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ESTROGEN MODULATES INHIBITORY CONTROL IN HEALTHY HUMAN FEMALES: EVIDENCE FROM THE STOP-SIGNAL PARADIGM

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Abstract—Animal studies point to a role of estrogen in explaining gender differences in striatal dopaminergic functioning, but evidence from human studies is still lacking. Given that dopamine is crucial for controlling and organizing goal-directed behavior, estrogen may have a specific impact on cognitive control functions, such as the inhibition of prepotent responses. We compared the efficiency of inhibitory control (as measured by the stop-signal task) in young women across the three phases of their menstrual cycle (salivary estradiol and progesterone concentrations were assessed) and in young men. Women were less efficient in inhibiting prepotent responses in their follicular phase, which is associated with higher estradiol levels and with higher dopamine turnover rates, than in their luteal or menstruation phase. Likewise, women showed less efficient inhibitory control than men in their follicular phase but not in their luteal or menstruation phase. Our results are consistent with models assuming that the over-supply of striatal dopamine in the follicular phase weakens inhibitory pathways, thus leading to enhanced competition between responses. We conclude that gender differences in response inhibition are variable and state dependent but not structural.

Key words: inhibition control, estrogen, stop-signal task, dopamine, gender differences.

Increasing evidence suggests that the sex steroid hormone estrogen affects the striatal dopaminergic system. For instance, estrogen and progesterone have been shown to modulate striatal dopamine (DA) activity in female but not male rats. The DA content of striatal tissue in this species is also higher in females than in males (McDermott et al., 1994). DA turnover rates are higher during diestrus (rising estrogen level) than in estrus (low estrogen level) (Fernandez-Ruiz et al., 1991). Receptor autoradiography studies have shown that D2 receptor densities can increase in the presence of natural elevations in estrogen during the estrous cycle and after exogenous estrogen administration (Pazos et al., 1985; Di Paolo et al., 1988; Bazzett and Becker, 1994; Di Paolo, 1994). Consistent with this picture, other studies have suggested that the follicular phase (FP) is related to increases in DA release produced by high levels of estrogen (Di Paolo et al., 1986; Becker, 1999; Becker et al., 2001; Dazzi et al., 2007).

In primates, estrogen is known to play an essential role in maintaining the integrity of the nigrostriatal DA system (Leranth et al., 2000). In human females, behavioral effects of drugs that act primarily on brain DA systems, such as amphetamine and cocaine, differ as a function of menstrual cycle phase (Justice and de Wit, 1999; Sofuoglu et al., 1999; Evans et al., 2002; White et al., 2002; Evans and Foltin, 2006; Terner and de Wit, 2006). Wong et al. (1988) observed a trend toward lower striatal uptake of the D2 ligand [^{11}C]-*N*-methyl-spiperone in the FP compared with the luteal phase (LP), indicating either lower D2 receptor densities or higher striatal DA concentrations during the FP. Recently, Czoty et al. (2009) suggested that changes in DA receptor availability may be involved in the variation in symptoms of various neuropsychiatric disorders across the menstrual cycle, including differences in sensitivity to the abuse-related effects of stimulants.

Given that DA is crucial for controlling and organizing goal-directed behavior (Cools, 2006), the available evidence suggests an impact of estrogen on cognitive control. However, very little is known about this possible link between estrogen and control processes, especially in humans. There is some evidence that implicit memory and working memory performance varies across the menstrual cycle in healthy females. Although cycle phase does not seem to affect explicit memory (as measured by a category-cued recall task), performance on implicit memory (as measured by a category exemplar generation task) was found to be impaired in the FP (Maki et al., 2002). Moreover, women in their FP were reported to show impaired performance in a working memory task (delayed matching to sample) and elevated error rates for pictures of the facial expressions of sadness and disgust (Gasbarri et al., 2008). However, research has yet to systematically address whether or which particular control functions might be affected. At least three conceptually and empirically separable control functions can be distinguished: "Shifting" between tasks and mental sets; "updating" and monitoring of working memory (WM) representations; and the "inhibition" of prepotent responses (Miyake et al., 2000). There are two reasons why, from these three control functions, inhibition might be considered a particularly promising candidate to be affected by estrogen.

