Utrecht University
Master Psychology, Social Psychology

Thesis

Dopamine, context dependence and attribution: Menstrual cycle influences on behavior.

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28 juni 2011

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Abstract

During the menstrual cycle dopamine levels increase and decrease. Fertile women have high levels of dopamine and show a relative delay in responding towards less dominant stimuli. Because the change to a fertile phase is a very important feature from an evolutionary perspective, we propose there must be a potential beneficial process in the brain which also causes this symptom. Women reap rewards when be able to focus on specific male traits in the fertile phase. We therefore assume that this focus on important stimuli might be higher in women in their fertile phase compared to women in their non-fertile phase. To test the idea of women being more persistent on dominant stimuli, negating more peripheral stimuli, we conducted two studies. One study used an abstract measure for cognitive focus on the dominant target, but it did not show any results. The other study showed that naturally cycling women showed more dispositional attribution during the fertile phase in contrast to contextual attributions, but the effect was reversed in women using hormonal contraceptives. Nevertheless, these results could be interpreted according to the model that implies the effect on the brain shows an U-shaped curve. In this case that would be low and high dopamine levels causing more dispositional attribution, while the intermediate levels of dopamine cause less dispositional attribution.

We are driving a car and the traffic light in front of us turns red. We stop pushing on the gas, elevate our foot and move it to press the brake paddle. We are reading at home and the doorbell rings, we stop reading and walk towards the door to open it. These are very explicit examples of stimuli stopping the behavior we are performing and starting other behavior. Our daily live is a continuous stream of these events. Even during the performance of the examples mentioned above behavior is constantly modulated, like direction adjustments during walking. Without this cognitive function of inhibitory control we wouldn't be able to function at all in society.

In this paper we want to investigate the effects of dopamine on specific behavior. Dopamine is an important neurotransmitter within the brain regions that are responsible for inhibitory control (Hall & Nicolelis, 2001; Frank, Samanta, Moustafa & Sherman, 2007; Colzato, Hertsig, Wildenberg & Hommel, 2010). Supra-optimal levels of dopamine in the brain are thought to cause a general slowing down of non-dominant prepotent responses (e.g. to want to cross the street when waiting for the red traffic light), by making the inhibitory control region of the brain less flexible in reacting on new stimuli (e.g. the light turning green, Colzato, et al., 2010; Cools 2008). In other words, people with more than optimally high

dopamine levels react slower to stimuli triggering prepotent responses in their brain. There must be a cognitive mechanism which would make sense on a functional or evolutionary level which explains this delaying effect, because under natural circumstances and for probably hundred thousands of years there were and are people with repeating moments of supra-optimal dopamine levels: Women with natural menstrual cycles around their pre-ovulatory estrogen peak. We think of this delay being a symptom of actually concentrating on what is perceived as most important. Instead of thinking of a delay in reaction to new stimuli as a dysfunction of the "brakes", we like to think of it as a stronger "engine" pushing cognitively the dominant response you are performing and ignoring the context. We will test this relative ignoring of the context hypothesis in this paper. We will describe functioning of dopamine on the inhibitory control system in the brain, describe some recent findings in research area of dopamine and inhibition and conclude with a description of dopamine change during the menstrual cycle. Then we will be able to derive other insights to findings on dopamine effects and explain our hypothesis. Subsequently we will test our hypothesis with two studies and conclude with a general discussion.

Inhibitory control and the role of dopamine

What is this 'inhibitory control' in the brain? The basal ganglia regulate impulses from brain regions in the cortex back to the cortex itself. The thalamus in the basal ganglia is responsible for the actual inhibitory control of prepotent responses from the prefrontal cortex back to the cortex and other regions in the basal ganglia interact with this part of the basal ganglia (e.g. Frank, et al. 2007; Hall & Nicolelis, 2001; Colzato, van den Wildenberg, van Wouwe, Pannebakker & Hommel, 2009; Colzato et al., 2010). The effects of dopamine in the basal ganglia is widely investigated and acknowledged, yet the role of dopamine seems to be manifold, also playing a role outside the basal ganglia in the prefrontal cortex (PFC), and the effect of changing levels of dopamine on the brain is not fully understood (Humphries &

Prescott, 2010). Neurons with dopamine emitting synapses are mainly present in the substantia nigra pars compacta (SNpc) ending in the striatum (Hall & Nicolelis, 2001) and to a lesser extent from the tegmental ventral area towards the PFC (Cools, 2008). The striatum is divided into two regions which are under influence of the dopamine from the SNpc: the caudate and putamen. The putamen exerts its influence on the thalamus through a direct and indirect pathway. The thalamus functions as the actual 'relay station', which opens or closes specific signal pathways for signals to move back towards the cortex (Hall & Nicolelis, 2001). The thalamus also functions as the 'center of selection', where irrelevant and incorrect responses generally should be filtered out. The speed of this process determines the speed of reaction to a stimulus, in effect it decides whether to act on a stimulus or not.

Higher dopamine levels should, according to most models, indirectly inhibit the tonic inhibition of the thalamus and therefore make the thalamus more 'flexible'. This means it should respond more flexible towards input signals, which will lead to behavior adaptation (Cools, 2008). The dopaminergic effect on inhibitory control is also confirmed by patients suffering Parkinson's disease, since dopamine production from the degraded SNpc is reduced and this results in paucity of their response to stimuli (Cools, 2006; Hall & Nicolelis, 2001).

