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Dopamine-Dependent Task Performance over the Menstrual Cycle

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Graduate Program in Neuroscience
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Abstract

Estradiol (E2) has been found to influence dopamine (DA) activity in the nonhuman animal brain. While there has been very little research performed looking at E2's effects on DA-related cognitive function in humans, recent research found that women tested during high E2 phases of the menstrual cycle had significantly better performance on a DA-dependent spatial working memory task, than women tested during the lowest E2 phase. The current study utilized the natural hormone fluctuations that occur over the menstrual cycle to determine if E2 is associated with DA-dependent task performance. Using a repeated measures design, 47 women completed a battery of tasks, including 3 that are known to depend heavily on DA. The results showed that DA-dependent task performance was significantly associated with menstrual cycle phase. These findings provide preliminary evidence that variations in E2 over the menstrual cycle can affect central DA function in humans.

Keywords

Spatial working memory; reinforcement learning; dopamine; estrogen; estradiol; menstrual cycle; eye blink rate

Co-Authorship Statement

All research carried out for this thesis, which includes design of the experiment, data collection, data analysis, and writing, was performed by Alexandra de la Rúa under the supervision of Dr. Elizabeth Hampson. Radioimmunoassays were performed by Bavani Rajakumar under the supervision of Dr. Elizabeth Hampson. All experiments are original research carried out for this Master's thesis.

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List of Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
DA	Dopamine
dIPFC	Dorsolateral prefrontal cortex
E2	Estradiol
EB	Estradiol benzoate
EEG	Electroencephalography
eFSIQ	Estimated full scale intelligence quotient
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
FSIQ	Full scale intelligence quotient
IQ	Intelligence quotient
M	Mean
NAART	North American Adult Reading Test
OVX	Ovariectomized
PET	Positron emission tomography
PFC	Prefrontal cortex
POMS	Profile of Mood States
PST	Probabilistic Selection Task
RIA	Radioimmunoassay
SD	Standard deviation
sEBR	Spontaneous eye blink rate
SEM	Standard error of the mean
SPWM	Spatial Working Memory Task

WAIS-R	Wechsler Adult Intelligence Scale – Revised
WME	Working memory error
WM	Working memory

Chapter 1

Introduction

Estradiol (E2), which is the strongest and most abundant form of estrogen in women of reproductive age (Almeida, Milner, & Brake, 2015), is known to play a major role in the development of female sex characteristics. Lesser known however, is that a multitude of basic studies in laboratory animals have found E2 to influence the release, degradation, and reuptake of neurotransmitter molecules, such as dopamine (DA), in the brain, thus influencing cognition and numerous other processes in the central nervous system (CNS). In contrast to the large body of animal research implying that DA may be partially regulated by circulating levels of E2, there has been very little research performed looking at E2's effects on DA-related cognitive function and neurotransmitter activity in humans. A better understanding of E2's effects on DA and cognition in humans would have major implications for understanding DA-based neurological disorders in women, as well as for understanding the cognitive effects of E2-based hormone therapy.

In humans, there are four major DA pathways that exist in the brain: the mesolimbic pathway, mesocortical pathway, nigrostriatal pathway, and tuberoinfundibular pathway. Via activity in these diverse pathways, DA has been seen to play a major role in spontaneous eye blink rate (sEBR), reinforcement learning, and spatial working memory. Therefore, by measuring performance on tasks that involve these cognitive processes, it may be possible to determine if DA is affected by E2 in the adult female brain. The current introduction section will begin with discussions on the roles of DA in working memory (WM), reinforcement learning, and sEBR. This will be

followed by a review of the current literature on the relationship between DA and E2 in human and nonhuman animals and finally, I will summarize the main ideas previously discussed, followed by a detailed description of the rationale and hypothesis of the present study.

1.1 Dopamine and Spatial Working Memory

To begin, the important role of DA in WM function has been studied extensively, in both humans and nonhuman animals. WM refers to the cognitive system that is responsible for temporarily storing relevant information while simultaneously allowing for updating, processing, and manipulation of that information (Baddeley, Eysneck, & Anderson, 2009; Diamond, 2012). This type of memory is important in all tasks that require memory of past information to make sense of new, incoming, information and to perform ongoing reasoning and decision-making (e.g. understanding language and performing mental math) (Diamond, 2012). A distinction between verbal and visuospatial WM is often made, however the current study will focus only on spatial (referring to the relative locations of objects in space) WM, which involves the temporary maintenance and manipulation of spatial stimuli.

The neural basis of spatial WM was originally studied by testing non-human primates on a delayed response task (Jacobsen, 1936). The delayed response task was adapted from a task originally used to study WM in humans (Hunter, 1913) and it has been argued that the cognitive processes used by monkeys on the delayed response task mirror spatial WM processes that also occur in humans (Goldman-Rakic, 1995; 1987). The adapted delayed response task consists of a cue phase, a delay phase, and a response phase. During the cue phase a monkey watches as an experimenter baits one of two

spatial locations with a food reward. This is followed by a delay phase where the monkey's view of the two locations is blocked by an opaque screen, and finally during the response phase the monkey makes a response to retrieve the reward. In this task, the cues denoting both spatial locations are visually identical meaning that the monkey must rely only on memory when making a selection. Additionally, bait (and subsequent reward) locations are randomly varied between trials, meaning that the monkey must also update its memory of the information for each trial.

Using the delayed response task, Jacobsen (1936) discovered that bilateral damage to the prefrontal cortex (PFC) had a profound negative effect on task accuracy, while damage to other areas of the cortex did not affect performance. Since Jacobsen's initial study, multiple studies have found both bilateral and unilateral pre-existing and surgically-induced lesions of the PFC, as well as dorsolateral prefrontal cortex (dlPFC) deactivation through cryogenic cooling, to produce deficits in the mnemonic portion of spatial WM (Bauer & Fuster, 1976; Goldman-Rakic, 1987; Petrides, 1989; Yener & Zaffos, 1999). Specifically, lesion studies allowed researchers to pinpoint that the cortical region necessary for accurate performance of the delayed response task is within Brodmann area 46 in the dlPFC (Butters & Pandya, 1969; Goldman & Rosvold, 1970; Gross & Weiskrantz, 1962; Mishkin, 1957).

Lending support to the idea that the PFC plays an important role in spatial WM, electrophysiology studies have found that neurons in the lateral PFC become activated during the delay portion of the delayed response task (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971; Kubota & Niki, 1971). Additionally, neuroimaging studies have been performed in order to tease apart the mnemonic and

procedural roles of different areas of the brain during spatial WM (for review, see D'Esposito et al., 1998). Specifically, activation of the dlPFC is seen in humans during performance of adaptations of the delayed response task and other more complex spatial WM tasks (i.e. n-back) through the use of both positron emission tomography (PET) (Jonides et al., 1993; Smith, Jonides, & Koeppe, 1996) and functional magnetic resonance imaging (fMRI) (Courtney, Ungerleider, Keil, & Haxby, 1997; McCarthy et al., 1994; Owen, McMillan, Laird, & Bullmore, 2005; Zarahn, Aguirre, & D'Esposito, 1999).

In conjunction with the understanding that the cortical control processes required for spatial WM predominantly occur in the dlPFC, research has also focused on the specific neurotransmitters involved in this cognitive process. Specifically, it is widely accepted that DA is one of the main neurotransmitters underlying WM in humans (for review, see Ellis & Nathan, 2001). It has been shown that there is a high concentration of the catecholamine neurotransmitter DA, compared to other neurotransmitters, in the dlPFC of nonhuman primates (Brown, Crane, & Goldman, 1979). Additionally, patient studies looking at schizophrenia, which is a disorder characterized by prefrontal DA hypoactivity and mesolimbic DA hyperactivity (Davis, Kahn, Ko, & Davidson, 1991), have found that these patients show deficits when performing spatial WM tasks (Park & Holzman, 1992), which contributes to the idea that DA plays an important role in spatial WM. Furthermore, in monkeys, Brozoski, Brown, Rosvold, and Goldman (1979) discovered that depletion of DA in the dlPFC through the use of neurotoxin injections led to profound deficits on a spatial WM task (i.e. spatial delayed alternation) to the same extent as surgical ablation of the entire dlPFC. Importantly, in both patient and animal

studies, increasing DA level in the PFC through the administration of L-dopa or a DA agonist improved WM performance (Daniel et al., 1991; Lange et al., 1992), with a complete reversal of deficits occurring in the primates (Brozoski et al., 1979). Adding to this body of research, Sawaguchi, Matsumura, and Kubota (1988) discovered that iontophoretic application of DA agonists into the primate PFC enhanced neuronal activity during the delay portion of a delayed response task, an effect that was reversed by administration of DA antagonists. Similarly, Sawagushi and Goldman-Rakic (1991) injected DA antagonists into the PFC of primates, which caused the animals to perform poorly on a delayed response task, in a dose-dependent manner.

Electrophysiological studies have also lent support to the idea that DA plays an important role in regulating the excitability of neurons within the areas of the cortex that are involved in WM (for review, see Goldman-Rakic, 1995; 1996). For example, Williams and Goldman-Rakic (1995) recorded from DA neurons in the dlPFC of primates during a delayed response task and found that DA receptors modulate mnemonic processing through regulation of excitatory input to the PFC, specifically during the delay portion of the task. They also found that failure to excite these DA receptors during the delay period led to WM errors.

More specifically, both D₁-type and D₂-type DA receptors have been implicated in WM, however results are inconsistent (for review, see Cools & D'Esposito, 2011; Ellis & Nathan, 2001; Liggins, 2009). For example, Luciana & Collins (1997) found that bromocriptine, a D₂ receptor agonist, improved WM performance in humans on a visuospatial delayed response task, while haloperidol, a D₂ receptor antagonist, impaired performance. Additionally, Liggins (2009) argues that D₂ receptors may specifically be

important for spatial WM in humans. However, nonhuman (Sawagushi & Goldman-Rakic, 1991; Williams & Goldman-Rakic, 1995) and human (Müller, von Cramon, & Pollmann, 1998) primate studies have found D₁-type receptors but not D₂-type receptors to be involved in WM. Additionally, some studies implicating D₂ receptors in WM have found that the effect is dependent on baseline DA level (Kimberg, D'Esposito, & Farah, 1997), and researchers have seen an inverted-U response to D₁ receptor stimulation at the cellular level in nonhuman primates (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). However, despite the inconsistency in the DA receptor literature, the idea that spatial WM is dependent on DA activity in the dlPFC is strongly supported by both animal and human research, which show that DA facilitates spatial WM by increasing mnemonic neuron activity in the dorsal PFC.

1.2 Dopamine and Reinforcement Learning

The involvement of DA in cognition has also been studied extensively with respect to reinforcement learning. Reinforcement learning, which is a type of learning that is mediated by taking into account the positive and negative outcomes of our actions (Frank, 2005; Frank, Seeberger, & O'Reilly, 2004), is believed to depend heavily upon DA activity in the direct and indirect pathways of the basal ganglia (Frank, 2005; Mink, 1996). Early evidence for DA's importance in reinforcement learning came from nonhuman animal studies as well as studies on Parkinson's disease patients, which is a disease characterized by a loss of nigrostriatal DA neurons and a decrease in striatal DA concentration (Kish, Shannak, & Hornykiewicz, 1988). Before reviewing some of this evidence, I will first outline the anatomy of the direct and indirect pathways and their functional outcomes for behavioral action more generally. When the direct pathway is

active (see Figure 1.1), there is open communication between the thalamus and the frontal cortex, due to disinhibition of the thalamus via the internal segment of the globus pallidus. This in turn, allows for frontal cortex-mediated action facilitation. When the indirect pathway is active, the thalamus remains inhibited by the internal segment of the globus pallidus, and therefore frontal cortex-mediated action is suppressed. Therefore, whether or not an action is executed, has to do with the balance between direct and indirect pathway activation in the basal ganglia (Frank, 2005; Mink, 1996).

As mentioned previously, the activation of both pathways is known to rely heavily upon DA (Frank, 2005; Mink, 1996). Importantly, it has been seen through recording studies on rats and nonhuman primates, that positive reinforcement causes DA bursts in the basal ganglia, whereas negative reinforcement causes DA dips in the basal ganglia in primates (Hollerman & Schultz, 1998; Satoh, Nakai, Sato, & Kimura, 2003; Schultz, 1998, 2002; Schultz, Apicella, & Ljungberg, 1993; Schultz, Dayan, & Montague, 1997; Ungless, Magill, & Bolam, 2004). This pattern of DA activity has also been seen in humans, through the use of PET, which can measure changes in DA transmission, as well as through computational modelling (Holroyd & Coles, 2002; Zald et al., 2004). In turn, these bursts and dips in DA act as teaching signals, increasing and decreasing behaviour, respectively.