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Abbreviations: ACPI, advanced configuration and power interface; ANOVA, analysis of variance; DA, dopamine; DRD2, DAD2 receptor; DRD4, DAD4 receptor; FP, follicular phase; IQ, intelligence quotient; LP, luteal phase; MP, menstrual phase; MSE, mean squared error; η^2p, partial eta squared; PC, personal computer; RT, reaction time; SSRT, stop-signal reaction time; WM, working memory.

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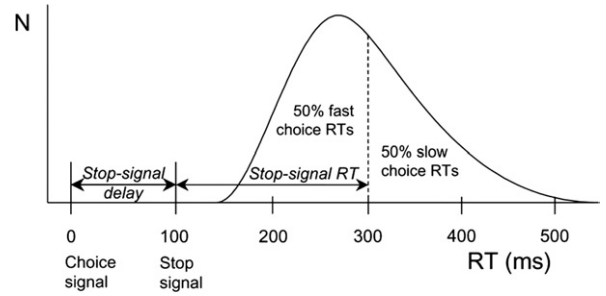

Fig. 1. Calculation of SSRT according to a race model (Logan, 1994; Logan and Cowan, 1984). The curve depicts the distribution of RTs on go trials (trials without a stop signal) representing the finishing times of the response processes. Assuming independence of go and stop processes, the finishing time of the stop process bisects the go RT distribution. Given that the button-press response could be withheld in 50% of all stop trials, stop-signal RT (200 ms) is calculated by subtracting the mean stop-signal delay (100 ms) from the median go RT (300 ms).

First, gender differences have been shown in the brain activation of a task tapping into inhibitory control: the stop-signal paradigm (Logan, 1994; Logan and Cowan, 1984). In this task, participants are first presented with a stimulus prompting them to execute a particular response, and this stimulus may or may not be followed by a stop signal calling for the immediate abortion of that response. The underlying theory provides an index of efficiency of stopping for each individual, i.e., inhibitory control (Logan and Cowan, 1984). On the basis of the mathematical considerations of Logan and Cowan (1984), the stop-signal paradigm provides a direct behavioral assessment of the individual ability to stop a planned or ongoing motor response in a voluntary fashion and a quantitative estimate of the duration of the covert response-inhibition process (the so-called stop-signal reaction time [SSRT]) (Fig. 1). Interestingly, for our purposes, men and women were shown to differ in their performance on this task (Li et al., 2006). For one, they exhibited rather different patterns of brain activation: among men, solving the task was associated with activation in the motor circuitry, whereas women seemed to rely on structures responsible for visual association or habit learning. At the behavioral level, men tended to be faster than women in inhibiting prepotent responses. Even though this difference did not quite reach the significance level ($P>0.15$), it is important to note that in this study women were not screened with respect to the phase of their menstrual cycle. It is thus possible that better control or the systematic variation of this factor renders these gender differences statistically significant.

Second, studies using the stop-signal task have provided converging evidence for the involvement of DA in general and, in particular, of the DA D2 system in response inhibition. Eagle et al. (2007) found that modafinil, a drug that activates the locus coeruleus by potentiating tonic DA excitation (Szabadi, 2006), significantly reduced SSRT. Enticott et al. (2008) reported that schizophrenia patients, who have subcortical/cortical DA imbalance (subcortical mesolimbic DA projections are hyperactive, resulting in hyperstimulation of D2 receptors) (Carlsson et al., 2000), inhibit responses less efficiently than control subjects do. Parkinson patients, who have damage to dopaminergic cells in the striatum (Kish et al., 1988), showed longer SSRTs (Gauggel et al., 2004) and impaired suppression of conflicting responses (Wylie et al., in press) compared with matched controls.

Studies investigating genetic variability associated with striatal dopaminergic polymorphisms and drug studies suggest a strong link between the DA D2 system (the system shown in receptor autoradiography to be particularly impacted by estrogen) and inhibitory control (Congdon et al., 2008; Colzato et al., unpublished observation, 2009; Colzato et al., 2007; Fillmore and Rush, 2002). Congdon et al. (2008) found a significant association between inhibitory control and the presence of the 7-repeat allele of the gene coding the DA D4 receptor (DRD4)—which also belongs to the DA D2 receptor family. Very recently, Colzato et al. (unpublished observation, 2009) found a comparable association between C957T polymorphism at the gene coding the DA D2 receptor (DRD2) and the inhibition of prepotent responses. In both studies, allele carriers directly associated with relatively increased striatal DA (DRD2 T/T homozygotes and DRD4 7-repeat carriers) showed greater difficulty in inhibiting a behavioral response to a stop signal. Consistent with this picture, both chronic cocaine users (Fillmore and Rush, 2002) and recreational users of cocaine (Colzato et al., 2007), who are likely to have a reduction in the number of striatal DA D2 receptors (Volkow et al., 1999), need significantly more time than nonusers to inhibit responses to stop signals.