The menstrual cycle: estrogen and dopamine

Estrogen level, a sex hormone which fluctuates over the menstrual cycle, is positively correlated with the dopamine level. The menstrual cycle shows a changing level of estrogen through different phases. One study reported average estrogen levels during the menstrual cycle for about 15 days before and after the peak of the luteinizing hormone (LH) (Stricker, Eberhart, Chevailler, Quinn, Bischof & Stricker, 2006). We adopted a figure from their study on estrogen and centered it around the estrogen peak, which is 24 hours before the LH peak (fig. 1). This figure resembles other study results on estrogen change over the menstrual cycle (e.g. Sherman & Korenman, 1975). In the follicular phase, between menstruation and

ovulation, estrogen levels reach a peak level 34 hours before ovulation. During the lutteal phase the estrogen level drops to an intermediate concentration and before the start of the menstruation declines to the lowest estrogen level. The menstruation phase shows the lowest estrogen levels of the total cycle, remaining low from two days before the start of menstruation until a couple of days after menstruation. The period of low estrogen depends on the next ovulation moment which in turn depends on the cycle length (Stricker et al., 2006; Lenton, Landgren & Sexton, 1984).

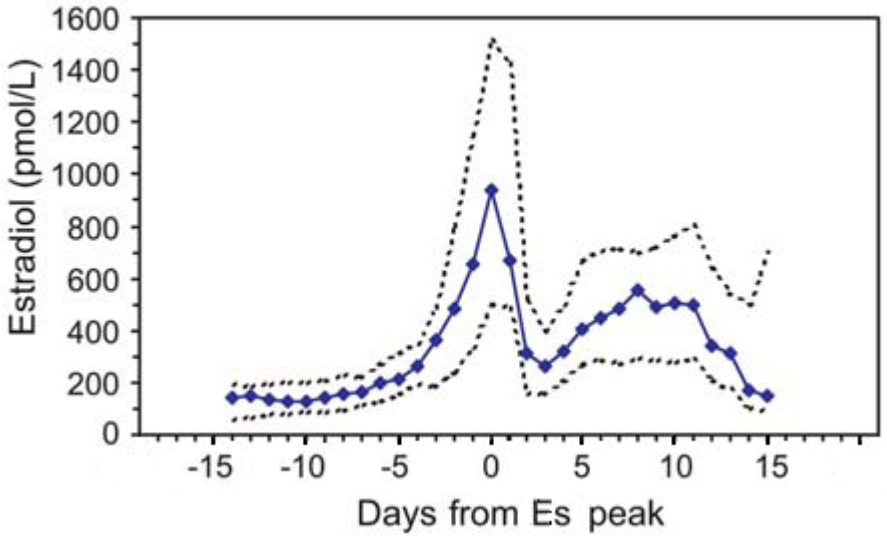

Figure 1. Estrogen levels in daily serum samples across the menstrual cycle for normal women. Solid lines represent median values; dotted lines represent 5th and 95th percentiles. (adapted from Stricker et al., 2006). Es = Estrogen.

Dopamine, inhibitory control and the menstrual cycle

Colzato et al. (2010) used this knowledge of the link between estrogen and dopamine and used female participants with natural menstrual cycles to look at the influence of natural changing levels of dopamine. Their results added new evidence for the link between dopamine fluctuation and inhibitory control utilizing a stop signal task. Women in their follicular phase performing a standard stop signaling task showed a relatively delayed response to inhibit a dominant response compared to women in any other phase of the

menstrual cycle. The variable measuring this delay, the so-called 'stop signaling reaction time' (SSRT), was significantly about 12 ms longer than women in luteal or menstruation phase or compared to control male participants.

The stop signaling reaction time task used by Colzato et al. (2010) consists of the repeated presentation on a computer screen of an green arrow, which sometimes turns red. The participant is supposed to push a button on the left if the green arrow points left and push a button on the right if the green arrow points right. If the arrow turns red the participant must as quickly as possible withdraw the finger from the key it is pressing. This delivers a reaction time between onset of the red arrow and the withdrawal of the finger. The reaction time is calculated from multiple trials, resulting in one SSRT per participant (Colzato et al., 2010). As, said women in their follicular phase had longer SSRT's, but were as quickly in responding on the green arrow compared to other menstrual phases and the male control group. Therefore, menstrual cycle changes didn't result in a change in response time for dominant responses, but did have an effect on the stop signal responses.

Why are higher dopamine levels causing a slower response after the stop signal? The effect of slower reaction under higher dopamine levels is contrary to what was expected by Colzato and colleagues (2010). The higher estrogen levels in the follicular phase causes relatively higher levels of dopamine and higher dopamine levels are thought to enhance the inhibitory system. Higher dopamine levels shorten the time to inhibit an ongoing response to be able to start a new response. Nevertheless, it is assumed dopamine levels should not be too high, as an surplus of dopamine might have an inhibitory effect on the response instead. Therefore, the effect of dopamine on the inhibitory system is assumed by Colzato et al. (2010) to follow an U-shaped curve: At lower levels more dopamine enhances and higher level more dopamine starts to have an inhibitory effect (Frank et al., 2007; Goldman-Rakic, Muly and Williams, 2000). The neurological model supporting this U-curve assumption makes clear

that too low dopamine levels cause cognitive and behavioral problems, as can be seen in Parkinon's disease patients. Too much dopamine also slows down inhibitory control, but is unclear if this can become as detrimental as the effects of Parkinson's disease. In between the excess low and high levels of dopamine concentrations is an optimum dopamine level causing the most efficient amount of cognitive control and inhibition.

Another study demonstrated that this optimum can differ between individuals depending on their baseline levels of dopamine (Jacobs & D'Esposito, 2011). This experiment compared different female genotypes associated with different dopamine levels in the PFC and investigated within-subjects the influence of dopamine fluctuations over the menstrual cycle. The results suggest that the baseline dopamine level accounts for some participants to perform worse on an increase of dopamine while others perform better.