Michael Frank has proposed that the specific way in which DA activity affects learning is through two distinct populations of DA neurons that are separately located in the direct and indirect pathways (Frank, 2005). Specifically, research using in situ hybridization histochemistry has shown that the direct pathway has a high concentration of D₁ DA receptors whereas the indirect pathway has a high concentration of D₂ DA

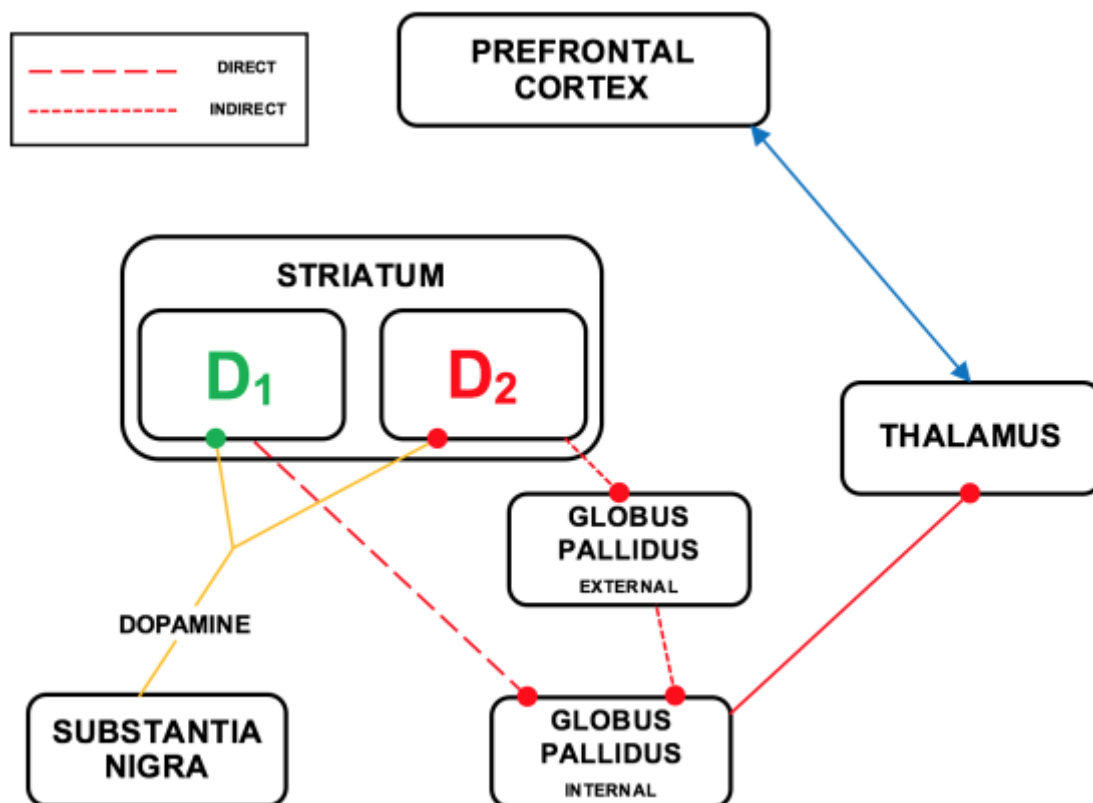


Figure 1.1. A representation of the direct and indirect pathways of the basal ganglia.

When D₁ receptors in the direct pathway are activated by dopamine they cause disinhibition of the thalamus via the internal segment of the globus pallidus. This allows for communication between the thalamus and the frontal cortex and frontal cortex-mediated action is facilitated. When D₂ receptors in the indirect pathway are activated, the thalamus is inhibited by the internal segment of the globus pallidus, and therefore frontal cortex-mediated action is suppressed.

receptors (Aubert, Ghorayeb, Normand, & Bloch, 2000; for review, see Gerfen, 1992). Even further, research has found that the D₁ receptors in the direct pathway are excitatory (Gerfen, 1992; Hernandez-Lopez, Bargas, Surmeier, Reyes, & Galarraga, 1997) while the D₂ receptors in the indirect pathway are inhibitory (Gerfen, 1992; Hernandez-Lopez et al., 2000). Therefore, during periods of positive reinforcement, bursts of DA cause an increase in excitatory D₁ receptor stimulation, leading to activation of the direct pathway, and consequently facilitation of the rewarded action. At the same time, DA bursts lead to an increase in inhibitory D₂ receptor stimulation, which suppresses the indirect pathway. Oppositely, during periods of negative reinforcement, DA dips cause a decrease in the activation of the direct pathway, while disinhibiting the indirect pathway by reducing inhibitory D₂ receptor stimulation, leading to suppression of the unrewarded action.

Furthermore, research has shown that a possible mechanism by which this implicit form of learning (based on reinforcement) takes place long-term, is through synaptic plasticity in the direct and indirect pathways. Specifically, electrophysiology research in rats has shown that bursts of DA and subsequent activity in the direct pathway leads to long-term potentiation in D₁ cells (increased future activity), while the inhibitory effects of DA on the indirect pathway lead to long-term depression in D₂ cells (decreased future activity) (Bear & Malenka, 1994; Calabresi et al., 1997; Centonze, Picconi, Gubellini, Bernardi, & Calabresi, 2001; Kerr & Wickens, 2001; Reynolds, Hyland, & Wickens, 2001; Shen, Flajolet, Greengard, & Surmeier, 2008; Wiecki & Frank, 2010). This experience-based synaptic plasticity ultimately leads to the learning of which behaviours should be increased in the future, and which behaviours should be avoided (Tsai et al., 2009; Zweifel et al., 2009).

In addition to a large body of research on reward learning and DA in animals (for review, see Wise & Rompre, 1989), the majority of our current understanding of reinforcement learning and DA in humans stems from research by Michael J Frank and collaborators (Cox et al., 2015; Frank, 2005; Frank & Kong, 2008; Frank, Moustafa, Haughey, Curran, & Hutchison, 2007; Frank & O'Reilly, 2006; Frank et al., 2004; Lighthall, Gorlick, Schoeke, Frank, & Mather, 2013; Maia & Frank, 2011; Slagter, Georgopoulou, & Frank, 2015). Based on the emerging knowledge of the two DA pathways in the basal ganglia, Frank proposed that learning based on positive and negative feedback occurs through DA-induced plasticity in both the direct and indirect pathways (Frank, 2005). In order to test his theory, a complex computational model was created, which issued predictions based on specific reinforcement criterion (Frank, 2005). This model was first tested in patients with Parkinson's disease (Frank, O'Reilly, & Seeberger, 2004), which as mentioned is a disease characterized by a loss of nigrostriatal DA neurons and a decrease in striatal DA concentration (Kish et al., 1988). Previously, this patient population has shown deficits on tasks that require learning from positive and negative feedback (Ashby, Alfonso-Reese, Turken, & Waldron, 1998; Knowlton, Mangels, & Squire, 1996; Shohamy et al., 2004). However, there has been inconsistency in the literature, with DA agonists leading to a further decrease in performance in some studies (Cools, Barker, Sahakian, & Robbins, 2001; Swainson et al., 2000).

Based on Frank's computational model, it was predicted that compared to controls, non-medicated Parkinson's disease patients (low levels of striatal DA) would have trouble learning from positive feedback, due to a decrease in DA bursts and therefore less activation in the direct pathway. They were also predicted to have enhanced

learning from negative feedback, due to more dramatic DA dips and therefore disinhibition of the indirect pathway. Finally, it was also predicted that the same patients, when medicated with L-dopa, and therefore in a higher DA state, should show a reversal of the aforementioned learning patterns (Frank et al., 2004).

These predictions were tested using a probabilistic reinforcement learning task, called the Probabilistic Selection Task (PST), developed by Frank and colleagues (2004), which requires participants to implicitly learn over a series of trials which stimuli are correct (rewarded) based on specific probabilistic reinforcement contingencies. Based on performance, this task is able to tease apart the degree to which each participant learns from positive and negative feedback (Frank et al., 2004). The results of Frank's 2004 study were consistent with the predictions made by his computational model, therefore providing initial insight into reinforcement learning and DA in humans.

Since Frank's early work, many subsequent studies have found similar results, which lends further support to the theory that DA affects reinforcement learning. Evidence is not only based on studies of patients with DA dysfunction, but also studies in healthy individuals. In an imaging study by Cools et al. (2009), the effect of baseline DA level on reinforcement learning was studied in healthy individuals. Using PET, the researchers found a positive correlation between high baseline DA in the striatum, as revealed by high uptake of a tracer that indicates presynaptic DA synthesis capacity (i.e. fluorometatyrosine), and learning from positive vs. negative reinforcement, on a reward-based reversal learning task, whereas low baseline DA level showed an opposite pattern (Cools et al., 2009). Additionally, another PET study by Cox et al. (2015), found that

binding of D₁ and D₂ receptors was correlated with positive and negative reinforcement learning, respectively.

DA's involvement in reinforcement learning has also been supported through pharmacological studies. For example, Pessiglione, Seymour, Flandin, Dolan, and Frith (2006) demonstrated that administration of DA-enhancing (e.g., L-dopa) or reducing (e.g., haloperidol) drugs to healthy subjects causes an increase or decrease in reward-based learning, respectively. Additionally, as previously mentioned, Frank et al. (2004) found that administration of L-dopa to patients with Parkinson's disease, who in an unmedicated state have high learning from negative outcomes and low learning from positive outcomes, reversed their reinforcement learning pattern. In a later study, D₂ receptor agonists and antagonists were found to cause a decrease and increase in negative reinforcement learning, respectively, due to the inhibitory actions of D₂ receptors on the indirect pathway of the basal ganglia (Frank & O'Reilly, 2006). Furthermore, depletion of a DA precursor, and therefore lower overall DA production, has been seen to cause an increase in negative reinforcement learning (Cox et al., 2015).

Finally, genetic studies have found a correlation between DA-related genes and reinforcement learning (for review, see Frank & Fossella, 2011). For example, positive reinforcement has been seen to cause accumulation of a specific DA-regulated phosphoprotein in the striatum, which is believed to be essential for D₁-dependent plasticity (Stipanovich et al., 2008). In another study, Frank et al. (2007) found that a polymorphism in the DARPP-32 gene, which affects synaptic plasticity at D₁ receptors and is activated via binding of D₁ receptors, was predictive of the degree to which participants learned from positive reinforcement. Additionally, they found that a

polymorphism in the DRD2 gene, which affects postsynaptic D₂ receptor levels in the striatum through D₂ mRNA translation, was predictive of the degree to which participants learned from negative reinforcement.

Overall, a large body of animal and human research suggests that reinforcement learning is in part due to DA activity in the direct and indirect pathways of the basal ganglia. Specifically, high DA activity is associated with increased learning from positive reinforcement, while low DA activity is associated with increased learning from negative reinforcement.

1.3 Dopamine and Spontaneous Eye Blink Rate

While not a cognitive process, a large body of literature indicates that sEBR is a strong marker of central dopaminergic function, particularly striatal DA function (for review, see Jongkees & Colzato, 2016). Specifically, it has been proposed that DA acts indirectly on the spinal trigeminal complex, which is believed to underlie activity of the spontaneous blink generator (Jongkees & Colzato, 2016; Kaminer, Powers, Horn, Hui, & Evinger, 2011; Kaminer, Thakur, & Evinger, 2015). DA has been seen to be positively correlated with the sEBR, as seen through multiple patient and pharmacological studies. Importantly, a large number of pharmacological studies have shown that administration of DA agonists, such as apomorphine, cause an increase in sEBR, while DA antagonists, such as haloperidol, have the opposite effect. This has been demonstrated in humans (Cavanagh, Masters, Bath, & Frank, 2014; Kaminer et al., 2011), nonhuman primates (Karson, 1983; Lawrence & Redmond, 1991), and rats (Kaminer et al., 2011), respectively. For example, Karson (1983) injected monkeys with apomorphine and saw a significant acute increase in sEBR through the use of direct observation and counting, an

effect that was blocked by pre-treatment with haloperidol. Typically, sEBR is measured using electroencephalography (EEG) or through counting via direct observation, however methods such as electromyography (EMG) and eyelid monitoring devices are also used.

Additionally, patient studies have found that sEBR is altered in individuals with disorders that are characterized by dysfunction of the DA system. For example, Parkinson's patients (low striatal DA) show a decreased sEBR compared to healthy controls (Deuschl & Goddemeier, 1998; Karson, 1983; Karson, Burns, LeWitt, Foster, & Newman, 1984; Karson, Lewitt, Calne, & Wyatt, 1982; Taylor et al., 1999), and this symptom can be reversed through L-dopa administration (Karson et al., 1982). Additionally, primates treated with MPTP, which is a dopaminergic neurotoxin that destroys nigrostriatal DA neurons, show a decrease in sEBR and an increase in Parkinson's-like motor symptoms (Lawrence & Redmond, 1991; Taylor et al., 1999). Furthermore, Taylor et al. (1999) found a positive correlation between post-mortem DA level in the caudate nucleus and pre-mortem sEBR in primates. In addition to sEBR abnormalities observed in Parkinson's patients, patients with schizophrenia, which as mentioned, is a disorder characterized by prefrontal DA hypoactivity and subcortical DA hyperactivity (Davis et al., 1991), show an increased blink rate compared to healthy controls. The administration of DA antagonist neuroleptics is able to decrease the sEBR (Adamson, 1995; Karson, 1983). Even further, sEBR has recently been seen to correlate positively with level of psychoticism (Colzato, Slagter, van den Wildenberg, & Hommel, 2009), which is a personality dimension that is believed to be reflective of DA function (Lester, 1989).

Imaging studies have also been informative, regarding the underlying DA basis of sEBR. Groman et al. (2014) used PET and found a strong positive correlation between sEBR and availability of D₂-type DA receptors (but not D₁-type receptors) in the ventral striatum and caudate nucleus in vervet monkeys. Additionally, Colzato, van den Wildenberg, and Hommel (2008) measured the sEBR of chronic cocaine users (individuals who maintained monthly cocaine use for a minimum of two years), who have been found to have a significant reduction of D₂ DA receptors in the striatum as well as decreased DA release (Volkow, Fowler, & Wang, 1999), and compared them to matched controls (individuals with no history of cocaine use), and found the cocaine users to have significantly lower sEBRs than the controls, an effect that was proportional to the amount of cocaine exposure (self-reported span/frequency/dose of cocaine use). In general, the majority of receptor research has found sEBR to be reflective of DA activity at D₂ receptors, however some conflicting studies have also found D₁ receptor activity to affect sEBR (for review, see Jongkees & Colzato, 2016). Therefore, it is supported through multiple areas of research that there is a strong connection between striatal DA and sEBR. Specifically, there is evidence that sEBR is a reflection of DA activity at D₂ DA receptors in the human striatum.

1.4 Estrogen and Dopamine

E₂, which as mentioned previously is the most potent form of estrogen in women of reproductive age (Almey et al., 2015), has been shown to have a major influence on the brain in other species. Importantly, estrogen receptors are transcription modulators, meaning that when bound by estrogens they are able to translocate into the nucleus of cells and bind to DNA, subsequently regulating the activity of different genes (Evans,

1988). Recently, estrogen receptors have also been discovered at non-nuclear sites within neurons, suggesting additional, non-genomic, effects of estrogens (for review, see Galea, Frick, Hampson, Sohrabji, & Choleris, 2016). For example, estrogen receptor α has been found in the primate (Perlman et al., 2005; Wang, Hara, Janssen, Rapp, & Morrison, 2010) and human (Montague et al., 2008; Perlman et al., 2005) dlPFC, and in the rat dorsal and ventral striatum (Almeida et al., 2015; Shughrue, Lane, & Merchenthaler, 1997). These regions of the brain are known to be heavily involved in DA-dependent cognitive function and reward learning, as discussed previously.