All these findings converge on the notion that the striatum plays a critical role in the suppression of responses that are incorrect or no longer relevant. They also fit with the assumption that first, DA, which innervates these circuits, plays a role in modulating response inhibition (Mink, 1996). Second, they suggest that the level of dopaminergic activity and the efficiency of dopaminergically driven processes follow an inverted U-shaped function (Goldman-Rakic et al., 2000; Muly et al., 1998). Indeed, several authors have suggested that optimal performance in tasks requiring cognitive control calls for a medium DA level, whereas too low or too high DA levels lead to impaired performance (Goldman-Rakic et al., 2000; Colzato et al., 2008). Considering that inhibiting prepotent responses does require cognitive control, we thus expected that elevated levels of estrogen, as in the FP of the menstrual cycle, are associated with impairments in inhibitory control.

The aim of this study was twofold. The first goal was motivated by the suggestion that, given the higher DA turnover rates and D2 receptor densities during diestrus (rising estrogen level) than in estrus (low estrogen level) (Fernandez-Ruiz et al., 1991; Pazos et al., 1985; Bazzett and Becker, 1994; Di Paolo, 1994), estrogen may modulate response inhibition via the link between estrogen and striatal DA D2 supply. To test that, we compared performance in the stop-signal paradigm in young women, across different phases of their menstrual cycle. All three phases were considered: the FP, which is associated with the highest level of estrogen compared with the LP and

menstruation proper (MP). Because estrogen is associated with higher DA turnover rates and if estrogen affects the DA functioning in driving inhibitory control, we would expect impairments of inhibitory efficiency (i.e., longer SSRT) in the FP (i.e., with the highest level of estrogen) compared with the LP and MP.

The second goal of the study was to investigate whether women differ from men in inhibitory control performance. As pointed out previously, it is possible that differences between men and women are restricted to particular phases of the women's menstrual cycle, so we made separate comparisons for the three cycles. Because estrogen modulates striatal DA activity in females but not in males (McDermott et al., 1994) and if estrogen affects the DA functioning in driving inhibitory control, we would expect gender differences to be most pronounced in, or even restricted to, women in their FP (which is associated with an elevated level of estrogen). In other words, women were expected to show impaired inhibitory efficiency (i.e., longer SSRT), as compared with men, mainly in their FP.

Inhibitory efficiency was assessed by means of a standard version of the stop-signal paradigm, in which participants responded to the direction of a green arrow by pressing a button with the left or right index finger (van den Wildenberg et al., 2006). The stop signal was a sudden and unpredictable color change of the arrow to red, signaling a deliberate effort to refrain from responding. As explained previously, this task provides an estimate of SSRT, with short and long SSRTs suggesting high and low levels of efficiency in inhibitory control, respectively.

EXPERIMENTAL PROCEDURES

Participants

Sixteen young healthy women, aged 19 to 28 years (mean age, 23.14±3.3) years, with a mean intelligence quotient (IQ) of 114.8±7.1, and sixteen young healthy men, aged 19 to 28 years (mean age, 23.15±4.3 years), with a mean IQ of 115.6±7.4, were compensated for their participation.

Women served in three experimental sessions held on three different days according to the phases of their menstrual cycle (menstruation, follicular, and luteal session). The menstruation session was held when the participants were in their first or second day of the menstrual cycle, the follicular session was held when participants were in their 9th to 12th day (when the estradiol level is higher), and the luteal session took place when participants were in their 17th to 27th day. Men also served in three sessions separated by 10 days, to match the corresponding time intervals between testing sessions in women. A randomized crossover design with counterbalancing of the order of sessions was used to avoid training effects. In the female group, six participants performed their first session in their menstruation phase, five in their LP, and five in their FP.

