

ABSTRACT

Title of Dissertation: CAFFEINE ABSTINENCE DURING THE
 MENSTRUAL CYCLE: AN EVALUATION
 OF MOOD COGNITIVE AND
 PSYCHOMOTOR EFFECTS OF
 WITHDRAWAL

Hoa T. Vo, Doctor of Philosophy, 2008

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 Psychology

The current is a study that extends our understanding of caffeine consumption patterns and withdrawal symptoms across the menstrual cycle. Forty-eight moderate habitual caffeine consumers, ages 18 to 25 years, were recruited from the University of Maryland. Exclusion criteria included current or past psychiatric conditions (within six months) and premenstrual syndrome (PMS). In addition to daily diaries (including the caffeine intake survey, premenstrual syndrome questionnaires, LH surge test, and the caffeine withdrawal checklist), the effect of caffeine abstinence on psychomotor tasks were assessed during the follicular (around day 5 of the menstrual cycle) and luteal phases (approximately 4 days after LH surge) of the menstrual cycle. Data analyses focused on withdrawal symptom ratings and psychomotor performance one day during the follicular phase and one day during the luteal phase of the cycle after 24 hours of caffeine abstinence. A series of repeated measures ANOVA were used to

compare within-subject differences on caffeine withdrawal and psychomotor performance during the follicular and luteal phases. The present data do not provide support for phase-differentiated effects of self-reported withdrawal symptoms or of psychomotor and cognitive performance differentials across the menstrual cycle. However, withdrawal, as a result of caffeine abstinence, did impact self-reported withdrawal ratings during select days of non-abstinence and days of abstinence during the both the follicular and the luteal phase. The present study is the first multi-method study to examine the effects of caffeine abstinence on habitual consumers across the menstrual cycle. The current findings provide evidence for caffeine withdrawal symptoms.

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EVALUATION OF MOOD COGNITIVE AND PSYCHOMOTOR EFFECTS OF
WITHDRAWAL

by

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Dedication

For my family; my parents who dedicated their life to this endeavor and my siblings, Kenny, Thịnh, Hiệp, Cường, and Giao, who provided support and love.

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Chapter 1: Introduction

Section 1: Study Purpose

Regular caffeine users often experience symptoms of withdrawal when they are abstinent (Juliano & Griffiths, 2004), and evidence suggests that the effects of this powerful stimulant vary with the phase of the menstrual cycle (Turner & Wit, 2006). Taken together, these observations suggest that the symptoms associated with caffeine abstinence in regular users should vary systematically as a function of menstrual cycle phase. The purpose of the present study is to assess the phase-differentiated cognitive, motor, and subjective mood and somatic withdrawal symptoms of caffeine abstinence in regular consumers of the drug.

Section 2: Background

Despite widespread interest in the interaction of phase-related menstrual physiology with caffeine consumption and withdrawal, there is a very limited body of relevant literature. In fact, only three studies have collected data across the menstrual cycle and addressed related caffeine effects (Pomerleau, et al., 1994; Rossignol, Bolander, & Phillis, 1991; Vo, Smith, & Rubinow, in preparation). All three investigations lacked hormonal verification of the cycle phase, which makes it more difficult to assess their results.

Vo and colleagues suggested that caffeine consumption pattern varies systematically across the menstrual cycle, as a function of the varied hormonal substrates that dominate the various phases of the cycle (Vo et al., in preparation). They found that that caffeine consumption was lower during the luteal than during the follicular phase, a

finding consistent with that of an unpublished investigation noted in a review article by Terner and Wit (2006). On the contrary, Rossignol and associates found no differences in the level of caffeine intake across the menstrual cycle (Rossignol et al., 1991). A second study, examining caffeine consumption across the menstrual cycle and using daily menstrual symptom diaries (Pomerleau, et al., 1994), likewise showed no differences in the level of caffeine intake across the menstrual cycle. It should be noted that this study employed a relatively small sample size ($N = 22$). It is clear that work to date has yielded mixed, inclusive results, thus warranting further investigation of the caffeine-menstrual cycle relationship.

Menstrual Physiology

Caffeine metabolism is modulated by the presence of reproductive hormones that vary with cycle phase (Fenster et al., 1999; Lucero et al., 2001; Stafford, Rusted, & Yeomans, 2007), hypothetically impacting both mood and psychomotor performance (Arnold et al., 1987). Briefly, the menstrual cycle consists of two predominate phases. The follicular phase is characterized by the increasing levels of estradiol, while progesterone is present primarily during the luteal phase (Vo, Smith, & Elmi, 2007). It is believed that the presence of estradiol during the follicular phase, in most women, is responsible for feelings of well-being, while significant increases in the levels of progesterone during the luteal phase are associated with negative mood states, impaired judgment, biased memory recognition (Rubinow, Smith, Schenkel, Schmidt, & Dancer, 2007), increased stress response (Frag, Vincent, McKey, Al'Absi, Whitsett, et al., 2006), and lowered psychomotor performances (Lieberman, Tharion, Shukitt-Hale, Speckman, & Tulley, 2002).

The interaction of caffeine with reproductive hormone substrates is based on the nature of the drug and its impact on physiology (Figure 2). Caffeine is an adenosine antagonist that binds to adenosine receptors, which reduce the inhibitory effects of the neurotransmitters that then result in increased excitation of the affected neural systems (Institute of Medicine, 2001). Since the central nervous system is responsible for the production of steroid hormones, including estradiol and progesterone, the depressant action of adenosine may be influenced by increases and decreases in the production of these hormones (Kaminori, Joubert, Otterstetter, Santaromana, & Eddington, 1999; Mandal, Batabyal, & Poddar, 2007).

Caffeine and Menstrual Physiology

A recent study found that long-term administration of caffeine in female mice decreased the production of progesterone (Mandal et al., 2007). Studies in rats have shown that the administration of progesterone suppresses the spontaneous firing of cerebral cortical neurons and prolongs the mean duration of adenosine-evoked inhibitors by about 56% (Phillis, 1985). Progesterone potentiates the action of adenosine (Phillis, 1986) by inhibiting its reuptake into neurons and glial cells. This action creates higher concentrations of adenosine in extracellular space, allowing for greater experiences of fatigue and depression associated with the luteal phase of the cycle for most women (Lucero, 2001). Because caffeine administration produces physiological reactions that reduce the effects of progesterone during the luteal phase, caffeine abstinence during this phase would then yield the opposite effect, thereby impairing psychomotor performance and increasing withdrawal symptoms. It is important to note that most women experience mood symptoms associated with increasing levels of progesterone during the luteal

phase, with or without caffeine (Teiner & Wit, 2006). However, it is theorized that in habitual caffeine consumers, abstinence of caffeine exacerbates these mood symptoms as a result of withdrawal effects (Juliano & Griffiths, 2004).

Unlike progesterone, estradiol increases the firing of relatively few neurons (approximately 9% compared to 42% attributable to progesterone; Phillis et al., 1985), resulting in only a weak ability to inhibit adenosine transport (Phillis, 1991). In effect, estradiol is much like caffeine, in that it feebly antagonizes the inhibitory actions of adenosine (Fenster et al., 1999). Phillis (1991) suggests that although estradiol concentration in the extracellular fluid of the brain is unlikely to reach levels at which the activity of the adenosine transporter is compromised, it may be sufficient to antagonize the actions of endogeneously released adenosine, exerting caffeine-like stimulating action on the central nervous system (CNS). Such action could account for the positive emotions attributed to the follicular phase of the cycle.

In sum, a moderate dose of caffeine enhances mood and psychomotor performance by inhibiting adenosine receptors (James, 1997; Smith, Gupta, & Gupta, 2007) and the presence of estradiol should facilitate the stimulating effect of caffeine (Phillis et al., 1991; Vo et al, in preparation); therefore, the interaction of the two substances may enhance psychomotor performance and alleviate withdrawal symptoms. On the other hand, progesterone inhibits the reuptake of adenosine, leading to an increased concentration of adenosine particles in the extracellular space that then manifests in more fatigue, depression, and sedative-type activities (Lieberman et al., 2002; Rubinow et al., 2007). As demonstrated, the action of caffeine is facilitated by the presence of estradiol and inhibited by progesterone. As such, the fluctuation of

progesterone and estradiol during the menstrual cycle also implicates differential physiological processes and withdrawal manifestations as it interacts with the absence of caffeine in habitual caffeine users.

The theory posited (Appendix A: Literature Review; p. 53) suggests phase-differentiated interactions between caffeine and the menstrual cycle. Therefore, differential caffeine withdrawal symptoms can also be posited. More specifically, caffeine abstinence may lead to differences in the severity of withdrawal symptoms experienced and in the level of impairment on psychomotor performance, during the luteal phase, as a function of (1) increasing levels of progesterone and decreasing levels of estradiol (2) the “dual-vulnerability factor”. First, progesterone is increased during the luteal phase, which leads to more mood and somatic symptoms that may impair cognitive and psychomotor performances (James, 1997; Lieberman et al., 2002). Secondly, the “dual-vulnerability factor” refers to the direct effects of progesterone on mood and then the addition of withdrawal in women who are habitual caffeine consumers. While habitual users experience withdrawal during the follicular phase, they are liberated (users and non-users alike) from the mood experiences associated with naturally occurring hormones.

On the contrary, during the follicular phase, regular caffeine consumption has also been shown to increase level of estradiol (500-mg/day can lead to estradiol increases up to 70% during the follicular phase; Lucero et al., 2001). Likewise, estradiol helps enhance memory functions (Rubinow et al., 2007; Stafford et al., 2007) and mood (Phillis 1991). Because caffeine administration enhances performance on tasks that tap at attention, lack of caffeine in both cycle phases will hinder performance during both

phases unless moderated by the effect of improvements on memory functions and alleviated-withdrawal during the follicular phase. In which case, it would be reasonable to expect that performance on attentional tasks to be better during the follicular when estradiol is high and memory and mood is better than the luteal phase.