The knowledge that estrogens can regulate gene activity coupled with the discovery of estrogen receptors in areas of the brain that are implicated in DA-dependent cognitive processes, implies that there may be a connection between circulating estrogens and DA activity in the adult female brain. Although human data is very limited, this idea is supported by numerous animal studies looking at the administration or depletion of estrogens, as well as natural variation in E2 over the ovarian or estrous cycle (for review, see Etgen & Garcia-Segura, 2010).

For example, Pasqualini, Olivier, Guibert, Frain, and Leviel (1995) saw an enhancement in DA synthesis, as quantified by measurement of total vs. tritiated extracellular DA in the striatum, after acutely injecting rats with physiological levels of E2. Additionally, concentration of striatal DA during proestrus and estrus, which are the phases of the rat estrous cycle with the highest levels of estrogens, was significantly higher compared to low estrogen phases of the estrous cycle or to ovariectomized (OVX) rats (Xiao & Becker, 1994)

With respect to DA release, in OVX female rats, who have subsequent low levels of circulating E2, acute in vitro exposure of striatal tissue to physiological doses of E2 caused an increase in amphetamine-stimulated and KCl-stimulated DA release (Becker, 1990; for review see Becker, 1999). In the same study however, chronic rather than acute E2 exposure led to a decrease in DA release (Becker, 1990), suggesting a down-regulation of the DA response under chronic exposure. Researchers have also shown that in rats, priming with estradiol benzoate (EB) enhances the effects of acute EB injection, such that amphetamine-stimulated DA release is higher in primed animals (Becker & Rudick, 1999). There has also been seen to be an increase in amphetamine-stimulated striatal DA release during high E2 phases of the rat estrous cycle such as proestrus compared with low E2 phases (Becker & Cha, 1989; Becker & Ramirez, 1981; Becker, Robinson, & Lorenz, 1982). Additionally, Thompson and Moss (1994) found that direct E2 injections into the rat striatum caused both a short- and long-term increase in K-stimulated DA release.

Apart from changes in its release, Di Paolo, Rouillard, and Bédard (1985) found that injection of E2 into OVX rats caused an increase in striatal DA turnover, which was apparent as an increase in DA metabolites but not actual DA concentration in the striatum. Estrous cycle studies have also found there to be an increase in striatal DA reuptake during high E2 phases of the cycle (for review, see Becker, 1999). Oppositely, a study by Disshon, Boja, and Dluzen (1998) found that administration of E2 to OVX rats caused a decrease in DA reuptake in the striatum by decreasing the DA transporter's affinity for DA. In a primate study by Kritzer and Kohama (1998), postmortem brain slices showed a decrease in tyrosine hydroxylase, an enzyme that converts tyrosine to

DOPA for DA synthesis (Daubner, Le, & Wang, 2011), in the dlPFC after OVX, an effect that was partially reversed through E2 administration.

There is also a growing body of animal research pointing to an effect of estrogens on striatal DA receptors, although evidence is conflicting. Specifically, in OVX rats, Bazzett and Becker (1994) saw a decrease in striatal D₂ DA receptor binding after a test injection of EB. Interestingly, the effect of EB injection was opposite in castrated male rats, who had an increase in striatal D₂ DA receptor binding. Additionally, fluctuations in D₂ DA agonist binding sites (Di Paolo, Falardeau, & Morissette, 1988) and D₁ DA receptor density (Lévesque, Gagnon, & Di Paolo, 1989) have been observed over the rat estrous cycle. In a rodent study by Lévesque and Di Paolo (1988) a shift was observed in D₂ DA receptor binding sites from high to low affinity states after acute injection of E2. In another D₂ study, *in vivo* measures of striatal D₂ DA receptor mRNA revealed a decrease in D₂ mRNA after chronic E2 administration (Lammers et al., 1999).

Despite the large amount of data from basic animal studies suggesting that estrogens can affect DA function, remarkably little research has been done in humans. This partly reflects the difficulty of quantifying central DA levels *in vivo*. Two very small studies using PET imaging have reported conflicting results. Nordstrom, Olsson, and Halldin (1998) found no change in D₂ receptor density over the menstrual cycle, while Wong et al. (1988) saw a slight increase in the binding rate constant of the D₂ receptor during high E2 phases of the menstrual cycle. More recent work by Jacobs and D'Esposito (2011) using fMRI, showed an effect of E2 on WM performance, with the direction of the effect being dependent on a specific genotype that affects baseline DA level in PFC, suggesting a potential effect of E2 on DA activity. However, sample size

was very small and a significant effect was only found for 1 of the 3 n-back conditions administered (i.e., 2-back). Additionally, evidence was indirect since DA could not be measured directly.

In humans, therefore, it is not currently known whether DA levels vary as a function of available E2 concentrations. However, recently researchers have found a positive correlation between E2 level and WM performance (recall that WM is known to depend significantly upon DA activity in the PFC). Specifically, Hampson and Morley (2013) found that women tested during high E2 phases of the menstrual cycle had significantly better performance on a spatial WM task than women tested during the lowest E2 phase, and differences across women in circulating E2 level significantly predicted the numbers of WM errors committed in a linear fashion. Using the same spatial WM task as above, Hampson (2017) showed in a group of women who used oral contraceptives, that women actively taking their oral contraceptive pills, and therefore in a higher E2 state, had significantly better accuracy on the WM task than women tested during their monthly week off of contraceptive pills when they were in a low E2 state (it should be noted that oral contraceptives contain ethinyl estradiol, not 17β -estradiol, the naturally-occurring form of the hormone). Additionally, in post-menopausal women, estrogen replacement therapy (e.g., conjugated equine estrogens, 17β -estradiol treatment) has been seen to improve WM function in several studies (Duff & Hampson, 2000; Keenan, Ezzat, Ginsburg, & Moore, 2001; Krug, Born, & Rasch, 2006). However, conflicting evidence has also shown no cognitive effect of estrogen replacement in post-menopausal women (Grigороva & Sherwin, 2006). Moreover, a study of much younger, pre-menopausal, women found that E2 suppression through the use of leuprolide acetate

caused a significant decrease in WM function (Grigorova, Sherwin, & Tulandi, 2006).

At present there is no evidence in the literature that directly addresses whether other DA-dependent tasks are influenced by E2 levels or other estrogens. A recent study by Evans and Hampson (2015) found a significant sex difference between males and females on a reinforcement learning task (PST; modified from Frank et al., 2004). A sex difference could potentially signal the presence of an estrogenic effect (although other mechanisms are possible, that can independently give rise to sex differences) (Hampson, 2017). As stated previously, reinforcement learning is believed to depend upon DA activity in the striatum. Additionally, research on Parkinson's disease patients, who have a loss of DA in the striatum, has shown that there is a negative correlation between the use of estrogen therapy and scores on the Unified Parkinson's Disease Rating Scale (a standardized scale in which higher scores indicate more severe motor symptoms) in postmenopausal women patients not on DA medication (Saunders-Pullman et al., 1999). Human research also lends indirect support for a possible link between DA and E2 through sex differences in the prevalence or symptom severity of other DA disorders such as schizophrenia (for review, see Sánchez, Bourque, Morissette, & Di Paolo, 2010).

Therefore, taken together, the human and animal literature implies that there may be a positive association between levels of circulating estrogens and DA in humans, an idea that needs to be explored further.

1.5 Summary and Hypothesis

To summarize, convergent evidence from both human and non-human studies has found that DA plays a major role in spatial WM, reinforcement learning, and sEBR. Additionally, it is well-established in the animal literature that the DA system is affected

by E2 in the female brain. Therefore, it is plausible that E2 may have a regulatory effect on DA activity in humans too.

In human research, there are two standard methods that are widely used to study the effects of estrogens on cognition. The first method involves manipulating E2 levels (or other estrogens) in naturally and/or surgically post-menopausal women. The second method involves comparing naturally-cycling women at different phases of the menstrual cycle, when ovarian hormones are at different concentrations. Advantages of the second method are that the hormones studied, their dosages, and temporal characteristics are physiological; either between-subject or more powerful within-subject study designs can be used; and it avoids the medical health risks shown to be associated with the use of exogenous estrogens in post-menopausal women (Writing Group for the Women's Health Initiative Investigators, 2002).

The objective of the current study was to use a menstrual cycle paradigm to test whether DA-dependent cognitive processes vary over the menstrual cycle in conjunction with E2 levels. We hypothesized that increases in E2, which occur during the human menstrual cycle, would lead to increases in DA, as seen in animal studies. Therefore, we predicted that performance on spatial WM and reinforcement learning tasks, which rely on DA activity in the PFC and striatum, respectively, would vary throughout the menstrual cycle. Additionally, we expected to see a change in sEBR, a behavioural measure that has been associated with striatal DA levels in human and nonhuman primate studies.

Specifically, we predicted that high levels of E2, as seen during the mid-luteal phase of the ovarian cycle, would be associated with an increase in DA availability and

therefore an increase in the accuracy of spatial WM, an increase in sEBR, an increase in learning based on positive reinforcement, and a decrease in learning based on negative reinforcement, relative to the menstrual phase of the ovarian cycle when E2 levels are lowest.

Chapter 2

Method

2.1 Participants

Participants were 47 healthy female undergraduate and graduate students as well as university staff members at the University of Western Ontario between the ages of 21 and 35 years ($M = 23.62$, $SD = 3.71$), an age range that coincides with the years of maximal mature ovarian hormone production (Lipson & Ellison, 1992). All participants had regular menstrual cycles that ranged in mean length from 25 to 35 days ($M = 28.61$, $SD = 2.34$). The mean estimated IQ of the sample was 107.54 ($SD = 7.75$). Exclusionary criteria on the basis of hormone disruption included the use of hormonal contraceptives at present or within the 4 months prior to testing, current pregnancy or lactation, the use of hormone replacement therapy or other medications that interfere with endocrine function, or a history of ovarian abnormalities, including amenorrhea (i.e., lack of a menstrual cycle) or oligomenorrhea (i.e., infrequent ovulation). Additionally, women who indicated a history of neurological (e.g., epilepsy) or mental health conditions (e.g., schizophrenia or untreated depression) were not considered eligible to take part in the study as these conditions may adversely affect working memory function.

2.2 Procedure

Potential participants were recruited through the use of informational posters displayed around the university campus. Interested volunteers were required to complete an encrypted online health questionnaire in order to determine their eligibility to

participate in the study. Women who met the criteria described above were contacted and invited to participate.

Using a repeated-measures design, eligible participants were tested at two target points during the menstrual cycle: once during the menstrual phase when E2 levels are at their lowest (target days +3 to +5 relative to the onset of menstruation), and once during the estimated mid-luteal phase when E2 levels are high (target days -5 to -10 relative to the onset of the next prospective menstruation). Phase of cycle on the first test day was counterbalanced across participants in order to account for the possibility of an order effect. The pattern of changes in E2 and progesterone over a 28-day cycle is shown in Figure 2.1.

The timing of menstrual cycle events cannot be predicted with certainty and women do not always provide accurate advance information about the length and variability of their cycles (Hampson & Young, 2008). Therefore, in order to retroactively confirm that each participant was in fact tested during the menstrual and luteal phases of her cycle, two standard verification procedures were used (Hampson & Young, 2008): (i) Two specimens of saliva were collected at each test session (one at the beginning of the session and one at the end, about 1.25 hr later). Radioimmunoassays (RIA) of the saliva were performed to quantify E2 and progesterone (see below for description of methods used). Secondly, (ii) following testing, women were asked to report the exact date of onset of their next (or current) menstrual period. Using a reverse day count method (Hampson & Young, 2008), these data were used to confirm the exact temporal day of the cycle on which the cognitive testing took place.

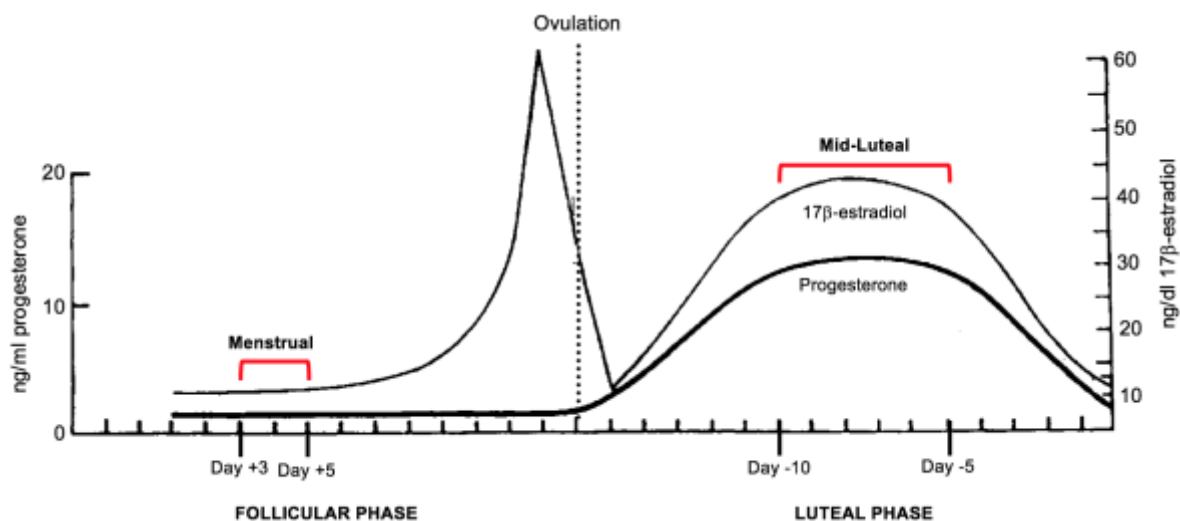


Figure 2.1. Pattern of changes in serum 17β -estradiol and progesterone that occur over a typical 28-day menstrual cycle. The day of onset of menstruation is always considered Day +1. There are two distinct phases in each cycle: the follicular phase and the luteal phase (Hampson & Young, 2008). The average length of the menstrual cycle is 29.5-days, however normal ovulatory cycles can range anywhere from 24 to 35 days in length (Vollman, 1977). Based on a 28-day cycle, the follicular phase begins on day 1 and lasts until about day 14, which is the date of ovulation. Assuming no fertilization occurs after ovulation, the luteal phase begins and lasts from days 15-28, when the cycle restarts and menstruation begins again. In general, the follicular phase varies greatly in length, both between and within women, but the luteal phase is a fixed length of between 13 and 15 days (Hampson & Young, 2008). During the menstrual subphase, which occurs from Day +1 to approximately Day +5 to +7, estradiol levels are low. During the mid-luteal subphase, which occurs between cycle days -5 and -10 (relative to the date of onset of the next menstrual period), estradiol and progesterone levels are high. Red brackets denote the days of the cycle targeted for cognitive testing in the present study.