Another view on the 'delay' during the follicular phase

With the current research we want to test an alternative interpretation for the observed delayed SSRT of women in their follicular phase as was found by Colzato et al. (2010). There must be a reason why women in their most fertile phase change and show this symptom of delay in inhibitory control when encountering non-dominant stimuli. It is unlikely that the evolutionary process resulted in fertile women to be generally inhibited in responding to non-dominant stimuli without any benefits. The first answer lies within rephrasing what happens. Instead of a delay of a less dominant stimulus, the continuation of the dominant process can as well be called persistence. It is also the trait persistence which is negatively correlated with the amount of one dopamine receptor type, underlining that this trait is connected to the dopaminergic system (Czermak, Lehofer, Wagner, Prietl, Lemonis, Rohrhofer, Schauenstein & Liebmann, 2004) . Persistence is in this case the cognitive focus on the dominant task, negating relatively disrupting stimuli. From the evolutionary perspective we know that during the fertile phase it is beneficial for women to focus on indicators of 'good genes' and pay less

attention to other stimuli (Gangestad, Thornhill & Garver-Apgar, 2005). Cognitively this would result in more attention to dominant targets and less to peripheral targets. And it is this more local focus on stimuli which could explain why a relatively less dominant or more global stimulus is longer ignored. In the experiment of Colzato et al. (2010) the direction of the green arrows forms a more dominant part of the experiment compared to the less common changing of the color of the arrow. If more dopamine leads to less context dependence, than this can be a possible explanation of the delay in reaction time in the experiment of Colzato et al. (2010).

Cognitive focusing on local versus global stimuli might seem to be far off from dopamine changing levels. Dopamine is active in the striatum, regulating the inhibitory control. Nevertheless, as mentioned before, there are dopamine projections toward the prefrontal cortex (PFC) where, among other processes, attention and spatial processing is regulated (Middleton & Strick, 2000; Hall & Nicolelis, 2001; Genovesio, Tsujimoto, Wise, 2011). If dopamine rises it might as well rise in the PFC. On top, if dopamine rises in the PFC, the dopamine decreases in the striatum and vice versa (Cools, 2008). There seems to be a compensatory regulation to induce either a more flexible (striatum) and distractable (PFC) brain or a more inflexible and stable brain (Cools, 2008; Akil, Kolachana, Rothmond, Hyde, Weinberger & Kleinman, 2003). Both flexibility/distractibility and inflexibility/stability might have their net advantages in different situations. Our reasoning is that during the fertile phase women tend more to cognitive inflexibility/stability, having the ability to channel attention to an important topic. As the group of women in their fertile phase was only about five percent longer in their response to a distraction from the main task than the women in the infertile phase we speak only of a small and relative difference between these two phases in the menstrual cycle. Nevertheless, it might have proven evolutionary useful to be a little bit more persistent and a little less distracted in the fertile phase. As Colzato et al. (2010) finds the

effect by a change during the fertile versus the infertile periods in the menstrual cycle, it is likely evolution plays a role. Fertility is essential in the evolutionary process and all kinds of changes in female behavior occur between fertile and non fertile menstrual phases (Gangestad et al, 2005). Perhaps it gives them an edge towards the signs of 'good genes' (e.g. facial symmetry) in potential mates as compared to a more broad view during the non-fertile phase when long-term partnership is of more importance. We postulate that the symptom found by Colzato et al. (2010) must be the effect of some process which must be beneficial and we thinks is likely the cognitive focus on more local stimuli. Our hypothesis is therefore that women in their follicular phase will be more focused on local stimuli and be less distracted and pay less attention to peripheral stimuli.

Then again, if it is not the inhibitory system which is less flexible after a change in dopamine levels, than a plausible reasons behind the delay in reaction time lies within a change in observational processing of the stimuli of the task. This again makes it likely there is an increase in cognitive attention towards local stimuli versus more global stimuli.

To investigate our hypothesis, we will measure focus on the central theme in contrast to the context, using one abstract and one social measure for women in different phases of their menstrual cycle. Specifically, our investigation will focus on the question whether the follicular phases of the menstrual cycle leads to effects such as less influence of context on observational processing and an increase of dispositional attribution versus contextual attribution, which could explain the symptom of delayed average stop signal reaction time. If these effects take place, they will be first indications of alternative explanations of a general less efficient inhibitory control in the basal ganglia.

Study 1: Context Dependence

The influence of context on observational processing can be captured in the construct of *context-dependence*. Context dependence is the degree to which one attends cognitively to the context (Avramova et al, 2010a). Avramova et al. (2010a) studied the effect of mood on context dependence. It followed that participants with a more positive mood were taking more context into account than less positive participants, regardless of abstract or social measures of the context dependence. The effect was not changed when the results were controlled for task effort. If not a less functioning inhibitory system is the cause of the delay during supra-optimal dopamine levels, a decrease in context dependence might hamper the reaction time towards contextual stimuli. As we assume fertile women attend more to the dominant stimulus, relatively negating the context, we predict that women in their follicular phase will be less context dependent compared to women in their menstrual phase.