It is also of practical significance that women generally experience more impairment than men during caffeine abstinence. Noting its methodological limitations, a community-based study of over 11,000 participants showed that among caffeine users 5.5% of females, compared to 0.9% of males reported symptoms significant enough to interfere with normal daily activities upon abrupt termination of caffeine (Dews, Curtis, Hanford, & O'Brien, 1999). Because females typically report more functional impairment compared to males, it is important to focus first on females in order to detangle possible effects of the menstrual cycle. Current results may inform further directions on caffeine withdrawal in women (Evans & Griffiths, 1999; Juliano & Griffiths, 2004). More importantly, understanding caffeine processes and withdrawal symptoms across the menstrual cycle may help women find an opportune timeframe during their cycles to reduce consumption.

Section 3: Study Rationale

In sum, the current project seeks to contribute to the research on caffeine intake across the menstrual cycle while also evaluating withdrawal symptoms (Appendix A: Literature Review; p. 43) and psychomotor performance in caffeine-abstinent-women during the follicular and luteal phases. Prior studies that have examined the effects of caffeine have typically employed mixed-sex samples (Christopher, Sutherland, & Smith, 2005; Rogers & Dencourt, 1998; Rogers et al., 2005; Warburton et al., 2001); these

studies obviously do not take into account the interaction of caffeine with menstrual physiology (Stafford, Rusted, & Yeomans, 2007).

Section 4: Study Aims and Hypothesis

Aim 1: To examine the effect of caffeine abstinence on psychomotor performance (e.g., memory and attentional tasks) and withdrawal symptoms (mood and somatic).

1. Concerning the effects of caffeine abstinence on memory performance (e.g., quality of working, speed, and episodic secondary memory; refer to description of Cognitive Drug Research battery), it is hypothesized that caffeine abstinence during the luteal phase will impair all memory related tasks due to heightened levels of progesterone (Rubinow et al., 2007) and the lack of estradiol because estrogen depletion is associated with impairments in memory functions (Paganinihill & Henderson, 1994; Williams, 1998; Gibbs & Aggarwal, 1998). On the contrary, increasing levels of estradiol during the follicular phase should also yield better performance on memory tasks. Therefore, it is likely that differentiated hormonal productive, specific to each phase of the menstrual cycle moderates that effect of caffeine abstinence on withdrawal symptoms and memory-specific task performances (Fig. 1).

1a. Regarding reaction time and attentional tasks, which are primarily direct effects of caffeine administration and abstinence (Hewlett & Smith, 2006; Rogers et al, 2005; Stafford et al., 2007; Warburton et al., 2001), it is hypothesized that significant differences on attentional tasks will not be detected because caffeine abstinence is not manipulated in both phases. If differences were detected on attentional tasks across the menstrual cycle, it is then hypothesized that the effect is a function of (or

moderated by) improvements mood and memory functions as a result of the presence of estradiol (Stafford et al., 2007).

1b. Regarding the effects of caffeine abstinence on self-reported mood and somatic symptoms, it is hypothesized that caffeine abstinence will lead to more severe experiences of withdrawal during the luteal phase, due to the “dual-vulnerability factor” mentioned, than during the follicular phase.

1c. In addition, it is also hypothesized that withdrawal symptoms were negatively correlated with level of performance on attentional tasks. That is, if mood is alleviated during the follicular phase, then performance on attentional tasks would also enhance.

Aim 2: To evaluate the level of caffeine intake in relation to phases of the cycle.

2. It is hypothesized that women will consume higher levels of caffeine during the follicular phase than during the luteal phase. Because caffeine is metabolized slower during the luteal phase (Fenster et al., 1999), less of it is needed during the luteal phase to achieve the same effects compared to the follicular phase. This is in line with previous findings (Vo et al., in preparation).

Chapter 2: Methods

Section 1: Definition of Cycle Phase

Definitions of cycle phases are adopted from Allen and colleagues (1996) and are similar to those used in many other studies (Allen, Hatsukami, Christianson, & Nelson, 1996; Hellstrom & Lundberg, 2000; Soderberg, Sundstrom Poromaa, Nyberg, Backstrom, Nordh, 2006). The first day of bleeding were defined as Day 1 of the menstrual cycle. The two cycle phases were defined as follows: the first day of the follicular phase as day 5 of the menstrual cycle; the 1st day of the luteal phase as 4 days after the luteinizing hormone (LH) surge as determined by hormonal verification using midstream ovulation test strips (see below).

Section 2: Participants

The present study is a repeated-measures design examining caffeine intake and withdrawal symptomatology in 63 undergraduate female students at the University of Maryland after screening procedures. After excluding participants with premenstrual syndrome (PMS; n=7), with incomplete daily diaries (n=6) and CDR data (n=2), the final sample consisted of 48 students, ages 18-25 ($M = 19.96$, $SD = 1.28$; Table 1: Sample Racial Distribution). Of the 48 participants (Table 2: Demographical Variables), 7 (14.3%) smoked, 12 (24.5%) reported current and history of familial depression (at least one person within the immediate family that had or is suffering from depression), 25 (51.0%) using oral contraceptives, and 1 who is married.

Participants were recruited from undergraduate psychology courses. Exclusion criteria during the screening phase included: pregnancy, diagnosed psychiatric condition (Kim et al., 2004; Akdeniz & Karadag, 2006) within the past six months, history of and/or current illicit drug use (Odber et al, 1998; Roca et al., 2003), irregular menstrual cycle, and failure to consume at least 200-mg of caffeine per day. Psychiatric conditions were an exclusion criterion because pathological depression and anxiety may affect hormonal changes in women across the menstrual cycle, thereby affecting physiological and neurological responses to caffeine abstinence (Kooiman, Jansen, & Peeters, 2007). Psychiatric disorders such as depression or anxiety disorders are also highly comorbid with experiences of PMS symptoms (Williams, Richards, Ameen, & Davies, 2007). Failure to account for the variables mentioned may confound the current purpose.

Section 3: Apparatus

The Participant Screening Form (Appendix B) is a demographic questionnaire created by the researcher that elicits the following information: age, marital status, racial and/or ethnic identity, current medication(s) regime, smoking habit, and level of habitual caffeine intake.

The Physician Health Questionnaire (PHQ; Spiller, 1997; Appendix C) is a tool provided to help primary care practitioners quickly diagnose mental disorders. The full PHQ is a four-page questionnaire derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD; Spiller, 1997). The first three pages assess for common mental disorders (somatoform, mood, anxiety, eating, and alcohol) and functional impairment. Many clinicians use only these first three pages, or only components, such as the 9-item depression module (PHQ-9; Spitzer et al., 1999). The fourth page includes questions

about recent stressors and, for women, questions regarding menstruation, pregnancy and childbirth. The measure has excellent internal and test-retest reliability with Cronbach's alpha value of above 0.84 in three different studies (Kroenke et al., 2001). Additionally, internal validity was 0.86 and validity of 0.70 and around that range depending on the disorder. The PHQ can detect major depression best (0.88) and is not as sensitive for detecting bodily pain (0.33). The current project included all four pages of the PHQ. The current study used PHQ instead of the Structured Clinical Interview for the DSM-IV (SCID-I) in order to save time. The PHQ has been proven to be very effective when used for research purposes even though its usage in clinical settings might be limited (Spitzer et al., 1999).

The Caffeine Intake Form (Appendix D) was used in the study to record daily caffeine consumption. It assesses the amount of consumption for various products containing caffeine. This form was included in the daily diaries.

The Self-Rating Scale for Premenstrual Tension Syndrome (PMTS-SR; Steiner et al., 1980; Appendix D) was used as part of the daily diary in order to record PMS symptoms. The correlation coefficients of the PMTS-SR compared with the Premenstrual Tension Scale for Others (PMTS-O) is 0.83 premenstrual and 0.84 postmenstrual as reported by Bergant and colleagues (2004). Reliability is 0.71 and 0.77 for the PMTS-O and PMTS-SR respectively. Thus, the PMTS-SR has predictive validity and is a highly reliable questionnaire used widely in PMS research. It is also a good cross-sectional measure. The PMTS-SR were used during the experimental phases also as a part of the daily diaries. This measure has been shown to be a reliable tool (Rubinow, & Schimdt, 1992; 1995) for detecting differences pre- and postmenstrually (Wewers & Lowe, 1990).

The Caffeine Withdrawal Questionnaire (Griffiths et al., 1990a; Subjective-Effects Questionnaire; Appendix D) is a checklist that asks participants to rate from 0 = (Not at all) to 3 (Very much) the extent to which they experience withdrawal symptoms (Table 3). The inventory assesses a total of 26 mood (e.g., irritability, depression) and somatic (e.g., lightheadedness, upset stomach,) symptoms. Studies assessing these symptoms show that 100-300-mg/day of caffeine results in a reliable caffeine withdrawal syndrome when a placebo is substituted. Moreover, caffeine withdrawal occurs whether the caffeine is ingested as a single dose in the morning or as three divided doses over the course of the day (Griffiths et al, 1990a; 1990b; Evans and Griffiths, 1992; 1999; Schuh & Griffiths, 1997). Juliano & Griffiths (2004) conducted a review consisting of 65 empirical studies from 1964 until 2004 and provided support for the symptoms used in this questionnaire.