Although serum concentrations are depicted here, saliva was used to measure both steroids in the present study. Saliva contains only the fraction of the total hormone that is biologically available to interact with tissue, so relative to serum it is thought to afford a superior representation of the hormonal fraction that is free to influence biological function (Hampson, Phillips, Soares, & Steiner, 2013).

All participants were tested individually by a trained examiner in an office setting. Each test session took between 60 and 75 min and included the tasks described below. Order of test administration is shown in Figure 2.2. Each task was administered once during each phase of the cycle with the exception of the North American Adult Reading Test (NAART), which was administered only during the first test session.

2.3 Spontaneous Eye Blink Rate

sEBR has been shown to be sensitive to changes in striatal DA level in both healthy and clinical populations, making it a good functional marker of central DA activity (for review, see Jongkees & Colzato, 2016). Additionally, D₂ DA receptor agonist and antagonist drugs have been shown to increase and decrease sEBR, respectively, in human (Cavanagh et al., 2014) and nonhuman primates (Lawrence & Redmond, 1991).

For this task, participants were seated approximately 66.5 cm in front of a ViewSonic Graphic Series G225 computer monitor (39.5 cm width, 30.6 cm height) positioned at eye level on top of a desk. In order to stabilize head position, participants placed their head into a chin and forehead rest facing the computer screen (see Figure 2.3). Following eye position calibration, participants were instructed to relax and silently view a slideshow of silent landscape images presented on the monitor. Participants were blind to the fact that eye blinks were being recorded.

The slideshow consisted of 27 landscape images (from the Mac OS X screensaver image folder) without obvious focal points (36.1 cm width, 20.6 cm height). Each image was shown for 12 s before slowly fading (3 s) into the next image (6 min 41 s total). sEBR was recorded and quantified using the EyeLink 1000 core system (SR Research

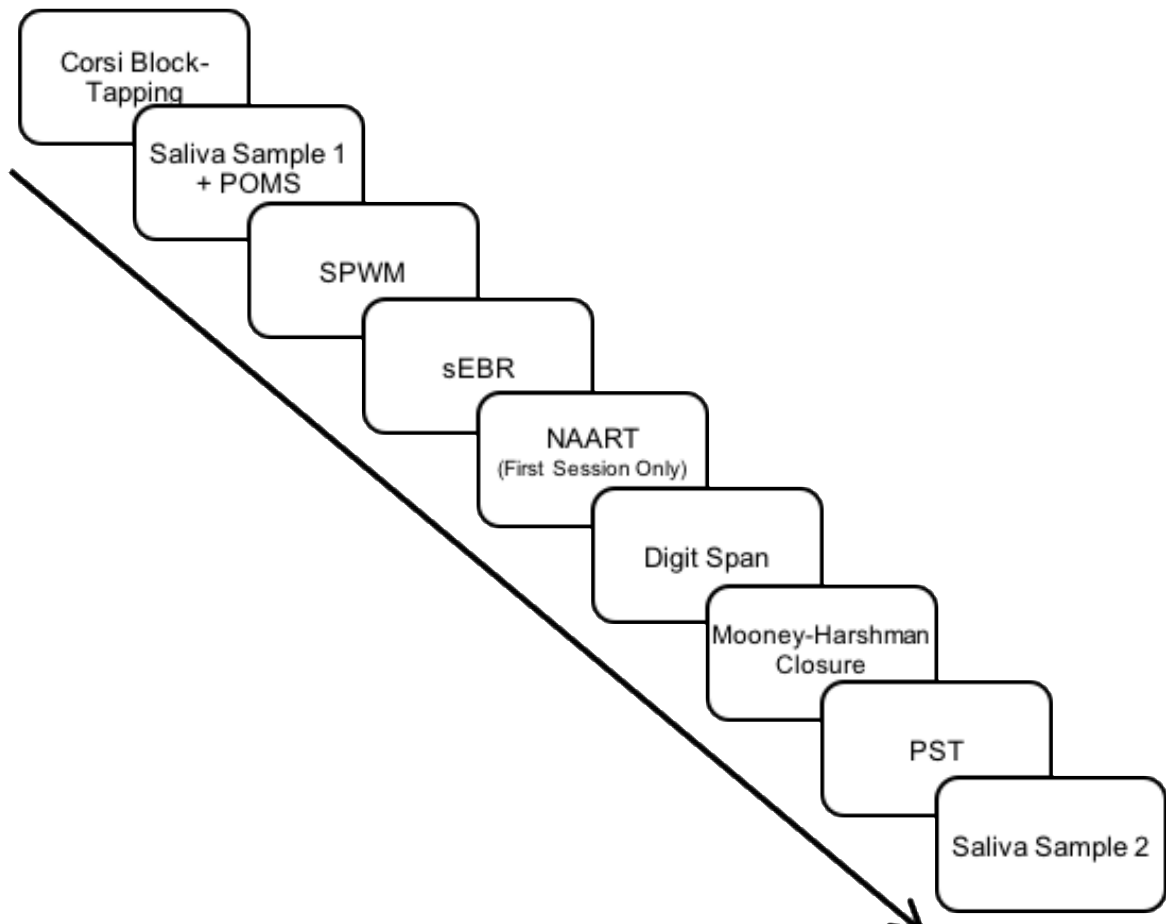


Figure 2.2. Order of test administration for both test sessions.



Figure 2.3. An image of the eye tracking set-up. Participants placed their head into a chin and forehead rest and looked forward at a computer screen while their spontaneous eye blink rate was quantified using the EyeLink 1000 core system via an infrared camera placed in front of them below the computer screen (shown in enlarged image).

Ltd., Mississauga, ON), with the camera located directly below the computer screen in a desktop mount. The EyeLink 1000 records blinks by tracking the reflection of infrared illumination off of the pupil, with a sampling rate of 500 Hz. Participants viewed the slideshow binocularly, however eye blinks were only stored for the right eye.

Number of blinks was recorded in six 60-s time bins (the residual 41 s remaining at the end of the slideshow was recorded but not analyzed in order to maintain consistency in the bin length over which blink rate was computed). A total blink score was summed and provided automatically by the EyeLink 1000 in an EyeLink output file, but in addition, the number of blinks per time bin were counted in an off-line analysis and then summed per individual and cross-checked with the total score provided by the EyeLink 1000. In no case was there a discrepancy between the off-line and automatic counts.

For purposes of statistical analysis, the first 60 s time bin was excluded to account for an initial adaptation period. Therefore, five 60-s time bins were available for each test session as estimates of each participant's sEBR.

Two different but equivalent versions of the slideshow were used. The slideshow presented at each session was counterbalanced across participants and within each phase of cycle.

2.4 Probabilistic Selection Task (PST; Frank et al., 2004)

The PST is a well-established reinforcement learning task that is widely used in cognitive neuroscience studies of DA function (Frank, 2005; Frank & Kong, 2008; Frank et al., 2004).

The PST is a two-alternative forced-choice implicit learning task. It was programmed in Millisecond (Inquisit 5, Seattle, WA). Stimuli were presented on a Windows 7 computer and participants responded on each trial by making a keypress response. The task consisted of a training phase and a test phase. During the training phase, participants were presented with three different pairs of stimuli (AB, CD, EF), one at a time, in a randomized order up to a maximum of 480 trials. Stimuli were non-verbalizable Japanese Hiragana characters (~ 7.5 cm width, 7.5 cm height) presented in black on a white background (see Figure 2.4). Participants were asked to choose one of the two stimuli presented on each trial by pressing a key on either the left (i.e., A) or right (i.e., L) side of a keyboard. Following each selection, participants received either positive (“Correct” printed in green) or negative (“Wrong” printed in red) feedback, however the feedback was probabilistic. In trials where the AB pair was present, choosing stimulus A resulted in positive feedback 80% of the time, whereas choosing stimulus B resulted in negative feedback 80% of the time (with the remaining 20% of trials being reversed). The two other stimulus pairs were less predictable, such that in trials where the CD pair was present, choosing stimulus C resulted in positive feedback 70% of the time, and in trials where the EF pair was present, choosing stimulus E resulted in positive feedback 60% of the time (with the remaining trials of both pairs being reversed). During the training phase, therefore, participants should implicitly learn to choose stimuli A, C, and E over stimuli B, D, and F. This may be accomplished by either learning to consistently choose the positively reinforced stimuli (e.g., choose A) or learning to consistently avoid the negatively reinforced stimuli (e.g., avoid B), or both.

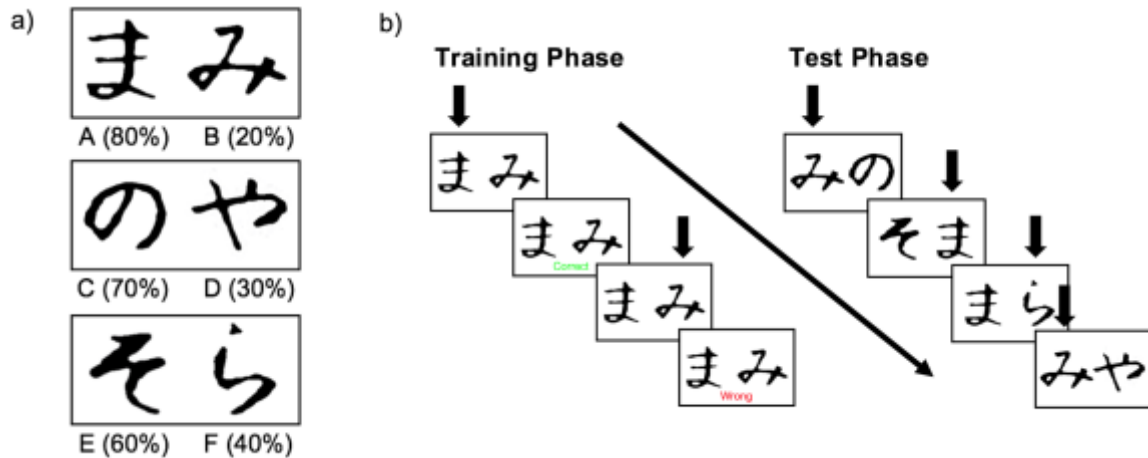


Figure 2.4. (a) One of the two stimulus sets used in the Probabilistic Selection Task (Frank, Seeberger, & O'Reilly, 2004). The percentages below each pair of Hiragana characters reflect their respective reinforcement contingencies (see Method for details). (b) A schematic of the training and test phases of the Probabilistic Selection Task. During the training phase, participants were presented with 1 of 3 fixed pairs of stimuli (AB, CD, EF) on each trial. Choosing one of the two figures via a buttonpress caused the feedback screen to appear. Over a long series of trials participants learned which stimulus in each of the 3 pairs was correct based on the reinforcements they received following each choice. The test phase began after a participant successfully reached a designated learning criterion. Participants who did not reach the learning criterion by the end of 480 trials did not move on to the test phase. During the test phase, pairs presented on each trial consisted of all possible pairings of the 6 original stimuli containing either an A or B. Participants were required to indicate (via a buttonpress) the stimulus in each pair that they believed to be correct based on what they had learned during the training phase. No feedback was given during the test phase. The black arrows in the figure represent the choices made by a hypothetical participant during each phase. In the test phase, learning through positive feedback was measured as the percentage of trials a participant chose A in all pairings where A was present, and learning through negative feedback was measured as the percentage of trials a participant avoided B in all pairings where B was present.

The learning phase was continued in blocks of 60 trials, with each pair being presented 20 times per block, until participants met a specific learning criterion or until they reached 480 trials. The performance criterion was evaluated automatically by the computer after each block of 60 trials and if it was not met, a further block of 60 trials ensued. This was done in order to ensure that all participants had reached a similar level of learning before advancing to the test phase. Following the procedures used in past studies, the learning criteria for the 3 pairs were: choosing A over B in 65% of AB trials, choosing C over D in 60% of CD trials, and choosing E over F in 40% of EF trials. In the EF pair, stimulus E is correct 60% of the time, however this is particularly difficult for individuals to learn and therefore a 40% learning criterion was used as in Lighthall et al. (2013). Participants who did not reach criterion by the end of the 480 trials of the training phase did not advance to the test phase.

Once participants reached criterion they advanced to the test phase in order to determine whether they relied more on positive or negative feedback. During the test phase participants were presented with novel combinations of the original stimuli involving either an A (i.e., AC, AD, AE, AF) or a B (i.e., BC, BD, BE, BF) and were once again required to choose one of the two stimuli in each pair shown, however this time they received no feedback after making their selections. The test phase consisted of 160 trials, with each stimulus pair presented 20 times. The measure of learning from positive feedback was the percentage of trials in the test phase where a participant chose A in all pairs where A was presented, and the measure of learning from negative feedback was the percentage of trials where a participant avoided B in all pairs where B was presented.

Two alternate versions of the PST were created, each with a distinct set of 6 Hiragana stimuli. The version of the task given during the first test session was counterbalanced across participants and within each phase of cycle. The alternate version of the PST was given to each participant during her second test session. Additionally, the six stimuli were randomized, so that across participants each of the 6 Hiragana figures was randomly designated as stimulus A and stimulus B. Additionally, the left-right position of each stimulus pair (e.g., AB or BA) was counterbalanced across trials.

2.5 Spatial Working Memory Task (SPWM; Duff & Hampson, 2000)

This task was developed for humans based on the classic search task used in nonhuman primates by Passingham (1985). Its cognitive demands resemble those of other spatial WM tasks used in human studies (Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Owen, Downes, Sahakian, Polkey, & Robbins, 1990) and nonhuman primates (Passingham, 1985). The number of working memory errors (WME) produced on the SPWM has been found to correlate significantly with the numbers of WME produced on other widely used standardized WM measures, including Digit Ordering (Petrides, Alivisatos, Meyer, & Evans, 1993), which is a verbal WM task, Digits Backward (from the Wechsler Memory Scale, 1981), and Self-Ordered Pointing (Petrides & Milner, 1982), a nonverbal WM task (see Duff & Hampson, 2001; Hampson et al., 2015).