To measure context dependence we adopted the framed line task (FLT) from the study on context dependence of Avromova et al. (2010a). The FLT is a size estimation task which can have beneficial or detrimental influence of the context on performance. The FLT has an objective amount of error which can be measured, namely the deviation from the correct response. In the *relative* version of the task participants have to copy an original line-to-frame ratio within a new and different sized frame. In this version more attention to the context would lead to better results. We put forward that women in the follicular phase are giving less attention to the context compared to being in the menstrual phase and would therefore perform worse on the relative task. In the *absolute* version of the task the participant must copy a original line within a changing context, therefore less attention to the context, or context dependence, should result in less error. We presume the women in their follicular phase, being less focused on the context, would perform better on the absolute task compared to women in their menstrual phase.

Study 1: FLT relative version

Method

Participants and design. For this study we required women with natural menstrual cycles and women with artificially hormonal regulated cycles as control. They all took part for two times in the study. The women with natural menstrual cycles were actively and passively recruited on the university and via email lists. These women had to meet certain criteria to be included, although these were not the same as the study from Colzato and colleagues (2010). First women needed to have menstrual cycles for at least two months prior to starting in their first experiment. Secondly, their cycles needed to be under no influence of artificial hormonal input for at least two months. When they reported to participate an evaluation was made of their recent cycle history. A menstrual cycle is defined as the day the menstruation starts until (and including) the day before the day the next menstruation starts. The first inferred occurrence of the menstrual phase or the estrogen peak was used to make an appointment for the first experiment. After doing the first experiment another appointment was made for the second experiment. When the first experiment was during the menstrual phase, the next experiment should be on or around the inferred estrogen peak, and vice versa.

The time of the menstrual phase was easily established because each participant knew when their menses started. After the start day of menstruation the estrogen levels are found by earlier research to remain low for at least 3 more days for most cycle lengths (Stricker et al, 2006; Chiazze, Brayer, Macisco, Parker & Duffy, 1968). Only very short cycles have possibly rising estrogen levels shortly after the start of menstruation. Therefore, the day of the start of menstruation was suitable for the experiment as a low estrogen day as were the 3 days following. Estrogen is already on low level two days before the starting day of menstruation, therefore a few participants were participating in the low estrogen experiment just up to two days before we expected menstruation to start. The menstruation pattern was later checked if

the inferred starting day indeed happened as expected and otherwise these measurements were not included.

The high dopamine phase, around the estrogen peak, is yet less easy to infer. As the assumption is that the estrogen rise also causes a rise of dopamine in the brain, we wanted to test women about 34 hours before ovulation. This is the moment estrogen is at its peak level. After deleting extreme short luteal phases, one study determined ovulation about 14.13 (SD = 1.41) days before the starting moment of the next cycle (Lenton et al., 1984). This period between ovulation and the moment the next menstruation starts is called the luteal period. The moment around ovulation, with the peak of estrogen and luteinizing hormone levels, seems to mainly determine the starting day of the next menstruation cycle as the luteal phase is the least variable phase in the menstrual cycle (Lenton et al., 1984; Stricker et al., 2006). To calculate the inferred day with the estrogen peak level we took the expected starting day of the next menstrual cycle and then counted 16 days back. For example, in a 29 day cycle, the next cycle starts at day '30' of the previous cycle and the estrogen peak is in this case calculated to be at day 14 of the first cycle. If an appointment could not be made on the inferred peak day an appointment one day before or after the inferred peak day was also acceptable for cycles of 23 to 26 days and two days before the inferred peak day for cycles with lengths from 27 days and more. These days had the highest expected estrogen level compared to the peak day without coming to close to the steep estrogen level demise after the estrogen peak, risking measuring on a very low estrogen level but counting it as a high estrogen level moment. One must remember we are inferring forward to the estrogen peak, and it is yet mostly luteal phase which is of the least varying length. This variability and therefore change of error in the estrogen peak day calculation was the reason the day after the calculated peak day was for most cycle lengths out of the question. Albeit still being high on estrogen 24 hours after the peak, measurement 48 hours later would result in estrogen levels

as high as around the menstrual phase (Stricken et al., 2006). During the luteal phase and within 96 hours after the estrogen peak this is elevated back to intermediate levels (see also Fig. 1).

Participants were gathered via canvassing at the university and by email. Of the original sample of 94 participants 68 remained for analysis. Participants who didn't meet the criteria to participate (n=11) like becoming pregnant or a miscalculated phase, were all removed from the analysis. Following, participants who used non-alcoholic drugs recently or medicine which interferes with the dopaminergic system (n=12) and who had a dependent measurement with three standard deviations from the mean (n=3) were also removed from the analysis. This resulted in a group of 36 women using no hormonal contraceptives, aged 17 to 37 years (M = 25.78, SD = 5.95), and a control group of 32 women using hormonal contraceptives, aged 18 to 33 (M = 21.50, SD = 3.15).

Each participant participated in two experiments. The participants with natural cycles were admitted to one of the two experiments, being either in a inferred phase which is high on estrogen or low on estrogen, whichever comes first. The second experiment was in their cycle on a moment where the estrogen level was supposed to be contrasted to the first experiment (e.g. low estrogen, when the first experiment was on a high estrogen moment and vice versa).

The control group participants were admitted to the first experiment as soon as possible, usually direct after they walked into the lab. The appointment for the second experiment was made about 5 to 14 days after the first one to copy the same time delay as the participants with natural cycles. The 'low' and 'high' on estrogen for the control group was inferred from their hormonally induced cycle stories *after* participating in both experiments. We did ignore individual cycle phase history for controls when planning their experiment dates because we assumed estrogen concentration doesn't change much over cycles when using hormonal contraception. The appointments for the second experiment were based on

when it was appropriate for the participant to come. An appointment was *not* made based on the phase with supposedly an inverse level of estrogen (high after low or low after high) compared to the first experiment, like with the natural cycle group. The most appropriate moment to come back for control participants was mostly the same day in the week after the first experiment. Therefore most control participants had a time delay of 7 days between both experiments. The high and low estrogen phases for the control group was nevertheless made as best as could based on their cycle stories. When participants were in measured during the same phase, they were randomly divided in one phase as high and the other phase as low. Participants who had hormonal contraception without any stopping period were also randomly divided over the high or low estrogen levels. The resulting quasi-experimental factorial design consisted of 2 (natural vs. hormonal contraception, between subjects) x 2 (high vs. low estrogen, within subjects) conditions.