Participants were all students from Leiden University and were recruited via ads posted on community bulletin boards and by word of mouth. On the basis of the study by Gasbarri et al. (2008), participants were screened in accordance with the regularity of their menstruation cycle. We considered women with regular menstrual cycles who reported variations of less than 8 days between their longest and shortest cycles. Our female participants had a mean cycle length of 30 days (±1.5).

In accordance with Elzinga and Roelofs (2005), Colzato et al. (unpublished observation, 2009), and Colzato et al. (2009a), participants were selected by use of the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997). The following exclusion criteria were applied: any form of oral contraceptive within the last 3 months, medication for chronic illness, neurologic or psychiatric disorders, and substance abuse. To assess ovarian function and verify the cycle phase in women, noninvasive salivary measures of estradiol and progesterone levels were used.

All participants were tested individually and completed the stop-signal task and the intelligence test immediately after the collection of salivary samples. Written informed consent was obtained from all subjects; the protocol and the remuneration arrangements (€20) were approved by the local ethical committee (Leiden University, Institute for Psychological Research).

Apparatus and stimuli

The experiment was controlled by an advanced configuration and power interface (ACPI) uniprocessor personal computer (PC) running on an Intel Celeron 2.8-GHz processor, attached to a Philips 109B6 17 inch monitor (LightFrame 3, 96 dpi with a refresh rate of 120 Hz). Responses were made by pressing the "Z" or "?" of the QWERTY computer keyboard (DELL, Round Rock, TX, USA) with the left or right index finger. Participants were required to react quickly and accurately by pressing the left or right key in response to the direction of a left- or right-pointing green arrow (go trials) of about 3.5×2.0 cm with the corresponding index finger.

Stop-signal task

Each experimental session consisted of a 30-minute session in which participants completed a version of the stop-signal task adopted from Colzato et al. (2007) and Colzato et al. (2009b). Arrows were presented pseudo-randomly for a maximum of 1,500 ms, with the constraint that they signaled left- and right-hand responses equally often. Arrow presentation was response terminated. Intervals between subsequent go signals varied randomly but equiprobably, from 1,250 to 1,750 ms in steps of 125 ms. During these interstimulus intervals, a white fixation point (3 mm in diameter) was presented. The green arrow changed to red on 30% of the trials, upon which the choice response had to be aborted (stop trials). A staircase-tracking procedure dynamically adjusted the delay between the onset of the go signal and the onset of the stop signal to control inhibition probability (Levitt, 1971). After a successfully inhibited stop trial, the stop-signal delay in the next stop trial increased by 50 ms, whereas the stop-signal delay decreased by 50 ms in the next stop trial when the participant was unable to stop. This algorithm ensured that motor actions were successfully inhibited in about half of the stop trials, which yielded accurate estimates of SSRT and compensated for differences in choice reaction time (RT) between participants (Band et al., 2003) (Fig. 1). The stop task consisted of five blocks of 104 trials each, the first of which served as a practice block to obtain stable performance.

Intelligence quotient

Individual IQs were determined by means of a 30-minute reasoning-based intelligence test (Raven Standard Progressive Matrices [SPM]). The SPM assesses the individual's ability to create perceptual relations and to reason by analogy independent of language and formal schooling; it is a standard, widely used test to measure the Spearman *g* factor as well as fluid intelligence (Raven et al., 1988). Participants completed the SPM and subsequently performed the behavioral task measuring inhibitory control.

Immunoassay protocols

Salivary estradiol and progesterone concentrations were analyzed by an independent laboratory using commercially avail-

able radioimmunoassay kits adopted for the analysis of salivary samples (DSL, Sinsheim, Germany). In contrast to venipuncture, this technique is noninvasive but provides accurate measures of estradiol and progesterone concentrations (Worthman et al., 1990; O'Rourke and Ellison, 1993; Lipson and Ellison, 1996; Lu et al., 1999).

Saliva sample collection. Subjects were asked to collect the saliva by passive drool into polypropylene tubes of 10 ml. For each experimental session, the saliva samples of all participants were collected at the same hour (14:00). Participants were asked to avoid alcohol consumption 24 hours before sample collections, not eat within the 60 minutes before sample collection, not brush teeth within the 3 hours before sample collections, and wash mouth out with water 10 minutes before giving a sample.