Participants sat in front of a white board (45 cm width, 41 cm height) (see Figure 2.5). The board consisted of a 4 x 5 array of 20 randomly arranged coloured dots. There were 10 colours in total (red, orange, yellow, green, blue, purple, pink, fuchsia, black, white), and two dots of each colour. Each coloured dot was 3 cm in diameter and was completely hidden behind a white hinged flap (8 cm width, 4.5 cm height). Each dot was

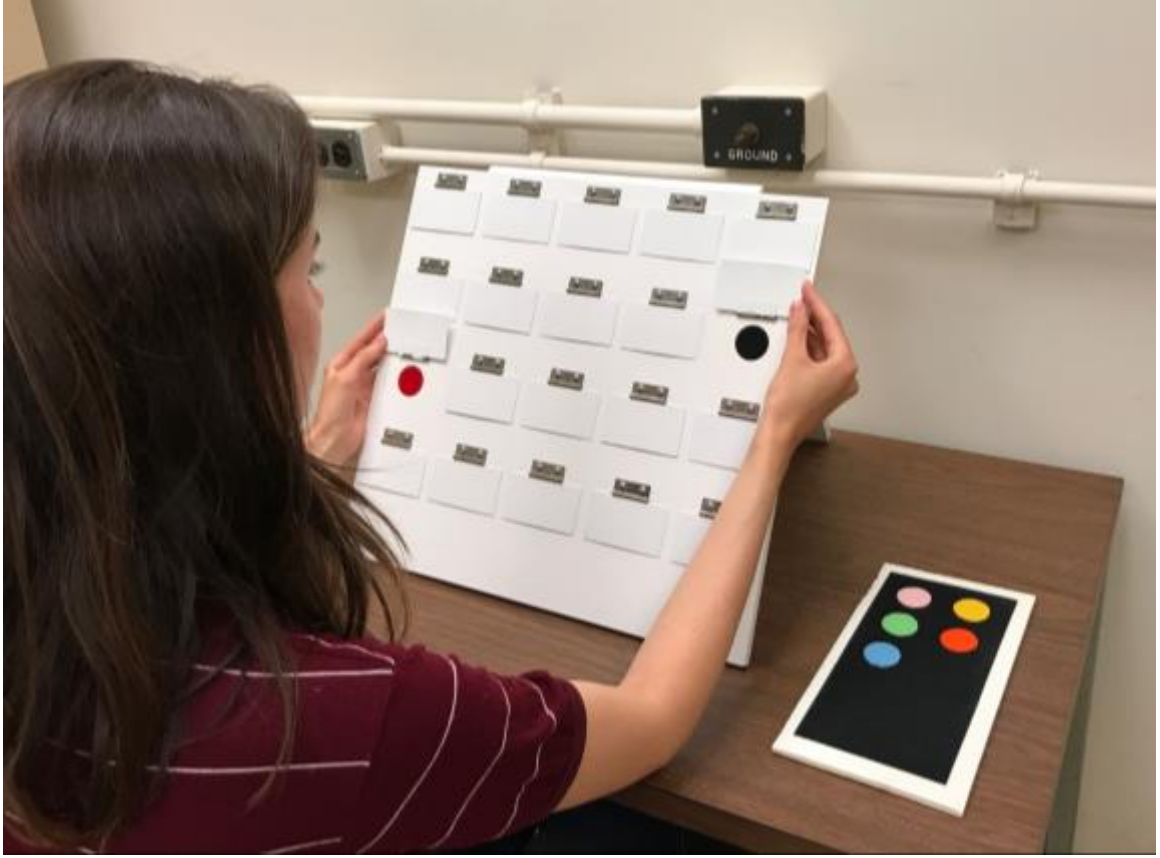


Figure 2.5. A participant selecting a non-matching pair of locations on the Spatial Working Memory board (Duff & Hampson, 2001). Participants were instructed to find all 10 matching pairs of coloured dots in as few tries as possible by lifting 2 flaps at a time. A working memory error was recorded whenever a participant searched a pair of locations that had already been searched but did not match, or anytime they revisited an already matched pair.

only visible when its corresponding flap was temporarily lifted by a participant. Participants were instructed to find all 10 matching pairs of coloured dots in as few choices as possible, by lifting 2 flaps simultaneously. Participants were told that they would be timed while working on the task, but that the main goal was to find all matching pairs in as few searches as possible. When a flap was not being lifted by the participant, it was closed and completely covered the dot beneath. To perform the task efficiently, therefore, participants had to maintain and update in their WM, the locations of the pairs of dots that they had already matched, and the locations of the dots not matched yet, as they continued searching for the remaining pairs. A participant was considered to have made a WME anytime they chose a pair of locations that had already been searched but did not match, or anytime they revisited an already matched pair.

During the task, as each pair was found, a corresponding coloured token was placed onto a felt pad beside the array by the experimenter. This was done to avoid the need for participants to remember which colours they had already matched. Therefore, participants only had to keep track of the *locations*, of the matched and unmatched dots while working through the task.

On each test day, participants completed three consecutive trials of the SPWM. A trial was considered complete when all 10 matching pairs of coloured dots had been found. Alternate forms of the task were given on each of the two test days. The version given during the first test session was counterbalanced across participants and within each phase of cycle. The dependent variable was the number of WME produced on each trial.

2.6 Working Memory Control Tasks

Performance on the SPWM requires the active manipulation of information within WM, a function that is believed to be DA-dependent (for review, see Ellis & Nathan, 2001). However, differences in performance on the SPWM between the menstrual and mid-luteal phases of cycle could in principle alternatively be caused by E2-related changes in the capacity of passive short-term store, should such an effect of E2 exist. In order to ensure any menstrual cycle-related changes in performance on the SPWM were not due to a simple change in passive storage capacity, two control tasks that rely only on passive memory storage were used.

2.6.1 *Digit Span* (Wechsler Adult Intelligence Scale – Revised [WAIS-R]; Wechsler, 1981)

The Forward Digit Span task requires the immediate recall of digits without requiring any active manipulation or holding of that information. Neuroimaging research has found that the passive immediate recall of digits is mediated by posterior regions of the brain (perisylvian cortex) as opposed to the PFC (Postle, Berger, & D'Esposito, 1999). Performance of Digits Forward does not appear to be DA-dependent, as seen through studies of Parkinson's patients who do not show evident impairments in forward span (Warden, Hwang, Marshall, Fenesy, & Poston, 2016) and through DA agonist (i.e., pergolide) administration studies in neurologically healthy individuals (Kimberg & D'Esposito, 2003), which show no effect of DA agonists on forward span performance. In addition, patient studies show that lesions and/or excisions of the PFC do not significantly affect performance of the Digits Forward task (Canavan et al., 1989; D'Esposito & Postle, 1999; Petrides, 1995).

The Digits Forward subtest of the WAIS-R Digit Span was administered in the standard manner. Briefly, the examiner verbally presented a sequence of digits of progressively increasing length. Participants were required to repeat each sequence aloud immediately after presentation. The task was discontinued after failure of two tries at any sequence length. The dependent variable was the maximum number of digits that a participant was able to repeat correctly.

2.6.2 *Corsi Block-Tapping* (Milner, 1971)

This task is a visuospatial analogue of the Digits Forward task, in which locations rather than digits are presented. As in Digits Forward, it does not require any active manipulation of the information. Patient studies indicate that accurate performance on the Corsi Block-Tapping task is dependent on posterior regions of the brain (e.g., inferior parietal cortex) (Baldo & Dronkers, 2006) and lesion studies show no significant deficit in performance after lesions of the PFC (D'Esposito & Postle, 1999). Like Digits Forward, performance is minimally dependent on DA levels (Kimberg & D'Esposito, 2003; Morris et al., 1988).

On the Corsi task, participants observed as the examiner tapped out a spatial sequence of progressively increasing length on a set of 9 identical black cubes (3 cm) randomly arranged on a black wooden platform (27.7 cm width, 22.8 cm height). Immediately following each presentation, participants were required to tap out the identical sequence, in order. The task was discontinued after failure of two tries at any sequence length. A participant's score was the maximum sequence of spatial locations they were able to repeat correctly.

2.7 Other Control Tasks

2.7.1 *Mooney-Harshman Closure* (Adapted from Mooney & Ferguson, 1951)

This task was included to demonstrate the cognitive selectivity of any E2 effects documented in the present study. It requires visual object recognition processes but not WM. Previous research found that women tested during the menstrual phase were able to correctly identify a significantly higher number of the closure images compared to women tested during the mid-luteal phase (Hampson, Finestone, & Levy, 2005). Therefore, a similar result was predicted for the current study. Additionally, research has found a male advantage in accuracy on other perceptual closure tasks (Foreman, 1991; Verhallen et al., 2014), instead of the female advantage reported for the SPWM (e.g., Lejbak, Vrbancic, & Crossley, 2009). Enhanced performance during the menstrual phase, when E2 levels are low, is the *opposite* of what was expected on the SPWM and therefore this task was used to demonstrate the functional selectivity of any menstrual cycle-related effects observed during testing. Specifically, enhanced performance during the menstrual phase would rule out the possibility of an overarching facilitative effect of E2 on all brain functions.

Participants were shown 13 black and white images printed on rectangular cards (21.5 cm width, 27.9 cm height), one at a time. The images consisted of common objects but the images were visually incomplete or had parts missing. Upon viewing an image, the participant was given a maximum of 20 s to identify what the image was *of*, which was then recorded verbatim by the examiner. The dependent variables consisted of the total number of correctly identified items (max. 12) and the mean time taken to correctly identify an image in seconds (max. 20 s). Two equally difficult versions of this task were

used in order to minimize practice effects between the two test sessions. The version of the task was counterbalanced across participants and within each phase of cycle.

2.7.2 *Profile of Mood States (POMS; McNair et al., 1971)*

No effects of the menstrual cycle on mood were expected in the present study. Although a common stereotype, negative mood changes occur in only a small minority of healthy women (Abplanalp, Donnelly, & Rose, 1979; Schwartz, Romans, Meiyappan, De Souza, & Einstein, 2012) and not typically at the two phases of the cycle targeted here. Nevertheless, the POMS was given to detect any changes in mood that might impact cognitive performance. In particular, select mood states (e.g., clinical depression) can have a negative impact on objectively measured cognitive performance including WM (for review, see Cassens, Wolfe, & Zola, 1990). The POMS is a standardized self-report inventory that is used to assess transient mood states in both healthy and clinical populations. Participants were asked to indicate how accurately 65 different mood-related adjectives (e.g., Friendly, Confused, Guilty) described how they were feeling on the day of testing. Each item was rated on a 5-point Likert scale ranging from 1 (*Not at all*) to 5 (*Extremely*). The responses were used to compute a total score for each of the six POMS subscales: Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, Vigor-Activity.

2.7.3 *North American Adult Reading Test (NAART; Blair & Spreen, 1989)*

The NAART is a quickly administered reading task that is widely used in clinical settings to estimate general intellectual ability. For this task, participants were asked to read aloud a list of 61 low-frequency English words (e.g., psalm, détente). Each word was scored for accuracy of pronunciation according to standard American and Canadian

pronunciation rules. The dependent variable was the number of correctly pronounced words (max. 61). Full scale IQ (FSIQ) scores were then estimated using actuarial prediction equations developed by the creators of the NAART.

Estimated FSIQ scores based on NAART performance have been validated as predictors of IQ scores on the WAIS-R (Blair & Spreen, 1989). The NAART was administered only to demographically characterize the sample. It was administered to each woman only once, during her first test session, in order to confirm that the two counterbalanced groups (women tested first during the menstrual phase and women tested first during the mid-luteal phase) were evenly matched in general intellectual ability. We predicted no significant difference in NAART scores between the two groups because previous studies have found circulating E2 levels to have no effect on other indices of general intelligence (Hampson, 1990; Hampson & Morley, 2013; Jacobs & D'Esposito, 2011; Sommer, 1972).

2.8 Saliva Collection and Radioimmunoassays

2.8.1 Saliva Collection Method

In order to quantify E2 and progesterone levels, saliva specimens were collected at the beginning and end of both test sessions. Participants were instructed in advance not to eat or drink anything other than plain water, smoke, chew gum, or brush their teeth for at least 45 min prior to the testing, in order to ensure that the saliva samples were free of contamination. Upon entering the testing room, participants rinsed their mouth with plain water in order to remove any food debris. Each sample consisted of approximately 3 mL of saliva collected into a polystyrene culture tube by passive drool. No saliva stimulants

were used. Samples were stored frozen at -20°C until a single-batch analysis at the end of the study.

2.8.2 Radioimmunoassay (RIA) Methods

Prior to analysis the saliva was thawed and centrifuged at 3000 rpm (4°C) for 15 minutes. To quantify E2 levels, the samples were analyzed without extraction using the DSL4800 Ultra-Sensitive E2 RIA (Immunotech, Prague, Czech Republic) adapted for saliva. The lower limit of detection of the assay was 0.4 pg/mL and the intra-assay coefficient of variation averaged $< 8\%$. Following most past research in the cognitive literature, women in the current study were tested during the mid-luteal phase instead of the preovulatory rise in E2 because the preovulatory surge is short-lived and exceedingly difficult to target successfully prospectively. Because progesterone, which is another steroid hormone that fluctuates over the ovarian cycle, is also raised during the mid-luteal phase, progesterone was also analyzed. Previous research has shown that progesterone does not influence performance on the SPWM (e.g., Duff & Hampson, 2000; Hampson & Morley, 2013), but its effects, if any, on the sEBR and the PST are not known. Therefore, progesterone was assayed from saliva using the ImmuChemTM Coated Tube Progesterone RIA (MP Biomedicals, Costa Mesa, CA). Progesterone levels were not yet available at the time of writing.

2.9 Confirmation of Phase of Cycle

In order to confirm that each participant was tested during the targeted phases of the menstrual cycle, two criteria had to be met: (1) Each test session had to have fallen on days of the menstrual cycle that are known to coincide with the menstrual phase (days +3

to +5) and the luteal phase (days -3 to -15), which were retroactively confirmed by determining the date of onset of each participant's next menstrual period subsequent to the test session. (2) The mean E2 level during the luteal phase had to be higher than during the menstrual phase. Four participants met the first criterion but not the second (probably indicating failure to ovulate), two participants met the second criterion but not the first, and three participants did not meet either criterion. Therefore, the final sample consisted of 47 out of the 56 women originally tested. In the final sample, 21 participants were tested at the menstrual phase first and 26 were tested at the mid-luteal phase first.

