralization of striatal dopamine in rats. *Brain Res. Bull.* **5,** 539–545.

Robinson, T. E., Camp, D. M., Jacknow, D. S., and Becker, J. B. (1982). Sex differences and estrous cycle dependent variation in rotational behavior elicited by electrical stimulation of the mesostriatal dopamine system. *Behav. Brain Res.* **6,** 273–287.

Roy, E. J., Buyer, D. R., and Licari, V. A. (1990). Estradiol in the striatum: Effects on behavior and dopamine receptors but no evidence for membrane steroid receptors. *Brain Res. Bull.* **25,** 221–227.

Schaeffer, A. A. (1928). Spiral movement in man. *J. Morphol.* **45,** 293–398.

Seltzer, C., Forsythe, C., and Ward, J. P. (1990). Multiple measures of motor lateralization in human primates (*Homo sapiens*). *J. Comp. Psychol.* **104,** 159–166.

Shapiro, R. M., Glick, S. D., and Hough, L. B. (1986). Striatal dopamine uptake asymmetries and rotational behavior in unlesioned rat: Revising the model. *Psychopharmacology* **89,** 25–30.

Steenhuis, R. E., Bryden, M. P., Schwartz, M., and Lawson, S. (1990).

Reliability of hand preference items and factors. *J. Clin. Exp. Neuropsychol.* **12,** 921–930.

Van Hartesveldt, C., and Joyce, J. N. (1986). Effects of estrogen on the basal ganglia. *Neurosci. Biobehav. Rev.* **10,** 1–14.

Villeneuve, A., Cazejust, T., and Coté, M. (1980). Estrogens in tardive dyskinesia in male psychiatric patients. *Neuropsychobiology* **6,** 145–151.

Villeneuve, A., Langelier, P., and Bédard, P. (1978). Estrogens, dopamine, and dyskinesias. *Can. Psychiatry Assoc.* **23,** 68–70.

Waziri, R. (1980). Lateralization of neuroleptic-induced dyskinesia indicates pharmacologic asymmetry in the brain. *Psychopharmacology* **68,** 51–53.

Wong, D. F., Broussolle, E. P., Wand, G., Villemagne, V., Dannals, R. F., Links, J. M., Zacur, H. A., Harris, J., Naidu, S., Braestrup, C., Wagner, H. N., and Gjedde, A. (1988). *In vivo* measurement of dopamine receptors in human brain by positron emission tomography: Age and sex differences. *Ann. N.Y. Acad. Sci.* **515,** 203–214.

Zimmerberg, B., Glick, S. D., and Jerussi, T. P. (1974). Neurochemical correlate of a spatial preference in rats. *Science* **185,** 623–625.