Procedure. All participants were put behind a computer in isolated cubicles or a room without disturbance. Participants received about the same order of assignments during both experiments. During the experiment the participant received first the FLT. The two versions of the FLT, relative and absolute, were presented in random order. Then participants completed some other tasks from another experiment, taking about 10 minutes to 20 minutes. They finished with a mood questionnaire (Forster, 2011) and filling in control questions about their cycle, age, drugs use and pregnancy. After completing their second experiment all participants were debriefed and received their compensation of ten euro's.

Materials and dependent measure

The FLT. We copied the relative FLT from Colzate and colleagues (2010), only changing the paper-pencil task into a computer task. In the relative FLT participants are first shown a line framed within a square. This picture is removed and following there is a pause after which a new square is presented with a different size compared to the first square. The task

starts with a practice trial after which five trials follow. The stimulus dimensions in millimeters for the six trials were, respectively (line in frame 1 - frame 1 - frame 2) 68-81-162, 22-108-162, 28-101-141, 90-141-102, 73-108-81, and 30-162-81. These trials were presented in random order to each different participant. In the relative version of the FLT the participant must try to draw a new line which is in the same proportion to the new square as was the original line to the first square. The task was performed on the computer, lines were drawn using the mouse cursor. Participants could take as much time as they needed to complete drawing the line or adjust its length. Line lengths were saved for each trial. The computer calculated the deviance in millimeters from the correct response on each trial. The absolute of these errors was averaged over the five trials, excluding the practice trial, to obtain a mean error score. This was our context dependence measure (see also Colzate et al., 2010; Duffy, Toriyama, Itakura & Kitayama, 2009; Kitayama, Duffy, Kawamura & Larsen, 2003) The more context dependent participant will take more context into account and will consequently perform score less error in the relative FLT.

Control variables. Age and mood were used as control variables. Because there was a difference in age between the natural cycle and control group, age should be controlled for. On top, age might also effect cognitive functioning. As mood has proven to influence performance in the FLT task, this variables should also be controlled for. To resemble the mood measure of Avramove et al. (2010) a mean mood score was obtained by collapsing some questions of a mood questionnaire by Forster (2011) on the theme of positivity (or negativity). The resulting scale has a high internal consistency (Cronbach's $\alpha = 9.24$).

Results

Mean age was higher for the natural cycle compared to the hormonal contraception group, M = 25.78 and M = 21.50 respectively, $t_{66} = 3.65$, $p = 0.001$. To investigate the differences of mood across the conditions we conducted a 2 (dopamine level) x 2 (hormonal contraceptive

use) ANOVA on mood. There was no interaction effect on mood between dopamine level conditions and hormonal contraception use conditions. $F < 1$, *ns*. Nevertheless, mood is higher in the higher dopamine condition compared to the lower dopamine condition, $F (1, 66) = 4.42$, $p = .039$. More important, mood seemed to be higher in the control group compared to the natural cycle group, $M = 5.53$ ($SD = .15$) and $M = 5.86$ ($SD = .16$) respectively, but this difference was not significant, $F (1, 66) = 2.47$, $p = .12$.

FLT. An 2 (estrogen level, within-subjects) x 2 (hormonal contraceptive use, between-subjects) Mixed Model ANCOVA on the FLT mean error scores didn't yield a significant interaction of hormonal contraceptive use with estrogen levels , $F < 1$, *ns*. The within-subjects main effect of dopamine level on the mean error scores was not significant as was the between-subject main effect of hormonal contraceptive use not significant, all $Fs < 1$, *ns*. Also post-hoc comparisons didn't yield any significant result or obvious trends. The differences within the natural cycle group on the FLT error means between the low estrogen ($M = 13.91$, $SD = 5.79$) and high estrogen ($M = 13.67$, $SD = 6.40$) conditions were not significant, paired samples $t_{35} = .206$, $p = .84$. The differences on mean error scores within the hormonal contraceptive group also did not differ significantly between the low estrogen ($M = 12.86$, $SD = 4.54$) and high estrogen ($M = 13.73$, $SD = 5.74$) conditions, paired samples $t_{31} = .693$, $p = .49$. The covariates mood and age did not have a significant effect on the mean error score, all $Fs < 1$, *ns*.

A similar analysis on the absolute version of the absolute FLT task yielded no results, nor any trends. The results were similar to study 1: no significant results in the expected directions, again no significant results at all and no trends which made sense according to our hypothesis.

Discussion study 1

The results did not yield the expected effects on the natural cycle group. We expected the natural cycle group to perform worse on the relative FLT when in the high estrogen condition compared to the low estrogen condition. The difference was not significant and not substantial. There shouldn't be a substantial difference between the estrogen conditions of the control group and this was found in the results. Highly unexpected was the almost non existent influence of mood on the task, as Avramova et al. (2010a) did find highly significant influences of this measure with smaller samples. On the other the mood might not differ enough across the sample, but it had a comparable standard deviation of the mood variable within each of the mood condition of Avramova et al. (2010a), although the difference between the mood manipulation conditions of Avramova might raise a little concern about the variation of mood in our experiment. It must be stated however that Avramova induced a *change* in mood, while we measured baseline mood states. It might be that the effect they find is a change of mood effect, not a mood effect in an absolute sense. On top, we think there might be something wrong in with the specific method we used to measure this task. We used the computer version of the task, while Avramova et al (2010a) did use a paper-pencil version. It might be that the computer version is not suitable to measure the context dependence in a right way. In our next study we will use a totally different measure to look at cognitive focusing on local versus global stimuli.