Chapter 3

Results

All results were analyzed using IBM SPSS Statistics 24 for Windows. Mixed effects analysis of variance (ANOVA) or covariance (ANCOVA) was used to test for phase of cycle differences. Except where stated otherwise, 2 x 2 ANOVAs were done, with phase of cycle (menstrual or luteal) as a within-subjects factor and order of testing over the two sessions (menstrual-luteal or luteal-menstrual) as a between-subjects factor. Pearson's product-moment correlation coefficient was used to examine correlations between salivary E2 levels and performance on the main tasks. The criterion for significance was $p < 0.05$.

In the current study, the mean levels of salivary 17β -estradiol in the final subject sample were 0.35 pg/mL ($SD = 0.31$) during the menstrual phase and 1.07 pg/mL ($SD = 0.47$) during the luteal phase. These E2 values are in accordance with previous reports of the acceptable physiological ranges at each phase (Hampson & Morley, 2013; Shirtcliff et al., 2000). The mean day of cycle was 4.02 ($SD = 0.82$) for the menstrual phase and - 6.87 ($SD = 2.82$) for the luteal phase, indicating that the cognitive testing was well targeted.

3.1 Spontaneous Eye Blink Rate (sEBR)

Ten participants could not be included in the sEBR analysis due to inaccurate calibration of the EyeLink 1000 apparatus and/or invalid blink tracking caused by the presence of irregular eyelash or eyelid shape or an inability to see without corrective lenses. In order to adjust for wide individual differences across women in overall eye

blink frequency, each participant's eye blink rate (in each time bin and phase of cycle) was expressed as a percentage of her individual baseline. Baseline was defined as the mean blink rate averaged across all 5 60-second time bins during the menstrual phase of the cycle (when E2 is lowest). The percentage of baseline rate was then calculated for each of the 5 60-second time bins for both the menstrual and luteal test sessions.

To test for a phase of cycle effect, a 2 x 2 x 5 mixed effects ANOVA was performed, using the percent of baseline sEBR scores as the dependent variable. Phase of cycle (menstrual or luteal) and time bin number (1, 2, 3, 4, or 5) were within-subjects factors. Order of testing (menstrual-luteal or luteal-menstrual) was a between-subjects factor. A significant main effect was found for phase of cycle, $F(1, 35) = 5.56, p = 0.024$ (see Figure 3.1). As predicted, women showed a significant increase in sEBR during the luteal phase of cycle, when E2 is high, compared to the menstrual phase, when E2 is low. No other main effects or interactions were significant.

3.2 Probabilistic Selection Task (PST)

Of the 47 women tested, a total of 36 reached the learning criterion and advanced to the test phase during their first test session (77%) and a total of 35 reached the learning criterion and advanced to the test phase during their second test session (74.5%). These retention rates are similar to those seen in other studies using the Frank et al. (2004) task (K. L. Evans & Hampson, 2015; Rustemeier et al., 2012). It is important to note however that the present study utilized a repeated measures design, therefore only participants who had test phase data available for both sessions could be included in the ANOVA. Thirty-one women reached criterion during both test sessions (66%), and proceeded to the test phase.

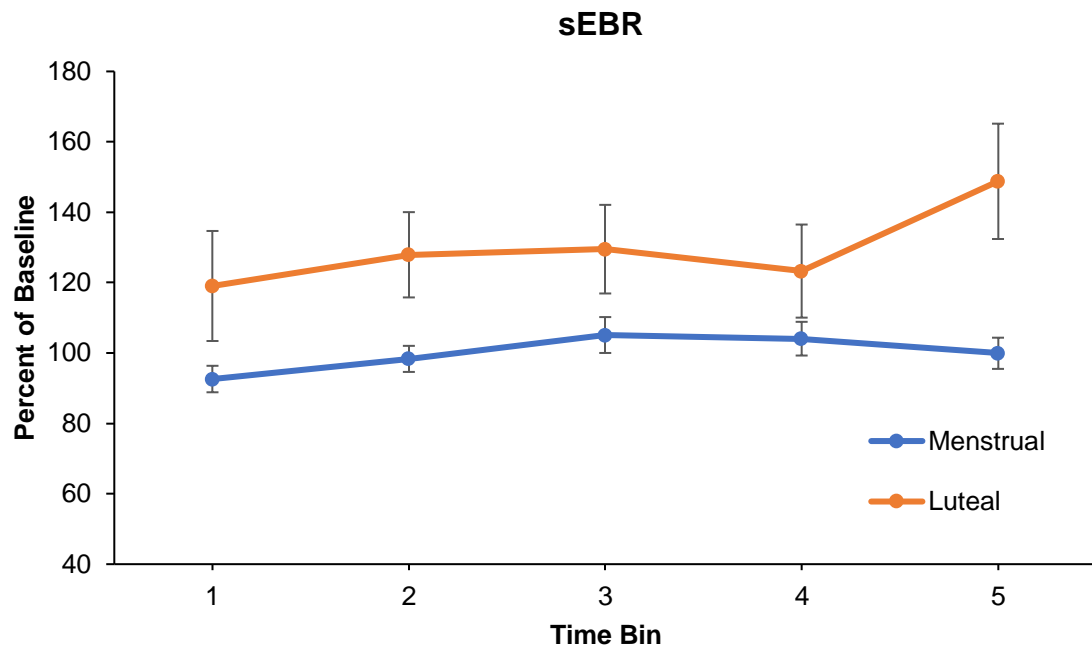


Figure 3.1. Spontaneous eye blink rate during the menstrual and luteal phases of the menstrual cycle ($n = 37$ women tested twice). Scores are shown as a percent of baseline. Women showed a significant increase in eye blink rate during the luteal phase of cycle compared with the menstrual phase. Error bars represent SEM.

As a result the sample size available for analyzing Choose A and Avoid B during the test phase was 31.

Separate 2 x 2 mixed effects ANOVAs were performed to examine positive reinforcement learning (mean percent accuracy on Choose A) and negative reinforcement learning (mean percent accuracy on Avoid B). Phase of cycle (menstrual or luteal) was the within-subjects factor and order of testing (menstrual-luteal or luteal-menstrual) was a between-subjects factor. Overall, no significant phase of cycle effects were found for positive reinforcement learning, $F(1, 29) = 0.98, p = .331$, or for negative reinforcement learning, $F(1, 29) = 0.02, p = .886$. The pattern of means for the group of women tested first at the luteal phase ($n = 16$) was in line with our predictions for positive reinforcement learning, such that they chose A more frequently during the luteal phase (high E2) than during the menstrual phase (low E2) (see Figure 3.2a). However, the same pattern was not evident in the group of women tested at the menstrual phase first ($n = 15$) (see Figure 3.2b). No other main effects or interactions were significant.

While no formal predictions were made for the training phase of the PST, in order to understand if there was any phase of cycle effect on *rate* of learning we performed a 2 x 2 mixed effects ANOVA on the total number of trials needed to reach criterion, with phase of cycle and order of testing as factors (same as above). We found no significant phase of cycle effect for number of trials taken to reach criterion, $F(1, 29) = 0.05, p = .827$. The mean number of trials taken to reach criterion was 150.97 ($SD = 99.04$) during the menstrual phase and 145.16 ($SD = 116.73$) during the luteal phase.

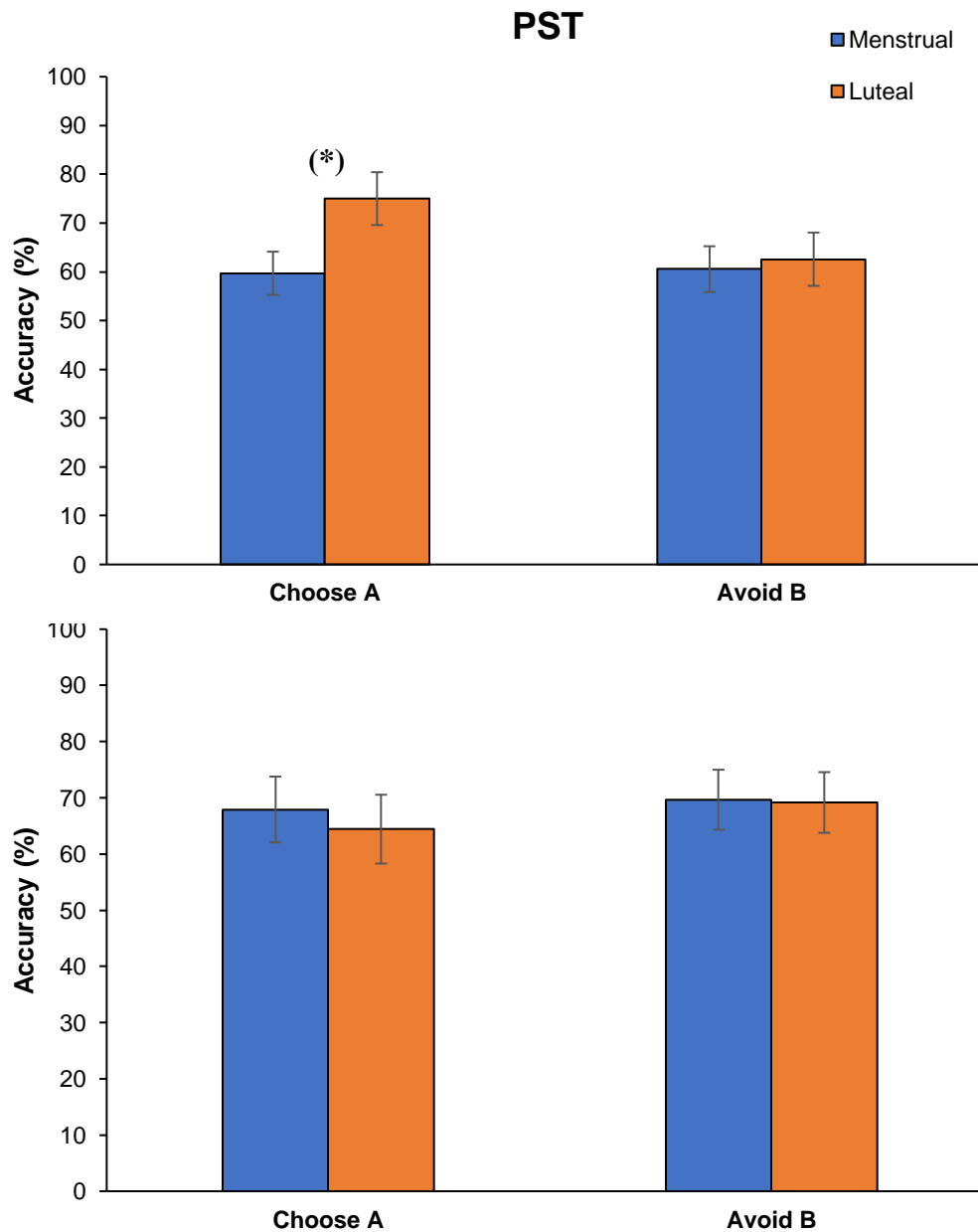


Figure 3.2. Mean percent accuracy during the test phase of the Probabilistic Selection Task for women tested at the menstrual and luteal phases of the cycle. Accuracy is shown separately for learning from positive (Choose A) and negative (Avoid B) reinforcement. Top panel (a) shows data for the group of women who were tested at the luteal phase first ($n = 16$) and bottom panel (b) shows data for the group of women who were tested at the menstrual phase first ($n = 15$). Combining the two order-of-testing groups, no significant difference between phases of the cycle was found, for either positive or negative reinforcement learning. Error bars represent SEM.

(*) indicates a p value of .057

3.3 Spatial Working Memory Task (SPWM)

For the analysis of the SPWM data, a stricter criterion was set for the minimum E2 level that had to be present during the luteal phase. Although it decreased the sample size available, this decision was based on previous studies involving the SPWM, which used stricter cutpoints to identify the luteal phase (e.g., Hampson & Morley, 2013; Segal, 2012), and allowed us to compare our data directly with those findings. For the SPWM, therefore, the salivary E2 concentration during the luteal phase had to be equal to or greater than 0.8 pg/mL. Although use of this stricter cutpoint would have been desirable when analyzing data on the PST too, it was not used due to the small sample size, which would have been further reduced using this criterion.

A 2 x 2 x 3 mixed effects ANOVA was performed on the SPWM scores¹, with phase of cycle (menstrual or luteal) and trial number (1, 2, or 3) as within-subjects factors and order of testing (menstrual-luteal or luteal-menstrual) as a between-subjects factor. The dependent variable was the number of working memory errors made on each trial. A significant main effect was found for phase of cycle, $F(1, 26) = 7.70, p = .010$ (see Figure 3.3). As predicted, women made significantly fewer working memory errors during the luteal phase, when E2 is high, compared to the menstrual phase, when E2 is low. Additionally, a significant main effect of trial was found, $F(2, 52) = 21.73, p < .001$, such that women made significantly fewer working memory errors by the third trial. There was also a significant interaction between order of testing and phase of cycle, $F(1, 26) = 12.13, p = .002$, whereby scores tended to improve on the second session as a result

¹ Two statistical outliers were removed who had error scores that were ≥ 3 standard deviations above the mean number of errors.