The Cognitive Drug Research (CDR) test battery (20-25 minutes to administer) is a computerized battery of tasks used by researchers in the area of medical (e.g., aging and cognitive function after stroke) and psychological research (i.e. schizophrenia and short-term memory functioning) research. The battery has also been used in several relevant studies evaluating the role of caffeine and caffeine withdrawal (e.g., Haskell, Kennedy, Wesnes, & Scholey, 2005; Scholey & Kennedy, 2004); also of the effects of other drugs (Haskell, Kennedy, Wesnes, Milne, & Scholey, 2007; Kennedy, Scholey, & Wesnes, 2000). As demonstrated, this widely used battery (Haskell et al, 2005; 2007; Kennedy et al, 2000; Scholey & Kennedy, 2004) includes a series of motor and memory tasks designed to assess aspects of cognitive functioning.

Simple Reaction Time. This task measures reaction time. The word ‘YES’ appears in the middle of the screen at irregular intervals. Participants were instructed to press the right arrow key on their keyboard as quickly as possible every time the word ‘YES’ appears. This task measures pure reaction time - it assesses alertness, ability to concentrate on the screen and the speed of reaction to an expected event (Christopher et al., 2005; Haskell et al., 2005; 2007; Hewlett & Smith, 2006; Scholey & Kennedy, 2004).

Digit Vigilance. This task measures continuity of concentration on a series of rapidly changing digits. A single digit appears on the right hand side of the screen and remains there for the duration of the task. A continuous series of digits appears, one at a time, in the middle of the screen. Every time the digit in the middle matches the one on the right, participants were instructed to press the right arrow key as quickly as possible, even if the digit in the middle has disappeared. This task requires sustained vigilance; if the participant’s attention wanders then targets were missed. The percentage of target digits correctly detected and the average response time for these detections are recorded. The number of times that the subject responds incorrectly (i.e. the number of false alarms made) and also be measured (Christopher et al., 2005; Haskell et al., 2005; 2007; Hewlett & Smith, 2006; Scholey & Kennedy, 2004).

Choice Reaction Time. This task measures both reaction and decision making time. Either the word ‘YES’ or the word ‘NO’ appears on the screen at irregular intervals. Participants were asked to press the right arrow key as quickly as possible every time the word ‘YES’ appears. Participants are instructed to press the left arrow key as quickly as possible, every time the word ‘NO’ appears. This is similar to the Simple Reaction Time task. Again, the task assesses alertness and ability to concentrate on the screen, but it also

requires a further element of information processing so that the subject can choose the correct response. The average time taken to respond as well as the percentage accuracy of the responses were recorded (Haskell et al., 2005; 2007; Scholey & Kennedy, 2004).

Spatial Working Memory. This task examines spatial memory. A picture of a house with windows, some of which are lit, will appear on the screen. The house will stay on-screen for 15 seconds. Participants are instructed to remember the location of the lit windows in the house. When the house disappears, participants will press an arrow key to continue the task. A series of pictures of the same house will appear on the screen, one at a time. Only one window of each of these houses were lit. For each house shown, if the window lit was also lit in the original house, participants will press the right arrow key as quickly as possible. If the window lit was not lit in the original house, they will press the left arrow key as quickly as possible. This task measures the ability to retain and retrieve spatial information using working memory. It involves the visuo-spatial scratchpad of working memory. The percentage accuracy of responses, average response time, and sensitivity index were recorded (Haskell et al., 2005; 2007; Scholey & Kennedy, 2004).

Numeric Working Memory. This task measures how well a short series of numbers can be held in memory and how quickly the numbers can be recognized. It is similar to remembering a telephone number for a short period of time. Five numbers will appear on the screen, one at a time, to be remembered. The screen then shows the message "Get ready to respond". Following this, a further series of numbers will appear on the screen, one at a time. For each of these numbers, participants were instructed to press the right arrow key as quickly as possible if it is one of the numbers included in the original series. If it is any other number, they are instructed to press the left arrow key.

The numbers do not have to appear in the order in which they were originally presented – they simply need to be from the original series. The task measures participant’s ability to hold information in working memory and how rapidly it can be retrieved, reflecting the operation of the internal auditory loop in working memory. The percentage accuracy of responses, average response time, and sensitivity index was recorded (Haskell et al., 2005; Scholey & Kennedy, 2004).

Word Presentation & Word Recall. This is the presentation component of a verbal episodic memory task. A series of words will appear on the screen, one at a time, to be recognized during the second part of the assessment, the Word Recognition task. In this, a second series of words appear on the screen, which include the original words mixed with new words. The task is often combined with an Immediate and a Delayed Word Recall task where as many words as can be remembered from the list are written down within a 60 second time period. The recall tasks measure the ability to remember words and retrieve them from memory. The percentage of accuracy of the words recalled were recorded, as well as the number of errors (Haskell et al., 2005; Scholey & Kennedy, 2004).

Word Recognition: This task is the recognition component of a verbal episodic memory assessment. The words shown during the Word Presentation task are mixed with distractor words, appearing on the screen one at a time. If a word is recognized as being an original word (presented during the Word Presentation task), participants will press the right arrow key as quickly as possible. If the word was not shown previously, participants are instructed to press the left arrow key as quickly as possible. This task

measures the ability to store and retrieve verbal information. The speed and sensitivity index of the responses were recorded (Haskell et al., 2005; Scholey & Kennedy, 2004).

Picture Presentation. This is the presentation component of the episodic memory task. A series of pictures will appear on the screen, one at a time, to be recognized during the second part of the assessment, the Picture Recognition task. In this, a second series of pictures will appear on the screen, which include the original pictures mixed with new similar pictures (Haskell et al., 2005; Scholey & Kennedy, 2004).

Picture Recognition: This task is the recognition component of an episodic memory assessment. The pictures shown during the Picture Presentation task are mixed with similar distractor pictures, appearing on the screen one at a time. If a picture is recognized as being an original picture (presented during the Picture Presentation task), participants are instructed to press the right arrow key as quickly as possible. If the picture was not shown earlier, they are to press the left arrow key as quickly as possible. This task measures the ability to store and retrieve pictorial information. The speed and sensitivity index of the responses were recorded (Haskell et al., 2005; Scholey & Kennedy, 2004).

Major measures are measures which, if affected, reflect upon the overall efficiency of the performance of the task. Supportive measures are those which, if affected by study treatment, will not in themselves reflect on the actual ability to perform the task, but was important in modulating the interpretation of any changes in the major measures. The overall procedure is therefore to determine whether any changes occurred for any of the major measures. If any changes occurred, an interpretation of the

consequence for task performance is made taking into consideration changes in any other measures of that task.

Ovulation test is a Midstream Test that works by detecting the “LH Surge,” the dramatic increase in luteinizing hormone that takes place before ovulation. The test has sensitivity to 20mIU/ml/lh, 99.9% accurate in anticipating ovulation, and 99.8% specificity (www.earlypregnancytest.com). To use, participants simply remove the cap and urinate directly onto the absorbent tip for several seconds. In five minutes results appeared on the window of the strip. Personal consultation with a professional in the field suggests that even though the brand name of the test is concealed, the LH testing technology is advanced enough to assume that the current device used is reasonably accurate (personal communication, D. R. Rubinow, M.D., March, 2007; Hedricks, Piccinino, & Udry, 1991).

Section 3: Procedures

The present study included three phases, orientation, daily diaries, and laboratory phase. Participants were required to attend an orientation to receive instruction for the study, and also to sign informed consents.

Subsection 1: Orientation

All potential participants were asked to attend an orientation session that can last up to 90 minutes. During the orientation session, participants signed informed consent (Appendix G) and underwent an initial interview with a trained undergraduate research assistant. The interview consisted of the Participant Screening Form and the PHQ. In the event that a participant did not meet

inclusion criteria, she was awarded 1 participation credit and was told she does not meet criteria to participate in the study. Qualified participants were given instructional handouts (Appendix F) and procedural demonstrations for (1) testing for ovulation using the provided kit, (2) accessing their daily diaries online, and (3) practicing computerized tasks. First, participants received instructions on how to complete the urine test using the ovulation kit every night and how to report the test result (negative or positive) on their daily diaries the following morning (Appendix D). Second, the researcher showed participants (one-on-one) how to access the daily dairies online using their University login and password. If participants were unable to login, the researcher helped troubleshoot. Third, participants had a chance to familiarize themselves with the CDR computerized tasks described above. The Cognitive Drug Research battery has standardized practice sessions that run approximately one hour long. These practice tasks were separate from those that were used during the actual testing sessions. This procedure helped ensure that participants understand the nature of each individual task in order to reduce carry-over effects during the two assessment sessions. In addition, the training session helped overcome initial test anxiety, helped familiarize participants with test procedures, and also enabled them to develop strategies for each task. Of note, all previous studies have maintained the order of each individual task within the CDR battery (Haskell et al., 2005; Scholey & Kennedy, 2004), and the present study therefore did the same.

Subsection 2: Daily Dairies

Participants proceed with daily entries online at the same time every morning for two complete menstrual cycles (approximately 60-80 days, depending on individual cycle length). Daily dairies were completed at the same time each morning to account for possible confounding variables, such as the time-of-day-effects on mood and caffeine withdrawal. Daily dairies included recordings of the ovulation test result of the previous night. Due to higher concentrations of LH and FSH hormones in urine in the morning, participants completed the ovulation test the night before and report results obtained the following morning. To help increase the likelihood that participants complete all daily dairies, researchers called and remind participants after one missed day. Those who miss one day of entry were able to make-up for the missed entry the following day by submitting two entries at the time they usually complete their entries. Participants who miss more than 2 daily dairies per month were eliminated from the final analysis. For timely completion of daily dairies, participants were assigned 6 credits to a psychology course of choice for the completion of their daily dairies.