Study 2: Attribution

The final study we performed to test our hypothesis about the change of observational processing in the brain during the menstrual cycle used the social psychological concept of attribution. Again, an experiment by Avramova et al. (2010b) was inspirational for our study. In their experiment they proved the influence of mood: Sad people made relatively more

dispositional attributions and happy people made more contextual attributions. The measure used is the similar to study 2 of Avramova et al. (2010b). Participants were shown behavior descriptions framed within one sentence. The sentences were not strongly informative about the target person's traits or context of his behavior. They were merely descriptions of something that happened to a person or was done by this person. People in general are displaying the tendency to underestimate the influence of the context on behavior. This tendency is called the fundamental attribution error (Ross, 1977). In this experiment there was no 'good' answer, the cause of the described behavior could be anything and everything could be a right answer. The primary thing we wanted to measure in the current experiment was whether a difference in estrogen would make a difference in attribution. The participant had to choose on a continuum between two extreme causes of the behavior: on the one end was always the option the behavior was totally caused by the actor, while the other extreme was always that the behavior was totally caused by circumstances outside the actor. If our hypothesis is right, women will change their observational processing during their fertile cycle towards relative more local attention at the cost of contextual attention. The target actor in each sentence is more central than the non-mentioned context outside the actor. In the follicular phase we expect less contextual inferences and more dispositional inferences compared to the menstrual phase.

Similar to study 1 we controlled for the effect of mood, as the effect of mood on attribution was clearly established (Avramova et al., 2010b). Also age was included as covariant, as age might determine speed of processing (Colzato et al., 2010) and there might be a systematic differences in age between people who are using hormonal contraceptives versus non-users.

Method

Participants and design. The same participants sample of study 1 was used for this study and the method to determine the menstrual cycle phases was also adopted from this study. Again, participants who didn't meet the criteria to participate (n=8) like becoming pregnant or a miscalculated phase, were all removed from the analysis. Following, participants who used non-alcoholic drugs recently or medicine which interferes with the dopaminergic system (n=13) were also removed from the analysis. Of the original sample of 94 participants 73 remained for analysis. There were 39 women using no hormonal contraceptives, aged 17 to 37 years (mean age = 25.54, SD = 5.84) and a control group of 34 women using hormonal contraceptives, aged 18 to 33 (mean age 21.44, SD = 3.07).

In this study one experiment was done by each participant. The participants with natural cycles were divided according to their calculated cycle phase (see study 1) either low or high on estrogen. The control group was split up in a different way compared to study 1. In study 1 every member of the control group had to be in either one low and one high estrogen condition. As described in study 1 timing of the experiments for the control participants left us with some participants in equal menstrual cycle phases. On top, there is the problem of people who are under non-stop influence of contraceptive hormonal means compared to the stopping week possibility with "the pill". In study 2 we didn't use a within subjects design and therefore we redid the coding of the high and low estrogen phases in the control group. Estrogen doesn't change much during hormonal contraceptive use and if there is a stopping period where intake of hormones is halted, estrogen dips a little. Therefore we recoded participants during hormonal intake into the high estrogen condition (n=25) and participants in their stopping period as low estrogen condition (n=9). As we did not actively recruited according to menstrual phase position in the control group, the chance of a participant in our control sample to be in their stopping period was much lower compared to a participant to be

in the hormone using period. Nevertheless, we thinks this division makes the most bio-chemical sense. Taken together, all conditions were between subjects, totaling a 2 x 2 (high or low estrogen x natural cycle or hormonal contraceptive use) factorial quasi-experimental design.

Procedure. All participants were put behind a computer in isolated cubicles or a room without disturbance. First they completed two computer tasks after which they performed the attribution rating task by rating four target sentences. The sentence tasks were randomly selected by the computer and after all four sentence tasks were performed, the participants moved to the last part. They finished with a mood questionnaire (Forster, 2011) and filling in control questions about their cycle. Questions about age, drugs use and pregnancy were answered on another occasion. After completing their experiment all participants were debriefed and received their compensation of ten euro's.

Materials and dependent measure

Target sentences. To determine the amount of attribution four target questions were adopted from Avramova et al. (2010b). They put forward that these sentences activated both actor-related and context-related inferences which Avramove et al. acquired from Ham and Vonk (2003). The sentences were in Dutch, but translations read as follows: "Fred jumps over the fence", "Rob gets an A on the test", "Wim cannot start the machine" and "Erik is lifting the a (house moving) box". The original name Ben from the first sentence was replaced with Fred as Ben was also the name of one of the experimenters in contact with the participants. Each sentence was presented with a question underneath asking to what extent two factors would have triggered the behavior or event described. For example, "Wim cannot start the machine" was presented with the question "To what extent did these factors contribute to the described event?" Participants could indicate their preference on a scale anchored by the two causes,

one always being dispositional and the other contextual (e.g., 1 = *The machine is broken*, 9 = *Wim is not technically skilled*). Two of the sentences were combined with ratings where higher ratings indicated more dispositional attributions and the ratings of the other two sentences indicated contextual attributions. Scores were later recoded such that higher ratings indicated dispositional attributions.