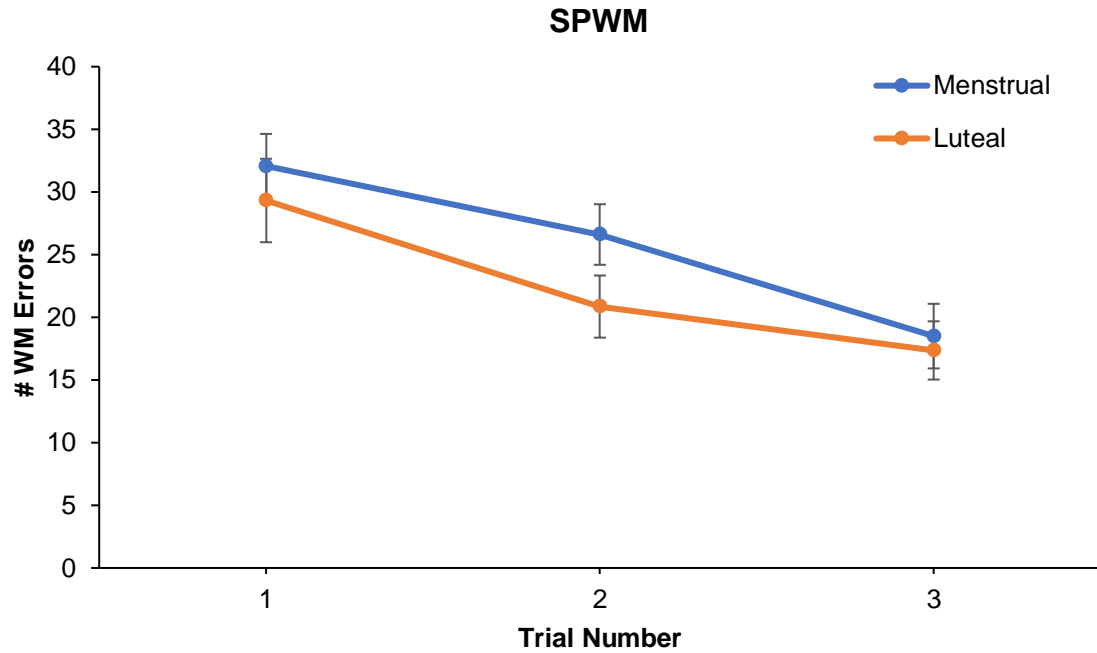


Figure 3.3. Mean number of working memory errors on the 3 trials of the Spatial Working Memory Task, during the menstrual and luteal phases of the menstrual cycle ($n = 28$ women tested twice). Women committed significantly fewer working memory errors during the luteal phase than during the menstrual phase. Error bars represent SEM.

of the previous exposure to the test (a practice effect). Specifically, women tested during the menstrual phase first showed an exaggerated decrease in working memory errors when tested for the second time during their luteal phase, whereas the expected deterioration in performance on the second session was greatly attenuated in women whose second session occurred during the menstrual phase.

3.4 Working Memory Control Tasks

It was hypothesized that E2 would have an effect on the active manipulation component of spatial working memory, which is mediated by the prefrontal cortex, rather than passive memory storage and recall, which is mediated by posterior regions of the brain (Postle et al., 1999). Therefore, a significant effect of phase of cycle was not expected on the two working memory control tasks (Corsi Block-Tapping and Digit Span).

3.4.1 Digit Span

A 2 x 2 mixed effects ANOVA was performed on the Digit Span scores. The ANOVA revealed no effect of phase of cycle on the Digit Span task, $F(1, 28) = 0.03, p = .869$ (see Table 3.1). This implies that the phase effect found on the SPWM is not due to changes between phases in women's passive memory storage capacity.

3.4.2 Corsi Block-Tapping

A 2 x 2 mixed effects ANOVA was performed on the Corsi scores. Unexpectedly, a significant effect of phase of cycle was found, $F(1, 28) = 6.41, p = .017$ (see Table 3.1), such that women had a higher spatial span during the menstrual phase of their cycle than during the luteal phase. Previous studies have not found performance on the Corsi task to

Table 3.1

Mean Scores (and SD) on the Control Tasks During Menstrual and Luteal Phases of the Cycle

Task	<u>Menstrual Phase</u>		<u>Luteal Phase</u>	
	M	SD	M	SD
Mooney-Harshman Time (sec)	5.42	1.89	6.21*	2.47
Mooney-Harshman # Correct, Session 1	8.63	1.95	6.58*	3.20
Digit Span	6.80	1.13	6.77	1.33
Corsi Block-Tapping	5.60	1.25	5.03*	1.13
NAART eFSIQ	107.15	8.49	107.86	7.23
POMS Anger	4.19	4.92	5.34	7.83
POMS Confusion	7.51	3.76	7.55	5.31
POMS Depression	6.79	8.97	7.68	11.28
POMS Fatigue	7.09	5.21	6.36	5.52
POMS Tension	8.89	7.36	8.87	7.77
POMS Vigor	12.43	6.00	13.30	5.98

Note. Higher scores on the Profile of Mood States (POMS) indicate a higher intensity of the indicated mood.

* $p < .05$ indicates that scores during the menstrual phase and luteal phase significantly differ.

be associated with E2 levels (Duff & Hampson, 2000; Leeners et al., 2017; Segal, 2012). However, the effect of phase in the present study was significant and was opposite to the effect of phase found on the SPWM, where enhanced performance was seen during the luteal not menstrual phase.

In order to determine whether the effect of phase of cycle on the SPWM was still significant when the Corsi Block-Tapping task was treated as a covariate, a 2 x 2 x 3 mixed effects ANCOVA was performed on SPWM scores, in the same way as stated originally for the SPWM, however this time with the absolute change in score on the Corsi Block-Tapping task from menstrual to luteal phase treated as a covariate. The result of the ANCOVA indicated that there was no significant covariate effect, $F(1, 25) = 0.01$, $p = .932$. This suggests the phase of cycle effect found on the SPWM was statistically independent of changes in the passive span.

3.5 Other Control Tasks

3.5.1 Mooney-Harshman Closure

A 2 x 2 mixed effects ANOVA was performed on the Mooney-Harshman Closure scores². The dependent variables were the number of correctly identified items and mean time to a correct response.

A significant main effect of phase of cycle was found for mean time to a correct response, $F(1, 42) = 6.22$, $p = .017$ (see Table 3.1). Women required less time to correctly

² Two outliers were removed whose number of correctly identified items were ≥ 3 standard deviations below the mean. Scores that are ≥ 3 standard deviations below the mean are problematic since they are seldom seen in a healthy neurologically normal population, so it suggests that these participants did not understand the test, thus their scores are of questionable validity.

recognize the items during the menstrual phase, when E2 is low, compared to the luteal phase when E2 is high.

No significant main effect of phase was found for the number of correctly identified items, $F(1, 43) = 2.19, p = .147$. However, there was a significant interaction between order of testing and phase of cycle (a practice effect), $F(1, 43) = 6.29, p = .016$, whereby similar to the SPWM, scores tended to improve on the second session as a result of the previous exposure to the test. Due to the fact that improvement on session 2 was quite large in conjunction with a maximum potential score of 12, the test was no longer able to capture the full range of the E2 effect on session 2 (there was not enough upward range available on the test for the hormone effect to be fully revealed). In other words, the scores had approached ceiling. Because the session 2 scores were therefore inadequate as a test of the phase of cycle effect, an independent samples t -test was run on the session 1 data only, comparing the number of items correctly identified by the two groups of women (i.e. women tested during the menstrual phase and women tested during the luteal phase on session 1).

The t -test revealed a significant effect of phase of cycle, $t(41.84) = 2.67, p = .011$ (see Table 3.1). A greater number of items were identified by women at the menstrual phase. Enhanced performance during the menstrual phase, when E2 levels are low, is the *opposite* of what was seen on the SPWM. This demonstrates that the menstrual cycle-related effect observed on the SPWM is selective. Higher E2 did not have an overarching facilitative effect on all brain functions.

3.5.2 North American Adult Reading Test (NAART)

An independent samples *t*-test revealed that both groups of women (i.e. women tested during the menstrual phase first and women tested during the luteal phase first) were evenly matched on the NAART with respect to estimated FSIQ, $t(44) = 0.31$, $p = .759$ (see Table 3.1).

3.5.3 Profile of Mood States (POMS)

A 2 x 2 multivariate ANOVA was performed on the POMS, with scores on the six POMS subscales (i.e. Anger, Confusion, Depression, Fatigue, Tension, Vigor) as the six dependent variables. The results showed no significant multivariate effect of phase of cycle on the POMS scores, $F(6, 40) = 1.47$, $p = .214$. Additionally, all univariate results were non-significant, $p < .323$ (see Table 3.1). Therefore, it is unlikely that the phase of cycle effects observed on our main cognitive tasks were attributable to changes in mood state between the menstrual and luteal phases of the cycle.

3.6 Correlations Between Estradiol and Main Tasks

The group differences presented above are consistent with the possibility that E2 did affect the sEBR and SPWM tasks. If the effect is mediated by E2, and not some other variable coincidentally associated with the menstrual cycle, then we might expect to observe a correlation between individual differences in the quantity of E2 present at the time of assessment and scores achieved on the tasks. Over the normal healthy menstrual cycle there is a very large amount of variance of E2 concentration observed within and between individual women, as well as between one woman's ovarian cycles.

Therefore, Pearson product-moment correlations were used to examine the relationship between salivary E2 concentration and scores on the SPWM, sEBR, and the Mooney-Harshman Closure (the tasks that showed significant phase of cycle effects in the ANOVAs). For sEBR the variable used, as above, was the sEBR during the luteal phase expressed as a percent of baseline sEBR and the corresponding estrogen variable was the percent of baseline E2.

As shown in Table 3.2, higher E2 was associated with a lower number of working memory errors on the SPWM (on session 2), which reached statistical significance for the total number of errors over all three trials ($r = -.44$, $p = .020$).

As shown in Table 3.3, the correlations were modest but positive for sEBR, and they approached significance for 3 of the 5 time bins that were examined.

We also found a significant correlation between E2 concentration and the number of correctly identified images on the Mooney-Harshman Closure task ($r = -.33$, $p = .025$). Higher E2 was associated with a lower number of correctly identified items. For the Mooney-Harshman task, only session 1 data was analyzed due to the practice and ceiling effects that were present in the session 2 closure data.

Because our sample size was modest, our power to detect correlations was limited. Therefore these correlations were considered purely exploratory.

Table 3.2

Pearson's Correlations Between Number of Working Memory Errors on the Spatial Working Memory Task and Salivary Estradiol Concentration (n = 28)

	WME Trial 1	WME Trial 2	WME Trial 3	WME Total
Session 1 E2	.08	.19	.21	.21
Session 2 E2	-.25	-.51**	-.32	-.44*

* $p < .05$, ** $p < .001$

Table 3.3

Pearson's Correlations Between Salivary Estradiol and Blink Rate During the Luteal Phase as a Percent of Menstrual Phase Values (n = 37)

Time Bin	Pearson's r	p value
1	.27	.123
2	.16	.390
3	.32	.069
4	.34	.053
5	.31	.078

Note. All *p* values displayed are for two-tailed tests of significance.

Chapter 4

Discussion

The objective of the current study was to test whether performance on DA-dependent tasks is sensitive to changes in E2 over the human menstrual cycle. Our hypothesis was based on the well-established connection between E2 and DA that has been seen in the nonhuman animal literature, as well as the knowledge that spatial WM, reinforcement learning, and sEBR rely heavily on DA-activity in the human brain. In particular, a multitude of studies indicate that increased DA activity is associated with enhanced WM (Brozoski et al., 1979; Daniel et al., 1991; Ellis & Nathan, 2001; Goldman-Rakic, 1995, 1996; Jacobs & D'Esposito, 2011; Lange et al., 1992; Sawagushi & Goldman-Rakic, 1991), increased sEBR (Cavanagh et al., 2014; Groman et al., 2014; Jongkees & Colzato, 2016; Kaminer et al., 2011; Karson, 1983), increased learning from positive reinforcement, and decreased learning from negative reinforcement (Cox et al., 2015; Frank, 2005; Frank & Kong, 2008; Frank et al., 2007; Frank & O'Reilly, 2006; Frank, Seeberger, et al., 2004; Lighthall et al., 2013; Maia & Frank, 2011; Mink, 1996; Slagter et al., 2015).

Two of the three tasks supported our hypothesis. As predicted, the results of our study showed an association between the E2 status of naturally cycling women and task performance on the SPWM and sEBR. Specifically, women showed significantly better working memory performance and a significantly higher sEBR during the high E2 luteal phase of their cycle, compared to the low E2 menstrual phase. The direction of change

over the cycle was in the predicted direction on both tasks. No effect of E2 status was found on the PST, however.

Our working memory results are consistent with previous studies showing a beneficial effect of estrogen replacement therapy on working memory in postmenopausal women who were treated with exogenous estrogens (Duff & Hampson, 2000; Keenan et al., 2001; Krug et al., 2006). This is in addition to more recent findings in healthy naturally cycling younger women showing that high E2 phases of the menstrual cycle are associated with superior WM performance compared to the menstrual phase (low E2) (Hampson & Morley, 2013). Although the biochemical basis for these effects is not presently known, one hypothesis is that changes in DA levels are responsible. As discussed, WM performance has been robustly found to depend on DA activity in the dlPFC (for review, see Ellis & Nathan, 2001), with depleted DA in the dlPFC being associated with poorer spatial WM performance (Brozoski, Brown, Rosvold, & Goldman, 1979). Therefore, the change in spatial WM performance between the high and low E2 phases of the menstrual cycle is plausibly due to changes in DA level in the dlPFC. Since E2 has been seen to increase DA activity in a large body of animal research (for review see Etgen & Garcia-Segura, 2010) and E2 receptors have been found in the human dlPFC (Montague et al., 2008; Perlman et al., 2005), this result lends preliminary support to our hypothesis that E2 is affecting DA activity in the human female brain.

The selectivity of our WM results being dependent on DA is strengthened by the results found on our two WM control tasks, both of which depend on posterior regions of the brain (Baldo & Dronkers, 2006) as opposed to the PFC (D'Esposito & Postle, 1999; Postle et al., 1999). Specifically, no effect of phase of cycle was found on the Forward

Digit Span task, a task in which performance does not appear to be DA-dependent, as seen through patient (Warden et al., 2016) and pharmacological studies (Kimberg & D'Esposito, 2003). Unexpectedly, we did find a significant phase of cycle effect on the Corsi Block-Tapping task, which similarly to the Digit Span task, does not appear to be dependent on DA levels (Kimberg & D'Esposito, 2003; Morris et al., 1988). It is possible that the menstrual cycle effect on the Corsi Block-Tapping task is due to performance being affected by another neurotransmitter or group of neurotransmitters, however an estrogen-related effect on the Corsi Block-Tapping task has not been seen in previous literature (Duff & Hampson, 2000; Hampson et al., 2015; Leeners et al., 2017; Segal, 2012). Importantly, an ANCOVA on SPWM scores with Corsi scores as a covariate indicated that there was no significant covariate effect. This means that the phase of cycle effect on the SPWM was independent of the effect observed on the Corsi task.