Subsection 3: Laboratory Phase

During one of the two menstrual cycles, in order to mask the purpose of the study, participants were asked to restrict their intake of certain foods and drinks (e.g., alcohol, coconut products, shellfish, and all foods containing chocolate products and caffeine; Jones, Herning, Cadet, & Griffiths, 2000) during

the follicular phase, beginning at noon of one day and continuing until after completing the laboratory session the next day. During the other menstrual cycle, they restricted food intake during the luteal phase. The cycles were counterbalanced as to phase of food restriction. To enhance compliance with the restriction requirement, each participant was given a handout containing a complete list that also appeared on the website (Appendix E).

During each of the laboratory sessions, participants were swabbed (their inner cheeks) for a saliva sample using a cotton Q-tip. Participants were told that saliva sample is collected in order to verify abstinence of the mentioned restricted foods and they are given the opportunity to reschedule the laboratory session if they report consuming any caffeinated foods during the restricted timeframe. Of note, the saliva samples were not checked (Aguinis, Pierce, & Quigley, 1993). Participants were also asked to complete their daily diaries online following the computerized behavioral tasks. Both computer tasks and questionnaires were completed using a computer provided (the researcher were in the lab, but not visible to participants). Participants received \$10.00 after each lab session they attended.

In the event that ovulation cannot be detected, participants were asked to attend the laboratory sessions, but their data was not used in the final analyses. Data obtained from participants with more than two missing ovulation test results were excluded from the final analysis unless it was demonstrated that ovulation did not take place during the missing day(s) (i.e. ovulation is detected later and can reveal information regarding the beginning of the luteal phase).

Subsection 4: Research Design

The present study is a repeated measures design. Comparisons were made across two phases of the menstrual cycle (follicular and luteal) in relation to self-report withdrawal symptoms and psychomotor and cognitive performances. The independent variable was cycle phase with two levels (follicular and luteal).

Dependent variables were primarily collected during the two days of abstinence during the laboratory sessions as follows:

Mood. In line with the current study hypothesis, intensity or severity of each withdrawal symptom were evaluated along with the total number of self-reported withdrawal symptoms. The withdrawal symptom questionnaire is designed to detect changes in mood and somatic experiences resulting from caffeine abstinence (Griffiths et al, 1990a; 1990b; Evans & Griffiths, 1992; 1999; Schuh & Griffiths, 1997). Symptoms endorsed during the luteal phase were compared to those from the follicular phase in order to obtain differences in withdrawal experiences.

Psychomotor. Performance on each computer task in the CDR battery including: short- and long-term memory, vigilance/attention, and reaction time were assessed during the luteal and during the follicular phases. It has been demonstrated that the increasing progesterone level during the luteal phase is associated with impaired memory recognition (Rubinow, Smith, Schenkel, Schmidt, & Dancer, 2007). Estrogen depletion has also been associated with impairments in memory functions in elder women (Paganinihill & Henderson,

1994; Williams, 1998; Gibbs & Aggarwal, 1998). If estrogen depletion is associated with memory impairment, then it is appropriate to suggest that women would show benefits of caffeine at the point of their cycle when estrogen levels peak (follicular phase). The CDR battery were administered, in the current study, not only to investigate the effects of psychomotor performances (Lieberman, Tharion, Shukitt-Hale, Speckman, & Tulley, 2002), but also memory (which lacked systematic empirical investigation) across the menstrual cycle in healthy young women. The present study seeks to use the CDR battery to examine psychomotor, memory, and attentional functions. The same battery was previously used by other researchers (e.g., Haskell & colleagues (2005) and Scholey & Kennedy (2004)) in order to evaluate outcome variables in investigations related to psychomotor performance and caffeine administration and abstinence.

Caffeine Intake. Secondary aim involves the evaluation of the level of caffeine intake (using values published in Juliano & Griffiths, 2004) across the menstrual cycle. Averages of reported daily consumption levels during seven days of the follicular were compared to the mean intake across seven days of the luteal phase. Because participants are instructed to complete daily diaries for two cycles, there were two average scores for each phase.

Chapter 3: Statistical Procedures

Section 1: Statistical Procedure

For purposes of the data analysis, scores for each relevant variable were first derived and analyses then conducted.

Caffeine Consumption

Mean caffeine intake was computed for each participant for each phase of the cycle. The final consumption figure for each phase was determined by calculating the average intake for that phase across the two menstrual cycles (caffeine values adopted from Juliano & Griffiths, 2005). Mean caffeine intake was the average across two months of daily dairies, excluding the two days of abstinence (once during each month).

Premenstrual Syndrome Symptoms

Scores for PMS were based on the Self-Rating for Premenstrual Tension Syndrome, a 5-point-likert scale (PMTS-SR; Appendix D). In order to meet criteria for PMS and to be excluded from the final sample, participants had to endorse at least a 30% increase in symptom severity during the luteal phase, as compared to the follicular phase, for 2 consecutive months. The PMTS-SR assessed for symptoms such as mood swings (sudden sadness or tearfulness), depression, anxiety (tension and nervousness), irritability, avoidance of social activities, sensitivity, and loss of enjoyment or hopelessness. Percent increase was

calculated using the difference between premenstrual and postmenstrual time periods.

Caffeine Withdrawal Symptoms

Withdrawal scores based on the self-report questionnaire (Appendix D) were obtained for each day of abstinence (once during the follicular and once during the luteal phase) and also for two randomly selected non-abstinence days. Specifically, for non-abstinence data on each participant, one day of usual caffeine intake during the follicular phase of the menstrual cycle (days 5-10) was randomly selected to represent non-abstinence and one day during the luteal phase (days 20-25) was similarly selected. Ratings (on a 4-point Likert scale) of each individual symptom from the scale were summed to achieve a total withdrawal score (Appendix A, p. 40). For instance, if participant X scored a 3 for *headaches*, 2 for *sleepiness*, and 4 for *irritability*, her total withdrawal score would be 9. Withdrawal scores were examined further using frequency of individual withdrawal symptom scores during abstinence and non-abstinence days. The most common symptom was also selected for additional comparisons, whereby rated withdrawal symptom during abstinent was the dependent variable (DV) and the score of withdrawal during non-abstinent was the independent variable (IV).

Cognitive Drug Research Scores

Scores for individual tasks on the Cognitive Drug Research (CDR) psychomotor task battery were calculated for the present data set and provided by

the research group at CDR (personal communication with project coordinators, Anna Wesnes and Brian Saxby; Simpson, Surmon, Wesnes, & Wilcock, 1991; Wesnes, Ward, McGinty, & Petrini, 2000). The tasks include power of attention (Reaction Time), continuity of attention (Attention Vigilance), quality of episodic memory (Delayed Recall), quality of working memory (Immediate Recall), and memory speed (Speed of Immediate Recall). These scores served as dependent variables in 5 separate repeated measures ANOVAs across both cycle phases (e.g., performance on each factor during the follicular phase was compared to the corresponding score during the luteal phase). The independent variable in each ANOVA was phase of the menstrual cycle.

Chapter 4: Results

Section 2: Data Analyses

A series of analyses addressed cognitive performance, mood and somatic symptoms, and caffeine consumption.

Section 3: CDR Factors

In accordance with the primary aims of the study, five repeated measures ANOVAs were conducted examining each of the five factor scores from the CDR battery. As hypothesized, analysis suggested no significant differences between the luteal and follicular phases in *power of attention*, $F(1, 47) = 0.495, p = 0.485$ (ES = 0.010), or *continuity of attention*, $F(1, 47) = 1.97, p = 0.167$ (ES = 0.040), as shown in Table 7. However, results also failed to support the current hypothesis regarding variables related to memory. There were also non-significant differences across the menstrual cycle, during abstinence, on performances that tapped *quality of working memory*, $F(1, 47) = 0.164, p = 0.607$ (ES = 0.003), *quality of episodic secondary memory*, $F(1, 47) = 2.69, p = 0.107$ (ES = 0.050), and *speed of memory*, $F(1, 47) = 0.955, p = 0.333$ (ES = 0.020) (as reflected in Table 8). The effects of caffeine abstinence did not have phase-differentiated impact on psychomotor and cognitive task performance.

Section 4: Phase-Differentiated Effects of Caffeine Abstinence

As with the CDR variables, current data do not provide support for phase-differentiated effects of caffeine abstinence on total subjective self-report of withdrawal symptoms, $F(1, 47) = 0.015, p = 0.904$ (ES = 0; Table 6 & 9).

To further address this issue, each frequently occurring mood symptom and each frequent somatic withdrawal symptom was analyzed. Of the 26 symptoms on which data were collected, caffeine craving was endorsed by 25.4% of participants during both phases of the menstrual cycle during caffeine abstinence (Tables 10 & 11). In particular, ANOVAs were used to examine this symptom more closely with respect to abstinence vs. non-abstinence and also abstinence effects during the luteal compared to follicular phases of the menstrual cycle. During caffeine abstinence, there were no significant differences between caffeine craving during the luteal and during the follicular phase of the menstrual cycle, $F(1, 47) = 0.00, p = 1.00$ (ES = 0.00) (Table 12). Caffeine craving was also not significantly different during non-abstinence compared to abstinence during the follicular phase, $F(1, 47) = 0.175, p = 0.678$ (ES = 0.004). Likewise, abstinence effects were not detected during luteal and follicular phases, $F(1, 47) = 0.00, p = 1.00$ (ES = 0.00) and $F(1, 47) = 0.047, p = 0.830$ (ES = 0.001), respectively (Table 12).