We combined the four scores of each sentence task by using a reliability analysis. We did not find the same strong pattern as Avramova et al. (2010b). Our identical four item scale reliability was considerably lower compared their scale's reliability (Cronbach's $\alpha = .37$ and Cronbach's $\alpha = .71$, respectively). In our reliability analysis it proved beneficial for scale consistency to remove the scale of the sentence "Rob gets an A on the test", resulting in a higher scale consistency for the three remaining sentence task scores combined (Cronbach's $\alpha = .49$). No further improvements could be made to the scale consistency. The three remaining scales were collapsed and averaged to form the mean attribution score. Higher scores on this dependent variable indicate relative more cognitive attention on the main actor.

Control variables. Age and mood were used as control variables for the same reason as study 1. Age differs between the natural cycle and control group. Mood is of proven influence on mean attribution score in the study of Avramova et al. (2010b). The same mood score as in study 2 was obtained in this study, again displaying high internal consistency (Cronbach's $\alpha = 9.24$).

Results

The 2 (estrogen level) x 2 (natural cycle versus hormonal contraceptive use) ANCOVA revealed an interaction effect, $F(1, 67) = 9.05$, $p = .004$, partial $\eta^2 = .12$. Main effects of mood, age, estrogen level or hormonal contraceptive use were all not significant, $Fs < 1$, *ns*. The post-hoc comparing of the mean scores across the four conditions (see Table 1) revealed that in the natural cycle group higher estrogen correspond with more dispositional attribution,

while this pattern reverses for the hormonal contraceptive group. Actually, the natural group in the high estrogen condition (M = 5.82, SD = .33) corresponds with the hormonal contraceptive group in the low estrogen condition (M = 6.14, SD = .51). Conversely, the natural group in the low estrogen condition (M = 4.85, SD = .33) corresponds with the hormonal contraceptive group in the high estrogen condition (M = 4.96, SD = .29).

Table 1. Study 2: Means (Standard Deviations) of Dispositional Attribution Ratings across 2 (estrogen level) x 2 (natural cycle vs. hormonal contraception) conditions.

	Estrogen	
	Low	**High**
Natural Cycle	**4.85 (0.33)^{a}**	**5.82 (0.33)^{bc}**
Hormonal Contraception	**6.14 (0.51)^{c}**	**4.96 (0.29)^{ab}**

Mean Dispositional scores were collapsed and averaged from three 7-point scales. Higher ratings indicate more dispositional attributions. No equal superscript letters between conditions depicts a significant difference at $p < .05$.

Discussion Study 2

At first glance the results reveal only the predicted effect on the natural cycle group where dispositional attributions rise with higher estrogen levels. Nevertheless, we didn't account for the fact that the levels of estrogen where not on comparable levels between the natural cycle and control group. Estrogen levels under hormonal contraceptive influence fluctuate around 30 pg/mL, not exceeding far beyond 100 pg/mL (Schlaff, Lynch, Heather, Hughes, Cedars & Smith, 2004) and decline during stopping periods (Killick, Fitzgerald & Davis, 1998). Females using hormonal contraceptive continuously show the relative high estrogen values in this range (Schlaf et al., 2004). Estrogen levels in a natural cycle range from averaging around 100 pg/mL (menstrual phase) to an average around 400 pg/mL (estrogen peak) (Stricker et al, 2006). In retrospect the interaction result of study 2 seems to make sense. If estrogen levels

are as can be expected, the results depict the U-shaped curve of Frank et al. (2007). Low and high estrogen levels showing equal cognitive effects, as do the two condition on intermediate estrogen levels. Concluding, not only do the results from study 2 underline our hypothesis, they also add evidence to the U-curve assumption.

General Discussion and conclusion

Our two studies do not unanimously show support for the expected higher female estrogen level to stimulate more cognitive attention on local stimuli and pay less attention to peripheral stimuli. Study 1 showed no effects of a difference in the inferred difference in estrogen level and context dependence. In contrast, study 2 did show the effect of a change in estrogen level on attribution. Participants high on estrogen in the natural cycle group showed more tendency to attribute behavior to the personality of the actor. The differences of no effect in study 1 and an effect study 2 would be most likely on the level of what is measured, not on differences in the sample as study 2 used almost the same sample and the same estrogen high or low differentiation for the natural cycle group.

First, the computer task in study 1 could have been failing to measure the concept of context dependence, as this was a change from the proven paper-pencil task. A small test on performance on both the computer and paper-pencil version of task would resolve this issue.

Secondly, the dependent measure in study 2 might have been measuring something conceptually different than the dependent measure in study 1. The attribution measure might have a component which is actually effected by changing estrogen (hence dopamine) levels and this component is not present in the context dependence measure of study 1. One explanation could be that the line task was not relevant enough for fertile women, not attracting more attention than women during infertile phases. Nevertheless, our hypothesis was on a change in perception, a change in the focus from global to more local in fertile phase women, not on a change in amount of attention. A shift towards more local focus in fertile