Saliva sample analysis. Saliva samples were analyzed with high-sensitivity salivary estradiol or progesterone enzyme immunoassay kits from Diagnostic Systems Laboratories, Inc. (Webster, TX, USA), by use of the procedure recommended by the company, without any modifications. The levels of estradiol or progesterone were computed by fitting the optical density reading of each saliva sample to obtain the standard curve. The minimal concentration of estradiol and progesterone that can be distinguished is 1 and 5 pg/ml, respectively.

Statistical analysis

First, to assess ovarian functioning in women and verify the cycle phase, statistical differences of estradiol and progesterone levels between cycle phases were analyzed by means of a repeated-measures analysis of variance (ANOVA) with cycle phase (MP vs. FP vs. LP) as the within-subject factor. Independent-samples *t* tests were performed for analyses of age and IQ differences between men and women.

Second, for all three menstrual phases, mean RT for go trials (i.e., trials without a stop signal) and SSRT for stop-signal trials were individually calculated to index response execution and response inhibition, respectively. For women, both measures were analyzed separately by means of repeated-measures ANOVAs with cycle phase (MP vs. FP vs. LP) as the within-subject factor and order of phase as covariate (to account for possible order effect). Independent-samples *t* tests were performed for analyses of phase differences on mean RT for go trials and SSRT for stop-signal trials between men and women. Phase-specific comparisons between men and women were carried out between the corresponding subset of data from the women and an equivalent subset of data from men—to equate the compared data sets in terms of the number of trials considered, practice level, variance, and so on. This was achieved by creating dummy cycle phases in men by yoking every male participant to a female participant and assigning the corresponding phase of the female to him.

Third, Pearson correlation coefficients were computed between hormone levels and mean SSRT for stop-signal trials to test whether the magnitude of inhibitory control is proportional to salivary estradiol and/or progesterone concentrations.

A significance level of $P<0.05$ was adopted for all statistical tests, and all reported *t* test results refer to two-tailed testing.

RESULTS

No significant group differences were obtained for age ($t_{30}=-0.113$, $P=0.91$) and intelligence ($t_{30}=0.32$, $P=0.75$).

Hormonal levels

Estradiol and progesterone levels in participants in FP, LP, and MP were obtained by interpolation of data, by use of a logarithmic linear regression straight line. (Estimating hormone levels by interpolation is a standard approach, given that data often behave as a log function of X and Y in the following least-squares regression formula: $\log Y=B_0+B_1[\log X]$, where *X* is disintegrations per minute and *Y* is the dependent variable [e.g., amount of hormone].) The mean standard errors of estradiol levels in the FP, LP, and MP were 5.05±0.29 pg/ml, 3.91±0.56 pg/ml, and 3.02±0.81 pg/ml, respectively. Repeated-measures ANOVA showed a significant difference between cycle phases: $F_{2,30}=6.88$, $P<0.05$, mean squared error (MSE)=2.369, partial eta squared (η^2p)=0.315.

The mean standard errors of progesterone levels in the FP, LP, and MP were 49.18±6.94 pg/ml, 94.15±20.48 pg/ml, and 41.31±6.73 pg/ml, respectively. Repeated-measures ANOVA showed a significant difference between cycle phases: $F_{2,30}=5.80$, $P<0.05$, MSE=2,242.79, η^2p=0.279.

These results indicate significantly higher levels of estradiol in the FP and progesterone in the LP as confirmation of normal ovarian functioning in our participants.

Stop-signal task

Women, in all three cycle phases, were able to stop their responses on stop-signal trials successfully about half of the time, indicating that the dynamic tracking algorithm worked: 50.8% in FP (SE=0.2%), 50.2% in LP (SE=0.6%), and 50.8% in MP (SE=0.3%). The percentage of choice errors in go trials was low in all three cycle phases: 1.2% in FP (SE=0.2), 0.7% in LP (SE=0.2), and 1.0% in MP (SE=0.3).

Mean RT in go trials was not modified by cycle phase ($F<1$), indicating that participants reacted equally fast in FP (392 ms, SE=6.8 ms), LP (399 ms, SE=15.5 ms), and MP (394 ms, SE=8.8 ms) (Fig. 2). No significant interaction of order of phase on mean go RT was found ($F<1$).

In contrast, SSRTs yielded a significant effect of cycle phase ($F_{2,30}=3.50$, $P<0.05$, MSE=282.13, η^2p=0.19) due to a longer SSRT in FP (221 ms, SD=6.3 ms) than in LP (206 ms, SD=5.5 ms) or MP (209 ms, SD=5.3 ms) (Fig. 2). No significant interaction of order of phase on SSRTs was found ($F<1$).