Overall, the present study does not provide support for phase-differentiated effects of caffeine withdrawal on self-reported mood, somatic symptoms, or cognitive-behavioral performance. Although a higher percentage of participants reported experiencing greater symptom severity during the luteal compared to the follicular phase, mean reports of symptoms for the two phases were not significantly different.

An additional analysis was conducted to examine possible effects of the order of laboratory visits (luteal-follicular verses follicular-luteal). The order effects were not significant, $F(1, 47) = 0.007, p = 0.934, (ES = 0.00)$.

Section 5: Abstinence Effects

Withdrawal scores were obtained for each day of abstinence and also for two randomly selected non-abstinence days (follicular day 5-10 and luteal 20-25) for each participant. Specifically, for non-abstinence data, a number was selected ranging from 1 to 6 for each participant (1 = day 5 during the follicular phase and day 20 during the luteal phase). Withdrawal effects were examined during the two normal days compared with two days of abstinence during the follicular and luteal phases. This analysis indicated a significant effect of abstinence on mood and somatic symptoms during the follicular phase of the menstrual cycle, $F(1, 47) = 6.32, p < 0.15, (ES = 0.116)$. Means were 20.80 (SD = 5.48) and 22.27 (SD = 4.54) for non-abstinence and abstinence days respectively. Similar effects were detected during the luteal phase, $F(1, 47) = 6.21, p < 0.016, (ES = 0.115)$. Means were 20.29 (SD = 4.60) and 22.18 (SD = 5.15) respectively for non-abstinence and abstinence days (Table 13).

Section 6: Caffeine Consumption

Corresponding to the second aim of the study which was to evaluate caffeine intake levels across the menstrual cycle, there were no significant (Table 19) differences detected in the level of consumption, $F(1, 47) = 0.717, p = 0.401 (ES = 0.015)$, across the menstrual cycle, with means of 290.29 (SD = 142.34) and 306.11 (SD = 131.71) during

the follicular and luteal phase, respectively. Moreover, there was no indication that level of habitual caffeine intake affects differences in the intensity of withdrawal symptoms during abstinence.

Chapter 4: Discussion

The present study involved a repeated-measures design with counterbalancing that examined the effects of caffeine abstinence across the major phases of the menstrual cycle. Theoretically, the cognitive and emotional sequelae of caffeine withdrawal should vary systematically with the changing hormonal physiology that produces and accompanies the sequential phases of the menstrual cycle (Hampson, 1990; Hampson & Kimura, 1988). However, most prior caffeine abstinence studies have not attempted to take these physiological changes into account (Stafford, Rusted, & Yeomans, 2007). The present study was an initial effort to address this gap in our knowledge. The primary goal of the study was, therefore, to examine phase-differentiated effects of caffeine abstinence, in habitual caffeine consumers, on objective measures of psychomotor and cognitive tasks and on self-reports of mood and somatic symptoms.

Overall Withdrawal Effects. Overall, present data show that caffeine abstinence in women who consume on average 349.33 mg/day results in withdrawal effects on self-reported measures of mood and somatic variables, including, in particular, increases in caffeine craving (Griffith et al., 1990; Juliano & Griffiths, 2004), sleepiness (Hewlett & Smith, 2006; Rogers et al., 2005), and fatigue (Hewlett & Smith, 2006; Smith et al., 1999; Warburton et al., 2006).

The brain mechanisms underlying the aforementioned effects of caffeine abstinence are not entirely understood in the current literature. However, the molecular target of action of caffeine is known. Caffeine antagonizes the activity of the brain

neuromodulator adenosine at specific receptor subtypes (e.g., A1 and A2A receptors). Adenosine is a nucleoside that is widely available in cerebral cortex, and its actions are associated with a reduction in neural activity and with cerebral vasodilatation. In general, the blockage of adenosine by caffeine results in cerebrocortical activation and vasoconstriction. It is unclear which of these effects, or others, underlie which specific symptoms of withdrawal.

Symptoms such as fatigue, sleepiness, and decreased alertness have been demonstrated in previous studies (Hewlett & Smith, 2006; Rogers et al., 2005; Smith et al., 1999; Warburton et al., 2006). The underlying cause of fatigue can be extrapolated from the known mechanisms that involve the inhibitory action of caffeine on adenosine receptors. Caffeine serves to primarily inhibit adenosine receptors in the medial reticular formation (mRF). This activity of the mRF in the brain stem is gated through the reticular nucleus of the thalamus to cortical areas. One implication may be that the effects of caffeine depend on the existing level of cortical arousal, suggesting that the impact of caffeine and of its withdrawal are, in part, state-dependent (Nehlig, 1999). In fact, caffeine-induced elevations in cortical arousal manifest as increases in the frequency and amplitude of the EEG (Snel & Lorist, 1999). Since these effects depend on the combined effects of many concurrently running facilitatory and inhibitory neural processes, fatigue may follow withdrawal as a result of increasing demands on the system as a whole.

Not surprisingly, withdrawal symptoms resulting from caffeine abstinence have been quite consistently demonstrated in prior studies, including those mentioned above. Caffeine withdrawal has been associated with increases in the severity of several mood and somatic symptoms, including, headache (Lane, 1997; Silverman et al., 1992),

difficulty concentrating (Garrett & Griffiths 1998; Griffiths et al., 1999; Jones, Herning, Cadet, Griffiths, 2000), and irritability (Griffiths et al., 1990; 1999; Silverman et al., 1992; Roger et al., 2005), in addition to those found in the present study. However, it is important to note that not all symptoms are present in all studies (Juliano & Griffiths, 2004).

One common withdrawal symptom is headache, though it has not been reported in all studies (Lane & Phillips-Bute, 1998). Quite extensive research on this symptom shows that it results primarily from significant caffeine withdrawal-induced increases in cerebral blood flow, consistent with vasodilatation, in habitual caffeine users (Couturier, Laman, Duijn, & Juijn, 1997; Griffiths & Mumford, 1995; Jones et al., 2000; Silverman et al., 1992). The primary cause of the headache is likely the resultant increase in cerebral blood flow velocities. The vasodilatation itself is probably a consequence of reversing the long-term exposure to caffeine that causes changes in adenosine receptor expression. This mechanism may also contribute to the development of tolerance and dependence. The withdrawal-induced changes are subject to individual variability, and behavior genetic studies indicate that genetic contributions are important in rendering some people more vulnerable than others to experiencing caffeine withdrawal headaches (Lane & Phillips-Bute, 1998). Furthermore, difficulty with concentration and irritable mood may be secondary to the presence of headache and fatigue.

The reported mood and somatic symptoms that result from withdrawal can negatively impact performance on cognitive, psychomotor (Lane & Phillips-Bute, 1998), and perception (Rogers et al., 2005) tasks. Impaired performance on attention vigilance (Lane & Phillips-Bute, 1998; Stafford et al., 2007), choice reaction time, and verbal

reasoning (Hewlett & Smith, 2006) tasks have been reported in some studies, but not in all (Judelson, et al., 2005; Phillips-Bute & Lane, 1997).

Withdrawal Effects and the Menstrual Cycle. Given prior research findings on the moderating effects of estrogen on memory tasks (Paganinihill & Henderson, 1994; Williams, 1998; Gibbs & Aggarwal, 1998), one of the primary goals of the study was to examine phase-differentiated effects of caffeine abstinence on tasks tapping memory performance. Specifically, greater impairment was expected during the luteal phase than during the follicular phase, due to decreasing levels of estradiol, which has been shown to facilitate performance on memory-related tasks (Jacobs, et al., 1998; James, 1997; Maki, Zonderman & Resnick, 2001; Shewin, 1988).

The present data did not support the menstrual phase hypothesis regarding memory. Since no other study has ever addressed menstrual phase differences in caffeine withdrawal, there is no direct scientific evidence with which to compare the present finding. However, some researchers have demonstrated in estrogen hormone replacement therapy studies that estrogen enhances memory functions in older women (HRT; Jacobs, et al., 1998; James, 1997; Maki, Zonderman & Resnick, 2001; Shewin, 1988), while others have not been able to replicate this effect in younger women with naturally occurring hormones (Maki, Rick, & Rosenbaum, 2002).

One possible explanation for the lack of phase differences across the menstrual cycle is that estrogen may have no effect on explicit verbal memory in younger women (Maki et al, 2002), despite its apparent beneficial effects in older women (James, 1997). It can be also postulated that younger women, on the whole, experience less cognitive deficits, and therefore a ceiling effect was observed in the current sample on administered

tasks. For instance, the range of recall on immediate and delayed verbal memory tasks was from 9 to 14 words, which is above the average for the population as a whole (e.g., Miller's magic number 7 ± 2 ; Miller, 1956; Baddeley, Thomson, & Buchanan, 1975).

The second hypothesis related to the first study aim referenced performance on tasks that tapped attention and reaction time. Performance on attentional tasks has repeatedly been shown to be impacted by both caffeine administration and caffeine abstinence (Hewlett & Smith, 2006; Rogers et al., 2005; Stafford et al., 2007; Warburton et al., 2001), and it was hypothesized here that there would be no significant differences on attention-related tasks between the luteal and follicular phases of the cycle. As expected, there were no differences in performance on attentional tasks across the cycle. To date, empirical investigations that examine effects of caffeine withdrawal on attentional tasks have employed only mixed-sex samples (James, 1998; Smith et al., 1999; Stafford et al., 2007; Warburton et al., 2001). These studies, overall, have not found sex differences in performance level on reaction time and digit vigilance tasks.