women should still have resulted from study 1 too, even if attention is on equal levels between high and low estrogen phases. The difference might be that the more local focus in fertile phases is only present on themes which are important for women in this phase. If this is the case it explains our different effects in study 1 and study 2. Study 2 might have an effect as it is about actual humans, males actually. Male humans are targets for potential mating during fertility, and maybe this taps the brain into a persistence in focusing on the main target in each sentence. However, then it is merely an attention shift onto relevant targets during the fertile phase and not the general more local focus from our hypothesis. It seems plausible, as in the fertile phase a potential mate is screened on 'good genes' indicators and the most direct indications are coming from the person itself. The wealth indicators like a nice looking car might become less relevant. It is now important what this person is in terms like antiviral capacities (taste), muscular strength, build and a symmetrical body. It is therefore a more person focused mindset which would make sense. Wealth and status indicators might be relatively more important in the non-fertile phase, when women are also searching for a more durable relation with a caring father figure and a man capable of providing resources to raise the children (Gangestad et al., 2005). It is obvious that if this new hypothesis is true, we are not finding results which can be viewed as cognitive explanations for the delay in the very abstract stop signal task of Colzato et al.(2010). It might be unorthodox undermining ones own initial hypothesis, but we are not working to prove we are right, we want to know what is happening. We think it is interesting to redo study 2 and make different actor categories to see if mating target concordance might change the results. For example, besides male actors, also female and animal actors might be included. Will there still be a comparable strong concentration on the subject of the sentence when women in their fertile phase read a sentence like "the tree falls down" and rate the between the answer extremities "the tree was weak" and "the tree was cut down"?

One important extra note needs to be made. Avramova et al.(2010b) find out that it is actually the most salient stimulus which is influenced, in their case by mood changes, not a more local focus against a global focus. Mostly the local stimulus is more salient, but this is not necessary so and future research should keep this distinction in mind.

Finally, if study 1 was our only study, we could have sufficed by thinking it is the individual variability in the baseline estrogen levels of women which blur the effect op supra-optimal estrogen levels (Jacobs & D'Esposito, 2011). Baseline dopamine level data for each individual help to disentangles on which part of the U-shaped curve a woman is. Low dopamine baseline women will see more flexibility of the striatum in relaying prepotent responses (Colzato et al., 2010) and more PFC working memory capacity (Jacobs & D'Esposito, 2011) with rising dopamine levels, while, in contrast, women with relative high dopamine baseline levels will see opposing effects under rising dopamine levels. We concur with Jacobs and D'Esposito that baseline dopamine levels might help to find results where they would otherwise remain unseen. Nevertheless, the findings of Colzato et al. (2010) form the starting point of our study and it is yet this study which finds significant delayed reactions in a sample of similar young Dutch women during the follicular phase opposed to other menstrual phases, while *not* taking account of baseline dopamine levels. It is the same delayed reactions we wanted to disentangle using the estrogen-dopamine paradigm also used by Colzato and colleagues. Controlling for baseline estrogen levels could have made potential estrogen effects bigger in study 1, but without it there should have been a trend visible in the results. There was none. On top, the significant results from our estrogen measure on attribution in study 2 did show the baseline dopamine level was not what was directly missing in our studies. At least, if all assumptions about level phase, concordant estrogen and dopamine levels are true and if we actually measured the estrogen peak right. We think these assumptions were probably right, as were our phase inferences *on average*, otherwise the

results of study 2 would have been highly unlikely. We do have found evidence of the U-shaped curve relation between estrogen levels and attribution in study 2. Taking account of baseline dopamine should nevertheless be an addition to any further experimenting in this area, as it fits the U-shaped curve hypothesis. Some effects might stay out of sight as Jacobs and D'Esposito (2011) showed. For this reason we can only encourage future research to take individual baseline estrogen levels into account when searching for the reasons of this relative delay/persistence symptom in follicular phase women as it should make effects more visible and be a test for the U-curve model of dopamine influence.

Although we go along in this thesis with Colzato et al. (2010) on assuming the direct relation between estrogen levels and dopamine levels to derive our hypothesis, we cannot help but also doubt their and our assumption in retrospect. Colzato et al. (2010) could have found a result in the opposite direction, less delay in response towards more peripheral stimuli in the follicular phase, and still be able to explain this with U-shaped effect of dopamine on the inhibitory system. In this case they could have assumed the natural increase in dopamine during the follicular phase was still on levels were it enhances the inhibitory system to function more optimal. Another explanation is that dopamine change might be a 'third variable', not the real or main reason for observed changes. Many hormone levels change during menstrual cycle and a lot of bio-chemical changes must be occurring. The menstrual cycle is known for influencing other neurotransmitters besides dopamine. The principle inhibitory neurotransmitter GABA also fluctuates over the menstrual cycle (Epperson, Haga, Mason, Sellers, Gueorguieva, Zhang, Weiss, Rothman & Krystal, 2002) and there is evidence that estrogen modulates activity of glutamate (McCarthy, Auger & Perrot-Sinal, 2002). Adding to the diverse nature of the menstrual cycle was the report of some participants whom reported extremely extended cycles from the moment they participated. Sometimes we had to wait an extra two weeks for the menstruation phase to come and be able to make an

appointment for our experiment. Unfortunately we did not yet look into any structural effect, but it interesting to look at this effect of more thinking about ones own cycle onto the cycle itself.

As our study is only correlational and quasi-experimental, as is the research of Colzato et al. (2010), there is still more experimental research necessary to be more certain of the supposed link between dopamine and this cognitive persistence effect correlating with female fertility. Studies manipulating estrogen and/or dopamine levels externally would highly contribute to a stronger proof for effects of the respective substances. On top, to look at 'what is actually happening' by the chemical manipulations we think research should focus on the effects on and through cognitions.

Acknowledgements

I want to thank my supervisor Michael Häfner for his feedback and flexibility and especially for his everlasting optimism, which was necessary to keep my morale high. Of course I also want to thank my colleague Ellen Harsma for the cooperation during our joined experimental mission. I also want to show gratitude to my parents, Tom van Impelen en Greet Buis, who took so much work out of my hands besides the study, and Alexander Obermeyer for revising my thesis.

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