Men were also able to stop their responses on stop-signal trials successfully about half of the time (50.3%, SD=1.2%) and rather quickly (203 ms, SD=25.1 ms). Go responses were also fast (380 ms, SD=35 ms), and the percentage of choice errors was low (0.9%, SD=1.0).

Independent-samples *t* tests on mean RT for go trials showed no difference between women and (phase-yoked) men in any of the three phases: FP ($t_{30}=-0.66$, $P=0.514$), LP ($t_{30}=-1.12$, $P=0.272$), and MP ($t_{30}=-0.40$, $P=0.968$) (Fig. 2). However, as expected, *t* tests on SSRTs yielded a significant difference between men and women in FP ($t_{30}=-1.952$, $P=0.047$) but not in LP ($t_{30}=-0.57$, $P=0.573$) and MP ($t_{30}=-0.60$, $P=0.553$) (Fig. 2).

A significant positive correlation was found in women between mean SSRT for stop-signal trials and estradiol levels ($r_{16}=0.501$, $P<0.05$) but not with progesterone levels ($r_{16}=0.093$, $P=0.73$) (Fig. 3).

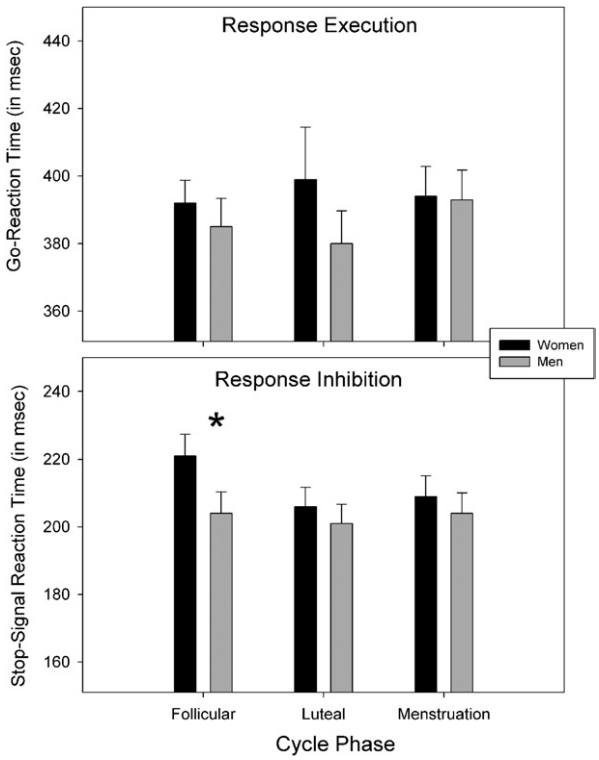

Fig. 2. Mean go-signal RT (response latency) and mean SSRT (stopping latency) in FP, LP, and MP for women and for men (fictive). Vertical capped lines atop bars indicate standard error of the mean. Significant group difference: *$P<0.05$.

DISCUSSION

Our findings show that inhibitory control, as measured by a stop-signal task, varies across the menstrual cycle of healthy human females. In particular, women show a comparatively longer SSRT in their FP, which is associated with higher levels of estradiol, higher DA turnover rates, and higher D2 receptor densities (Fernandez-Ruiz et al., 1991; Pazos et al., 1985; Bazzett and Becker, 1994; Di Paolo, 1994) than in the other two phases of their menstrual cycle. Importantly, there was no evidence of a general decrement in response execution, as witnessed by the absence of any effect of cycle on go performance. That is, the effect of menstrual cycle was process specific. We consider this as first evidence that estrogen impacts on executive control functions in humans.

Also of interest, women showed less efficient inhibitory control than men in the FP but not in the other two phases of their menstrual cycle. The two gender groups were matched for intelligence and age, with the latter being particularly important: Although inhibitory control does not seem to be related to general intelligence (Logan, 1994), there is evidence that inhibitory processes decline throughout the adult lifespan (Logan, 1994; Williams et al., 1999). Our observation that estrogen modulates inhibitory control may explain why Li et al. (2006) found gender differences in a stop-signal task with respect to some but not other measures. Given that women were not screened with respect to their menstrual cycle, it is possible that the observed gender differences were mainly driven by females in their FP—an effect that may or may not reach significance depending on the ratio of women in this phase as compared with other phases.