Regarding the effects of caffeine abstinence on reporting of mood and somatic symptoms, it was hypothesized that caffeine abstinence leads to more severe experiences of withdrawal during the luteal phase, due to the "dual-vulnerability factor," than during the follicular phase. Prior studies have focused on the impact of increasing levels of estradiol during the follicular phase and likewise with progesterone during the luteal phase (James, 1997; Kitts, 1987; Lucero et al., 2001; Phillips, 1986; 1991). Research has shown that the increasing level of estradiol during the follicular phase contributes to the experience of positive emotions (Backstrom et al., 1983; James, 1997). Similarly, the elevated levels of progesterone seen during the luteal phase have been associated with

feelings of fatigue and depression (Phillips, 1991). As such, systematic hormonal fluctuations during the menstrual cycle may have predictive value for mood changes.

In addition, hormonal processes of the menstrual cycle have been theorized to interact with caffeine consumption (Vo et al. 2007). Theoretically, caffeine intake reduces the impact typical of progesterone, thereby leading to decreases in negative mood symptoms (Phillips, 1986; 1991). Prior findings on the phase-specific impact on mood that theoretically results from the interaction of normal menstrual physiology with caffeine provide grounds to suggest that caffeine abstinence during these two primary phases would also associate with differential phase-specific withdrawal mood and somatic experiences (Vo et al., 2007).

Two factors may account, at least in part, for the lack of support for this theoretical perspective. First, women in the present study may not have experienced withdrawal symptoms potent enough for phase differences to be detectable, in part because they consumed relatively low doses of caffeine ($M = 349.33$ mg/day). Although other studies have shown that caffeine withdrawal can develop in low caffeine consumers (<300 mg/day; Evans & Griffiths, 1999; Nehlig, 1999), it is likely that the low level of consumption in this college student sample is nevertheless a factor in the failure to confirm the hypothesis. This factor may have also contributed to the relatively low severity of withdrawal symptoms experienced, thereby reducing the likelihood of detectable differences during the follicular and luteal phases.

The second factor may be the “menstrual normality” of the women in the sample. Women with PMS, PMDD, and irregular cycles were systematically screened out of this study. It may be less likely that external factors, such as caffeine consumption, will

affect phase-differentiated symptomatology in women with normal menstrual cycles and little menstrual distress than in a more heterogeneous sample (Vo et al., 2007). Although no studies have directly addressed this issue with regard to caffeine, some research has shown that women with normal cycles and little or no distress are less likely to report differences between the luteal and follicular phases in mood or somatic symptoms (Backstrom et al., 1983; Lucero et al., 2001)

Although these two factors may account for the nonsignificant differences observed, it must be acknowledged that the theory itself may be incorrect or inadequate. Perhaps the hypothesized phase differences simply do not exist. Since this was the first study to test for these differences in caffeine withdrawal effects, it is too early to reach a firm conclusion on this point.

Caffeine Consumption and Menstrual Phase. The second purpose of the present study was to evaluate levels of caffeine intake during the follicular and luteal phases of the menstrual cycle. Based in part on the author's earlier work (Vo et al., in preparation), it was hypothesized that caffeine intake would be higher during the follicular phase due to the faster metabolic rates seen during that phase (Fenster et al., 1999) than during the luteal. Hence there would be a need to consume more during the follicular phase, in order to achieve the desired effect (Turner & Wit, 2006; Vo et al., 2007). Present data failed to support this hypothesis, a result consistent with one other study in this literature (Caan et al., 1993). On the other hand, this finding does not support results seen in Vo and colleagues (in preparation), which employed similar (though not exact) methodologies. There are, however, two important differences between these two studies that may well account for this difference in results. First, the present study employed a sample of

women with normal menstrual cycles, whereas the earlier study involved a sample of women with PMS. Second, the earlier study allowed participants the flexibility of choosing how often and how much caffeine to ingest; whereas women in the present were recruited because they habitually consume at least 200 mg daily in order to participate. This restriction may have decreased possibilities for consumption by choice and thus creates less range to detect variability.

Chapter 5: Study Limitations

The impact of caffeine withdrawal on the measures employed in the present study was not differentially affected by the phases of the menstrual cycle. This failure to support the hypotheses may have resulted, in part, from several limitations. First, the present study did not establish prior withdrawal experiences resulting from caffeine abstinence. This may have been important because not everyone experiences caffeine withdrawal as a result of abstinence (Juliano & Griffiths, 2004; 2005; Nehlig, 1999). A second limitation was the inability to control for environmental variables (e.g., academic and interpersonal stressors), which could impact self-reports of mood experiences and also performance on CDR tasks, thereby adding extraneous variance. Third, though the hormonal verification technique used during the study to detect ovulation is quite accurate (Hedricks, et al., 1991; personal communication, D. R. Rubinow, M.D., March, 2007), a stronger approach would have been to test blood samples to determine hormone levels at the times of laboratory visits. Fourth, it was not feasible to control directly for the use of oral contraceptives, and this may have affected results. Other limitations included the lack of biological verification of abstinence, our inability to control for the amount of sleep during abstinence, which has been found to potentially affect withdrawal (Rogers et al., 2005), and the fact that the withdrawal checklist used in the present study has not been formally validated. It should be noted however, that this checklist has been used in numerous studies (e.g., Griffiths et al., 1990a; 1990b) and has consistently detected withdrawal symptoms resulting from caffeine abstinence. And, finally, the current sample consisted of college students, which may limit generalizability to other

populations. In addition, the current sample were not all “morning coffee drinkers” therefore may not experience withdrawal in the morning as oppose to later in the afternoon. As such, future efforts should be considered in other age-groups.

Chapter 6: Conclusion and Future Directions

The goal of the present study was to examine the effect of caffeine abstinence across the menstrual cycle, testing cognitive, psychomotor, mood, and somatic effects. The present study was one of the first to examine both the effect of caffeine abstinence in women and of caffeine withdrawal on psychomotor performance. As previous studies also demonstrated, there was no evidence to suggest differential memory effects as a result of caffeine abstinence. Furthermore, there were no differences on memory tasks between the follicular and luteal phases of the menstrual cycle. There are presently no data available for comparison of the presence of phase difference results, due to the novelty of this study; however, this area of research warrants additional efforts in order to understand the effects of caffeine abstinence across the menstrual cycle, especially in women of different age groups, such as in college students, middle age, and elder women.

As previous studies have shown, mood/somatic withdrawal affects were detected during abstinence in women who habitually consumed on average 349.33 mg of caffeine daily. It is important to replicate such findings in low vs. high consumers based on length of exposure and intensity of use, since some withdrawal symptoms, such as headache, may be caused by longer-term use and characteristic changes in blood flow velocities (Nehlig, 1999), whereas others likely result in “temporary/state” (Snel & Lorist, 1999) changes (e.g., craving or fatigue). More generally, because caffeine withdrawal may be more severe in women than in men (Dews et al., 1999), the present topic warrants further research. Such research should address differences in both caffeine intake and caffeine withdrawal effects in low, moderate, and high habitual consumers and also investigate

phase differentiation effects in these groups. Also in these studies, account for possible effects of sleep deprivation. In addition, it would be informative to conduct experimental studies, in which varied doses of caffeine are administered in the laboratory during the follicular and luteal phases of the menstrual cycle. Such research could examine the immediate differential effects of caffeine on cognitive, psychomotor, mood, and somatic variables in women of differing age groups, as well as those with normal menstruation and those with menstrual disorders. In addition to the cognitive tasks used in the present study, future investigations may examine more emotionally-oriented stimuli. Across many of these studies, the diary technique developed by the author could be applied for purposes of both data collection and screening. Withdrawal effects could also be examined within the context of these designs by testing their frequencies and magnitudes in groups of women of varied age, habitual caffeine intake, and menstrual history. Additionally, biological, physiological and genetic components can strengthen this line of research. For instance, studies examining differences in individual metabolic rate and also vulnerability factors for caffeine consumption and withdrawal would be informative.

Table 1: Sample Racial/Ethnic Distribution

	Number of Participants	Percent of Participants
White	42	85.70
Black	1	2.00
Hispanic	2	4.10
Asian	3	6.10
Mix Racial	1	2.00

Table 2: Demographical Variables

	<u>Number of Participants</u>	<u>Percent of Participants</u>
Smoke (Yes)	7	14.30
Familial Depression (Yes)	12	24.50
Oral Contraceptives (Yes)	25	51.00
Age (Mean)	19.96 (SD = 1.28)	

Smoke = Number of participants who regularly smoke

Familial Depression = Depression diagnoses among immediate family members

Oral Contraceptive = Number of participants who use oral contraceptives

Age = Mean age of sample

SD = Mean standard deviation

Table 3: Empirically Validated Caffeine Withdrawal Symptoms

Mood	Behavioral	Somatic
Irritability/Grumpy	Alert/Attentive	Lightheaded/Dizzy
Decreased Well Being	Decreased Talkativeness	Upset Stomach
Anxious/Nervous	Decreased Urge to work	Blurred Vision
Decreased Concentration	Drowsy/Sleepy	Cerebral Fullness
Depressed	Decreased Energy/Active	Muscle Pain/Stiff
Lethargy/Fatigue	Jittery/Shaky	Blurred Vision
Decreased Content/Satisfied		Runny Nose
Muzzy/Foggy		Headache
Decreased Confidence		Flu-like Feelings
		Limb Tremor
		Sweating

Table 4: CDR Factor Score

Factor Score	CDR Task Measure
Power of Attention	Simple Reaction Time
	Choice Reaction Time
	Digit Vigilance - Speed of Detections
Continuity of Attention	Choice Reaction Time – Accuracy
	Digit Vigilance – Correct Detections
	Digit Vigilance – False Alarms
	Tracking – Mean Error
Quality of Working Memory	Numeric Working Memory – Sensitivity Index
	Spatial Working Memory – Sensitivity Index
Quality of Episodic Secondary Memory	Immediate Word Recall – Accuracy
	Delayed Word Recall – Accuracy
	Word Recognition – Sensitivity Index
	Picture Recognition – Sensitivity Index
Speed of Memory	Speed of Numeric Working Memory
	Speed of Spatial Working Memory
	Speed of Word & Picture Recognition