Additionally, our results for the Corsi task are in the opposite direction to what would produce a favourable effect on the SPWM, such that women tested during the low E2 menstrual phase had a *higher* span (better performance) than during the high E2 luteal phase. Therefore, we tentatively attribute the effect seen on the Corsi to a sampling variation and do not believe it to be consequential to our results. Therefore, the lack of an effect of phase of cycle (and therefore E2 level) on our control tasks, which are not strongly dependent on DA, in conjunction with the significant phase of cycle effect on the SPWM, support our hypothesis that E2 may be modulating spatial WM via a specific effect on DA pathways.

The argument that DA is responsible is bolstered to the extent that other tasks, that are also known to be heavily DA-dependent, exhibit a similar change under estradiol.

In agreement with the results on the SPWM, our sEBR results were also consistent with an estrogenic effect over the menstrual cycle. Specifically, the women in our study showed a significant increase in sEBR during the luteal phase when E2 is high compared to their sEBR during the menstrual phase when E2 is low. To our knowledge, the current study is the first to show that sEBR varies with the menstrual cycle. However, our results are consistent with a study by Chen, Chiang, Hsu, and Liu (2003), which reported that Chinese women over the age of 50 had significantly lower sEBR than younger women. Although this could be merely age-related, given that women over age 50 are likely to be postmenopausal this study points indirectly to the potential for an effect of E2 on sEBR in women. In addition, sEBR has been strongly linked to striatal DA and to D₂ receptor function (for review, see Jongkees & Colzato, 2016). Therefore, our finding of a change in sEBR over the menstrual cycle is consistent with the hypothesis that E2 affects DA activity.

While it is well known that spatial WM is dependent on the dIPFC, the neuroanatomy of the spontaneous eye blink response is not as well established. However, a small number of studies propose that DA activity at neurons in the spinal trigeminal complex are responsible for sEBR via the spontaneous blink generator circuit (Basso & Evinger, 1996; Basso, Powers, & Evinger, 1996; Evinger et al., 1993; Kaminer et al., 2011). Specifically, it is proposed that DA increases sEBR by inhibiting the spinal trigeminal complex via a pathway through the substantia nigra, superior colliculus, and nucleus raphe magnus. This pathway provides a possible mechanism by which an E2 mediated increase in DA may be affecting the sEBR in the women we studied.

Our results from the Mooney-Harshman Closure task indicate that our spatial WM and sEBR results are not due to an overall facilitative effect of E2 on brain function. Specifically, women showed a significant decrease in the time taken to correctly identify each image and a significant increase in the number of correctly identified images during the low E2 menstrual phase compared to the high E2 luteal phase. This low E2 advantage is in the opposite direction to what we found for sEBR and spatial WM and emphasizes the functional selectivity of E2's effects on perception and cognition. The direction of the effect is consistent with results observed on the Mooney-Harshman task in two earlier menstrual cycle studies, where the menstrual phase was likewise associated with significantly enhanced Mooney performance (Hampson, Finestone, & Levy, 2005; Segal, 2012; see also Maki, Rich, & Shayna, 2002). Additionally, studies have found accuracy on the Mooney-Harshman Closure to be negatively correlated with E2 levels in pregnant women (Hampson et al., 2015; Phillips, 2006). Therefore, the results on this task help to demonstrate that the effects that we saw on the SPWM and sEBR are due to the specific selective effects of E2 on the cognitive processes that we chose to study. The degree to which performance on the Mooney-Harshman task depends on DA pathways is unknown (Bondi, 1989; Doniger, Silipo, Rabinowicz, Snodgrass, & Javitt, 2001),

An exception to the support of our hypothesis that DA-dependent tasks would be influenced by E2 levels comes from our reinforcement learning findings. We found no significant phase of cycle effect on positive or negative reinforcement learning, which is a type of learning shown to depend upon DA activity in the striatum (Frank, 2005; Mink, 1996). Although it is possible that reinforcement learning is unaffected by E2 levels, it should be noted that the present study had limited statistical power to detect a significant

difference on the PST. Relative to other human menstrual cycle studies (Jacobs & D'Esposito, 2011; Nordstrom, Olsson, & Halldin, 1998; Wong et al., 1988), the current study had a large sample of participants, comparable to the numbers of participants normally used in studies employing the PST to assess healthy non-clinical participants (i.e., $n = 44$) (e.g., Frank & Kong, 2008). However, as mentioned, the PST is composed of both a learning and a test phase, and participants are required to reach a specified learning criterion during the learning phase in order to advance to the test phase of the task, which is used to analyze positive and negative reinforcement learning. Normally, about 75% of participants reach the learning criterion and move on to the test phase (e.g., Evans & Hampson, 2015; Rustemeier et al., 2012). This is what was observed for each session separately during our study. However, because our study utilized a repeated-measures design we lost an additional proportion of participant data because not all participants reached the learning criterion on both of their test sessions (66% retention rate).

While our end sample size of 31 for the PST was too small to detect a significant effect on either type of learning, the predicted pattern of means appeared to be present in women tested during the luteal phase first. These women displayed increased learning from positive reinforcement during the high E2 luteal phase, which in fact approached significance. This pattern is consistent with the sex difference reported on the PST in a recent study by Evans and Hampson (2015), which showed that females had significantly higher scores than males when learning from positive (but not negative) feedback. We do not have an explanation for why the same pattern was not observed for the group of women tested during the menstrual phase first. The small sample size of $n = 15$ women in

this group, combined with the high level of variance in performance between and within individuals, may simply have combined to occlude any potential effect. It is important to note that the set of women who were tested during the *luteal* phase first showed *enhanced* positive reinforcement learning during their first session and *reduced* learning during their second session, suggesting that their superior performance during the luteal phase was not due to the effects of practice or prior experience with the test, and therefore may represent a true phase of cycle effect.

In order to avoid the issue we faced with respect to data loss for the PST analysis, future research should either utilize a between-subject study design, so that two sessions are not required, or else a modification to the learning criteria that are normally used in PST studies may be necessary. We used standard criteria for the AB, CD, and EF pairs. However, because analysis of positive and negative reinforcement learning is specifically based upon learning the AB pair, it may be beneficial to change the learning criterion for the CD and EF pair, to be less strict. Alternatively, the task could be given as usual, but with all participants gaining access to the test phase after 480 trials, regardless of whether or not they had reached the passing criterion. This strategy would allow researchers to include as many participants as possible.

More generally, the use of a repeated-measures design in the present study had both strengths and limitations. Each participant was tested twice during her menstrual cycle and therefore acted as her own control. While the use of a repeated design increases study validity and allows us to conclude that our results are not due to a group difference in IQ, demographics, or other extraneous subject variables, this type of design introduces the issue of practice effects on cognitive tasks. Practice effects are a possible occurrence

in any cognitive research that requires participants to perform the same task on more than one occasion. While a simple increase in scores upon second exposure is not problematic, practice effects can interfere with validity of the testing if they are large enough to cause ceiling effects, or if a participant switches to a different strategy or approach to solving a task so that it does not measure exactly the same construct on the second occasion (Calamia, Markon, & Tranel, 2017). Practice effects pose a special threat to validity for tasks that have a “discovery” element. In the current study, we encountered a ceiling effect on session 2 in the Mooney-Harshman closure data, causing us to resort to analyzing session 1 data on its own.

Once the assay results are available, it will also be important for the present study to assess the contribution, if any, of progesterone to the present findings. Due to the nature of the human menstrual cycle, it is difficult to completely segregate E2 from progesterone, which is another hormone that is also high during the luteal phase and low during the menstrual phase. Past research has shown no effect of progesterone on WM (Duff & Hampson, 2000; Grigorova et al., 2006; Hampson et al., 2015; Hampson & Morley, 2013; Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Güntürkün, 2000; Maki et al., 2002; Segal, 2012). For instance, WM performance of postmenopausal women taking combined therapy did not differ from the performance of women taking estrogens alone. Because no association between progesterone and WM has been found in past studies, no association of progesterone with the SPWM was anticipated here. In contrast, however, the present study is the first human or nonhuman work to study sEBR and the menstrual cycle, so it is not presently known if progesterone as well as E2 might influence the sEBR. Additionally, rodent studies have found estradiol benzoate (EB)

(Bazzett & Becker, 1994; Becker & Rudick, 1999) and E2 (Morissette, Biron, & Di Paolo, 1990; Peris, Decambre, Coleman-Hardee, & Simpkins, 1991), but not progesterone to increase striatal DA activity. Alternatively however, a small number of conflicting rodent studies suggest that progesterone may actually oppose the effects of E2 on DA activity, by decreasing DA release and increasing activity of DA transporters in E2-primed animals (Dluzen & Ramirez, 1984; Luine & Rhodes, 1983). Therefore, we plan on analyzing progesterone via the saliva samples collected from our participants, in order to run correlational analyses between progesterone and performance on our main tasks. As mentioned, progesterone concentrations were not available at the time of writing. However, it is important to note that if progesterone does oppose the effect of E2 on DA activity *and* if progesterone is correlated in the reverse direction with our results, then the significant effects we found on our main tasks would only be strengthened.

In the future, in order to divorce the effects of E2 and progesterone, researchers could sample women during the menstrual phase and the preovulatory E2 peak, when progesterone has not yet risen to a significant degree. The reason why the preovulatory peak was not used in the current study, and is rarely used in menstrual cycle research, is because the preovulatory E2 peak is extremely transient (much more so than during the luteal phase) and therefore difficult to accurately pinpoint prospectively. Typical subject loss in such studies, due to failure to successfully target the timing of the preovulatory E2 peak, is $\geq 50\%$. Menstrual cycle studies are already based on probabilistic estimations of menstrual cycle length, and the timing of ovulation in any given cycle can additionally be affected by many outside factors, such as stress. Testing women during the preovulatory window, while worthwhile and important, would require much larger initial sample sizes

to account for the greater anticipated subject loss, and needs to employ rigorous phase of cycle verification. It is recommended that participant menstrual cycles be monitored for multiple months prior to testing in order to gain a more accurate understanding of their typical cycle length and variability so that testing can be accurately timed to preovulation.

The present study is among the first to provide empirical support for the hypothesis that DA-dependent cognitive processes vary over the human menstrual cycle in conjunction with E2 levels. No task is solely dependent on only one neurotransmitter, however. In an effort to focus the research, we chose tasks that have been established in cognitive neuroscience studies to depend prominently on DA (see Introduction) and that possess adequate sensitivity to reflect changes in DA levels. In addition, not one but multiple DA-dependent tasks were assessed simultaneously, in the same women. Covariation across multiple tasks sharing a common denominator (a high degree of reliance on DA transmission) helps to reinforce conclusions in terms of DA, even though the tasks may vary in the degree to which other biochemical pathways also contribute. This thesis work is part of a larger ongoing study investigating genetic polymorphisms in DA-related genes that can influence individual's baseline DA level. DNA data, collected for each participant, will eventually allow us to determine whether there is any interaction effect between baseline DA level and E2 status on cognitive task performance. This will help to better understand if DA is the main mechanism underlying changes in our main tasks. In the future, imaging techniques, such as PET, could be incorporated into this type of research, to more directly understand the relationship between E2 and DA.

In conclusion, our findings provide preliminary evidence that E2 over the menstrual cycle affects central DA function in humans. This study is the first of its kind

and paves the way for future research looking at the effect of endogenous hormones on neurotransmitter activity in humans, which will continue to provide insight into female cognition and mental health.

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**Western University Non-Medical Research Ethics Board
NMREB Delegated Initial Approval Notice**

Principal Investigator: Prof. Elizabeth Hampson
Department & Institution: Social Science/Psychology, Western University

NMREB File Number: 107904
Study Title: Estrogen, Dopamine and Cognition
Sponsor: Natural Sciences and Engineering Research Council

NMREB Initial Approval Date: May 17, 2016
NMREB Expiry Date: May 17, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Other	Debriefing Form	2016/03/31
Western University Protocol	Received May 12, 2016	
Other	Revised Follow-up Email Contact - Ineligible - Received May 12, 2016	
Letter of Information & Consent	Study Visit #1	2016/05/12
Letter of Information & Consent	Screening Questionnaire	2016/05/12
Instruments	Session Two Questionnaire - Received May 12, 2016	
Instruments	Session One Questionnaire - Received May 12, 2016	
Instruments	Screening Questionnaire - Received May 12, 2016	
Recruitment Items	Standardized Initial Email Letter - Received May 12, 2016	
Advertisement	Revised Recruitment Poster - Received May 12, 2016	
Advertisement	Recruitment Ad for Western News and Gazette - Received May 12, 2016	
Instruments	Forward Digit Span stimuli - Received May 12, 2016	
Instruments	Landscape images to be shown in the eye tracking task, Set 2 - Received May 12, 2016	
Instruments	Landscape images to be shown in the eye tracking task, Set 1 - Received May 12, 2016	
Instruments	Photo of remote eye tracker - Received March 23, 2016	
Instruments	Stimuli to be used for the PST task - Received March 23, 2016	
Other	Follow-up Email Letter for Eligible Participants - Received March 23, 2016	
Instruments	Corsi Block Tapping_photo of the block apparatus - Received March 23, 2016	
Instruments	Mooney Harsman Closure Task_stimuli to be used - Received March 23, 2016	
Instruments	Profile of Mood States - Received March 23, 2016	
Instruments	Spatial Working Memory Task (SPWM) - Received March 23, 2016	
Instruments	NAART Task_List of words to be used - Received March 23, 2016	

The Western University Non-Medical Research Ethics Board (NMREB) has reviewed and approved the above named study, as of the NMREB Initial Approval Date noted above.

NMREB approval for this study remains valid until the NMREB Expiry Date noted above, conditional to timely submission and acceptance of NMREB Continuing Ethics Review.

The Western University NMREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the Ontario Personal Health Information Protection Act (PHIPA, 2004), and the applicable laws and regulations of Ontario.

Members of the NMREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The NMREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000941.

Ethics Officer on behalf of Dr. Riley Hanson, NMREB Chair or delegated board member

Ethics Officer to Contact for Further Information: Erika Basile ___ Nicole Kamiki ___ Grace Kelly ___ Katelyn Harris ___ Vikki Tran ___

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Honours and Awards: Dean's Honor List
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