Correlational analyses showed a significant positive association of estradiol level, but not of progesterone levels, with SSRT for stop-signal trials. This finding confirms that estrogen, and not progesterone, was responsible for the observed changes in inhibitory control. It interesting to note that reduced supply of DA, as with chronic (Fillmore and Rush, 2002) and recreational (Colzato et al., 2007) cocaine users, affects inhibitory control the same way as the over-supply of DA does, as in women in their FP. This fits with the assumption that the relationship between DA production and the efficiency of cognitive control follows an inverted U-shaped function, with a median DA level being associated with best performance (Goldman-Rakic et al., 2000; Colzato et al., 2008). Given that our participants were screened for several psychiatric and neurologic disorders, they can be assumed to roughly fall into the central area of this function so that elevated estradiol levels in the FP increased the DA level to a degree that rendered cognitive control less efficient. However, it important to consider that this scenario only holds for the group results and may or may not hold for particular individuals. For instance, women with a relatively low average DA level might well benefit in control efficiency from estradiol-induced increases in DA supply.

It is also interesting to note that our observations are consistent with the model proposed by Frank et al. (2007), according to which the basal ganglia support adaptive decision making by modulating the selection of frontal cortical action plans. In short, two main neuronal populations in the striatum are assumed to have opposing effects on action selection via output projections through the globus pallidus, thalamus, and back to the cortex. Activity in

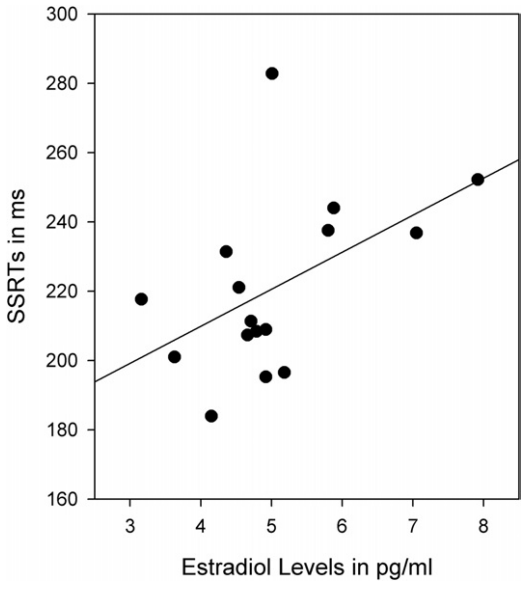

Fig. 3. Scatter diagram of estradiol levels (in picograms per milliliter) against SSRT (in milliseconds).

"Go" neurons facilitates the execution of a cortical response, whereas "NoGo" activity suppresses competing responses. DA bursts and dips that occur during positive and negative outcomes drive Go learning (via D1 receptors) to seek rewarding actions and NoGo learning (via D2 receptors) to avoid non-rewarding actions. Complementing this functionality, the subthalamic nucleus provides a self-adaptive dynamic control signal that temporarily prevents the execution of any response, depending on decision conflict. According to this model, supplying more DA than optimal (as it is presumably the case in the FP) decreases activity in the indirect pathway (NoGo), a process that would enhance the competition between responses. Even though the model of Frank et al. (2007) has not yet been implemented for the stop-signal task, we speculate that the observed delay in SSRTs in the FP might be a possible indicator of such enhanced competition.

Our findings raise a number of important and possibly far-reaching issues that call for further investigation. First, given that almost all experimental tasks involve some components of executive control, they raise the question of whether gender effects reflect structural differences, the often-favored conclusion, or rather variable, state-dependent differences that vary with the menstrual cycle. In other words, men and women may sometimes show comparable performance and sometimes show different performance, depending on when they are tested. Second, given that memory retrieval and working memory rely on executive control functions, it remains to be seen whether the demonstrated impact of the menstrual cycle on implicit memory (Maki et al., 2002) and working memory (Gasbarri et al., 2008) reflects a true effect of/on memory or, rather, an effect of/on memory-control functions. Third, given that our study addressed but one of at least three dissociable executive control operations, it would be interesting to know whether estrogen and the menstrual cycle also affect the "shifting" between mental sets and the "updating" and monitoring of working memory representations (Miyake et al., 2000).

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