Table 5: Summary of Study Administration

<i>Measures</i>	<i>Laboratory Orientation</i>	<i>Online Daily Diaries</i>		<i>Laboratory Test Sessions</i>	
		Month 1	Month2	T1	T2
Screening	X	--	--	--	--
PHQ	X	--	--	--	--
Caf. Int. Surv*	--	X	X	X	X
PMTS-SR*	--	X	X	X	X
Wdr Sx Rating*	--	X	X	X	X
CDR Battery	Practice	--	--	(F) or (L)	(F) or (L)
Ovulat Test*	--	X	X		

* Items are part of online daily diary

Table 6: Means for Caffeine Intake, Withdrawal Effects, and CDR Variables

	Caffeine Intake (SD)	Withdrawal Symptoms (SD)	Attention (SD)	Continuity of Attention (SD)	Working Memory (SD)	Episodic Memory (SD)	Memory Speed (SD)	Numerical Memory (SD)
Fol	391.27 (143.68)	22.27 (4.54)	294.93 (38.62)	97.41 (4.03)	98.89 (3.18)	8.63 (2.2)	631.77 (117.77)	96.80 (4.76)
Lut	307.49 (132.75)	22.18 (5.15)	300.50 (39.05)	95.74 (7.25)	98.61 (3.63)	9.08 (2.17)	606.08 (128.42)	96.39 (5.14)

Caffeine Intake = Mean caffeine intake

Withdrawal Symptoms = Mean withdrawal symptoms

Power of Attention = Reaction time (Seconds)

Continuity of Attention = Accuracy on vigilance task

Quality of Working Memory = Score of immediate word recall

Quality of Episodic Memory = Delay verbal recall

Speed of Memory = Speed of spatial memory recall

Numerical Memory = Accuracy of numerical memory recall

Table 7: ANOVA Table: Power & Continuity of Attention

<i>Power of Attention</i>	SS	df	MS	F	Sig. of F
Within Cells	744.208	47	744.208		
Cycle Phase	744.208	1	744.208	0.495	0.485
Error	70615.175	47	1502.451		
 <i>Continuity of Attention</i>					
Within Cells	66.667	47	66.667		
Cycle Phase	66.667	1	66.667	1.967	0.167
Error	1592.785	47	33.889		

Table 8: ANOVA Table: Quality, Episodic, and Speed of Working Memory

<i>Quality of Memory</i>	SS	Df	MS	F	Sig. of F
Within Cells	4.939	47	4.939		
Cycle Phase	744.208	1	744.208	2.494	0.121
Error	95.061	47	1.980		
<i>Quality of Episodic Memory</i>					
Within Cells	4.939	47	4.939		
Cycle Phase	4.939	1	4.939	2.692	0.107
Error	88.061	47	1.835		
<i>Speed of Working Memory</i>					
Within Cells	15848.420	47	15848.420		
Cycle Phase	15848.420	1	15848.420	0.955	0.335
Error	16590.820	47	16590.820		

Table 9: ANOVA Table: Self-report Withdrawal Symptoms

	SS	Df	MS	F	Sig. of F
Within Cells	0.163	47	0.163		
Cycle Phase	0.163	1	0.163	0.015	0.904
Error	533.840	47	11.120		

Table 10: Means and Severity Frequency of Caffeine Craving

	<u>Caffeine Craving</u>
Mean Nonabstinence Follicular (SD)	1.48 (1.20)
Mean Abstinence Follicular (SD)	1.43 (1.17)
Mean Nonabstinence Luteal (SD)	1.48 (1.25)
Mean Abstinence Luteal (SD)	1.51 (1.28)
Nonabstinence (%)	7.50
Follicular (%)	31.00
Luteal (%)	27.00

Note: SD = Standard Deviation of Means

Nonabst = Percent participants rated 3 on withdrawal scale during non-abstinence

Fol = Percent participants rated 3 on withdrawal scale during follicular phase of abstinence

Lut = Percent participants rated 3 on withdrawal scale during luteal phase of abstinence

Table 11: Means and Severity of Self-reported Symptoms

Withdrawal Symptoms	Means Fol (SD)	Fol Percent	Means Lut (SD)	Lut Percent
Decreased Well-being	1.79 (0.62)	6.8	1.81 (0.61)	8.5
Decreased Motivation Work	1.40 (0.80)	3.4	1.31 (0.93)	6.8
Decreased Concentration	1.42 (0.77)	5.1	1.65 (0.79)	11.9
Decreased Energy	1.38 (0.73)	1.7	1.23 (0.81)	3.4
Decreased Confidence	1.94 (0.63)	11.9	1.85 (0.71)	15.3
Muzzy	0.69 (0.78)	0	0.71 (0.74)	0
Headache	0.73 (0.94)	5.1	0.54 (0.92)	5.1
Sleepy	1.10 (0.86)	6.8	1.31 (0.88)	10.2
Decreased Alertness	1.44 (0.77)	3.4	1.54 (0.74)	6.8
Decreased Talkative	1.23 (0.75)	1.7	1.32 (0.81)	3.4
Irritability	0.44 (0.68)	1.7	0.42 (0.61)	0
Depressed	0.28 (0.50)	0	0.19 (0.45)	0
Anxious	0.38 (0.57)	0	0.42 (0.68)	0
Stomach Upset	0.31 (0.62)	0	0.15 (0.47)	0
Confused	0.23 (0.47)	0	0.21 (0.46)	0
Muscle Tension	0.44 (0.80)	3.4	0.38 (0.61)	0
Fatigue	0.98 (0.89)	6.8	1.02 (0.89)	8.5
Cerebral Fullness	0.71 (0.92)	5.1	0.67 (0.97)	5.1
Jittery	0 (0.28)	0	0.15 (0.41)	0
Dizzy	0.25 (0.56)	1.7	0.21 (0.46)	0
Impaired Function	0.55 (0.62)	0	0.56 (0.58)	0
Caffeine Craving	1.48 (1.20)	25.4	1.48 (1.25)	25.4
Impoverished Function	0.17 (0.43)	0	0.13 (0.39)	0
Decreased Ability to Completion Tasks	1.02 (0.79)	0	1.04 (0.83)	5.1
Decreased Content	1.63 (0.67)	3.4	1.71 (0.68)	8.5
Flu-like Symptoms	0.29 (0.54)	0	0.19 (0.45)	0

Note: Means Fol = Mean of withdrawal symptoms during follicular phase

Means Lut – Means of withdrawal symptoms during luteal phase

Fol Percent = percent of sample endorsed severe symptoms during follicular phase

Lut Percent = percent of sample endorsed severe symptoms during luteal phase

SD = Standard deviation of means

Table 12: Self-report Symptoms Abstinence, Nonabstinence, Luteal, Follicular

<i>Symptoms Abstinence</i>	SS	Df	MS	F	Sig. of F
Within Cells	0	47	0		
Cycle Phase	0	1	0	0	1.00
Error	43.00	47	0.915		
<i>Symptoms Nonabstinence</i>					
Within Cells	0.163	47	0.163		
Cycle Phase	0.163	1	0.163	0.175	0.678
Error	44.840	47	0.934		
<i>Symptoms Abstinence Luteal</i>					
Within Cells	0	47	0		
Cycle Phase	0	1	0	0	1.00
Error	11.0	47	0.234		
<i>Symptoms Abstinence Follicular</i>					
Within Cells	0	47	0		
Cycle Phase	0	1	0	0.047	0.830
Error	10.49	47	0.223		

Table 13: ANOVA Table: Withdrawal Symptoms Abstinence Follicular & Luteal

<i>Symptoms Abstinence Follicular</i>	SS	Df	MS	F	Sig. of F
Within Cells	52.90	47	52.90		
Cycle Phase	52.90	1	52.90	6.320	0.015
Error	402.10	47	8.377		
<i>Symptoms Abstinence Luteal</i>					
With Cells	88.26	47	88.26		
Cycle Phase	88.26	1	88.26	6.209	0.016
Error	682.25	47	14.210		

Table 14: Caffeine Intake across the Cycle

	SS	Df	MS	F	Sig. of F
Within Cells	6135.471	47	6135.471		
Cycle Phase	6135.471	1	6135.471	0.717	0.401
Error	410619.556	47	8554.574		

Figure 1. Summary of Study Aims

			Follicular	Luteal
Aim 1	H1	Memory	↑	↓
	H1a	Attention/RT	No Difference	
	H1b	Self-report	↑	↓
Aim 2	H2	Intake Level	↑	↓

Appendices

Appendix A: Literature Review

Menstrual Cycle

In order to provide a brief background of the menstrual cycle, it is important to identify the body parts that are involved. In addition to reproductive organs, the brain and the pituitary gland also play crucial roles in the regulation of hormonal productions (e.g., estradiol, progesterone) (Bancroft, 1993). Each month from menarche on, the hypothalamus acts as an interpreter of the body's rhythms and transmits messages to the pituitary gland, which then sets the menstrual cycle in motion (Norris & Sullivan, 1983). For instance, Gonadotropin releasing hormone (GnRH) is secreted from the hypothalamus in a pulsatile manner throughout the menstrual cycle. In order for the menstrual cycle to proceed normally, GnRH must be released in pulses. On average, the frequency of GnRH secretion is once per 90 minutes during the early follicular phase, increases to once per 60-70 minutes, and decreases with increased amplitude during the luteal phase. GnRH induces the release of both FSH and LH; however, LH is much more sensitive to changes in GnRH levels (Bancroft, 1993; Walker, 1997).

The length of a menstrual cycle is the number of days between the first-day of menstrual bleeding of one cycle to the onset of menses of the next cycle. A typical menstrual period lasts from three to five days. A cycle begins on the first day of a period and typically prolongs for 28 or 30 days. However, a cycle can range anywhere from 23 to 35 days (Khan-Sabir et al., 2004). The menstrual cycle is typically most irregular around the extremes of reproductive life, menarche and menopause, due to anovulation and inadequate follicular development (Eriksson et al., 2006). The luteal phase is relatively

constant with 14-day duration. The variability of cycle length is usually derived from varying lengths of the follicular phase of the cycle, ranging from 10 to 16 days.

The menstrual cycle is divided into the follicular and luteal phase. The follicular phase begins with the onset of menstrual bleeding designated as the first day of the cycle. By convention, the day of menstruation clearly delineates the termination of an endometrial cycle and the beginning of the new one. In general, the follicular phase is approximately 14 days and is variable. The luteal phase, however, is 12-14 days long and it remains generally constant (Allen, Hatsukami, Christianson, & Nelson, 1996).

Beginning the follicular phase of the menstrual cycle, a process called folliculogenesis ensues. It starts when a primordial follicle is recruited into a pool of developing follicles and typically terminates with ovulation (Khan-Sabir & Carr, 2004). Once menses begins, FSH levels decline, due to the negative feedback of estradiol and the negative effects of inhibin produced by the developing follicle (Sawetawan et al., 1996; Tsafiriri, 1994).

FSH then activates the aromatase enzyme in granulosa cells, which converts androgens to estradiol (Khan-Sabir & Carr, 2004). A decline in FSH levels leads to the production of a more androgenic microenvironment within adjacent follicles contributing to the growth of a dominant follicle. The granulosa cells of the growing follicle also secrete a variety of peptides that may play an autocrine/paracrine role in the inhibition of development of the adjacent follicles. Beginning the luteal phase, the corpus luteum (a transient endocrine organ) secretes progesterone. This is then followed by a secondary rise in estradiol levels during the mid-luteal phase with a decrease at the end of the menstrual cycle. The secondary rise in estradiol parallels the rise of serum progesterone and 17-hydroxyprogesterone.

The endocrinology of the menstrual cycle involves a series of phase-differentiated hormonal changes. During days 1-6, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are increased relative to baseline. Estradiol and progesterone levels are low at this stage (Carr, 2004). Beginning approximately eight days into the cycle, FSH levels decrease due to negative feedback at the level of the pituitary gland and estradiol levels increase due to previous stimulation by FSH at the level of the ovary (Tsafriri, 1994). One day before ovulation, a surge in LH occurs and FSH levels also increase, which then begins to decrease toward baseline levels almost immediately. By the time ovulation occurs, LH and FSH are on the decline (Tsafriri, 1994). Progesterone and, to a lesser extent, estradiol are produced by the corpus luteum, which evolves under the influence of the pre-ovulatory surge in LH. Both LH and FSH are under negative feedback control by these ovarian hormones at the level of the pituitary gland. In the absence of fertilization, the corpus luteum degenerates; progesterone and estrogen levels then subsequently fall. During day 28 of the average menstrual cycle, estradiol and progesterone are at their lowest levels. Negative feedback on FSH is removed, and FSH secretion can again increase to trigger the onset of the next cycle.

Caffeine

Caffeine is the most widely used psychoactive drug in the world. Caffeine is a (1, 3, 7-trimethylxanthine) compound found in numerous plants (Juliano & Griffiths, 2005; Smith et al., 2007) and is contained in a variety of foods (e.g., chocolate, coffee, tea, soft drinks etc), coffee and tea remain the predominate vehicle for caffeine intake (Smith et al., 2007). Analysis of data obtained by the U.S. Department of Agriculture published by Frary and colleagues (2005) indicated that over 85% of the population consumed caffeine

including children. Among those, women and men from the ages of 18-54 consumed most compared to the rest of the population. Even though caffeine is consumed widely among women during their reproductive age, there is limited understanding of sex-differentiated processes.

After oral consumption, caffeine enters the digestive system and readily crosses the blood-brain barrier. This characteristic of caffeine accounts for its rapid (within 30-45 minutes) ability to alter moods (James, 1997; Juliano & Griffiths, 2005; Lustyk et al., 2004). Mood effects of caffeine include increased in well-being, happiness, energetic arousal, alertness, and sociability (with doses from 20-200--mg). Larger amounts of consumption can produce negative affects such as induce anxiety, jitteriness, and or nervousness (Smith et al., 2005).

Caffeine's rate of metabolism is generally complicated by presence and amount of foods in the stomach, menstrual cycle phase, tobacco smoking (James, 1997; Smith et al., 2007). The half-life of caffeine is typically 4 to 6 hours (Juliano & Griffiths, 2005; Karch, 1998). Several variables can manipulate the rate of caffeine metabolism. Smoking increases caffeine metabolism about two-fold (Parson & Neims, 1978). Furthermore, oral contraceptives can double caffeine half-life (Patwardhan et al., 1980). Caffeine acts as an antagonist at adenosine receptors. Adenosine plays several roles in the central nervous system (e.g., inhibits neurotransmitter release and reduces spontaneous neuronal firing; Fredholm et al., 1999). Among the behavior manifestations of adenosine action includes depression of locomotor activity. This mechanism increase sleep-propensity likewise, reduces activities that promote wakefulness (Juliano & Griffiths, 2005). Caffeine can also produce a wide variety of physiological effects including, blood pressure, respiratory

functioning, gastric, colonic activity, urine volume, and exercise performance (James, 1997).

Caffeine Withdrawal Syndrome

Many individuals who consume low (approximately 100-mg; Evans & Griffiths, 1999) or moderate (approximately 300-mg) amounts of caffeine will develop withdrawal syndrome upon 12-to 24-hour abstinence of caffeine use (Evans & Griffiths, 1999; Griffiths et al., 1990; Silverman et al., 1992). Caffeine withdrawal has been documented (Evans et al., 1994; 1999; Griffiths & Mumford, 1996) in the literature for over 170 years (cf. critical review by Juliano & Griffiths, 2004). The first controlled study that examines caffeine withdrawal was performed by Dreisbach and Pfeiffer (1943). The authors reported that after seven days of heavy caffeine consumption, subjects had severe withdrawal symptoms such as: throbbing headache, nausea, vomiting, and drowsiness, disinclination to work, mental depression, and yawning. Evans and Griffiths (1999) found that caffeine withdrawal can be experienced by people who consume as little as 100-mg/day (Table 2).

The withdrawal effects of any drug can be comprehended in terms of the drug's ability to reinforce drug-seeking behavior, the users' increasing tolerance for the drug, and physical and or psychological dependence on the drug. The following are definitions of the mentioned constructs. Drug reinforcement refers to the ability of a drug to sustain regular self-administration. For instance, in the case of caffeine, consumers are negatively reinforced by administration of caffeine in order to escape withdrawal syndrome (Juliano et al., 2003). Drug dependence is defined as a pattern of behavior focused on the repetitive and compulsive seeking and taking of a psychoactive drug (Smith, et al., 2004).

Caffeine has reinforcing properties (Evans, Crithchfield, & Griffiths, 1994; Griffiths et al., 1986; Hughes et al., 1992; 1995; Schuh & Griffiths, 1997; Silverman, Mumford, & Griffiths, 1994). Drug reinforcement is the likelihood in which a drug is able to sustain regular self-administration—drug-intake behavior. Caffeine intake is likely negatively reinforced the absence of withdrawal symptoms (e.g., headaches, flu-like feelings, fatigue, etc.). For instance, regular caffeine users consume caffeine more generally to avoid negative withdrawal experiences. Schuh and Griffiths (1997) examined the role of reinforcement in moderate caffeine consumers (average 379-mg/day). In a laboratory test, participants in the placebo group were more likely to forfeit money in order to receive caffeine (\$0.38) and were willing to forfeit as much as \$2.52 in order to avoid receiving placebo again. The authors concluded that the choice of caffeine is more potently controlled by the avoidance of withdrawal rather than the positive effects of caffeine. Evans and colleagues (1994) found that caffeine functions as a reinforcer even when caffeine withdrawal was not present. They suggested that results were applicable to moderate caffeine consumers under caffeine-restricted conditions.

Likewise, Silverman and colleagues (1994) also demonstrated that caffeine can be reinforcing even without physical dependence. Therefore, it is likely that caffeine administration is more a function of avoiding withdrawal rather than alleviating withdrawal symptoms already in place. Dose parameter studies suggest that 100-mg of caffeine is enough to enhance its ability as a reinforcer (Evans et al., 1994; Hughes et al., 1992). The authors demonstrated that caffeine can reliably serve as a reinforcer in 2 of 11 participants at doses as low as 25-mg. Caffeine doses of 50-mg can serve as a reinforcer for 5 of 11 participants (45%; Hughes et al., 1995) or 5 of 6 participants (83%; Evans et

al., 1994). In sum, caffeine intake decreased the likelihood of endorsements on symptoms such as drowsiness, headache, and fatigue; more importantly, the severity of the mentioned symptoms were able to predict the level of reinforcement experienced from subsequent caffeine use (Hughes et al, 1992; 1995).

Most recently, Stafford & Yeomans (2005) explored the relationship between caffeine deprivation, attentional bias to caffeine-related stimuli and subsequent caffeine reinforcement measure. The authors found that participants who were administered caffeine (100-mg to 150-mg) were more likely to attend to caffeine-related stimuli and less likely than the caffeine-deprived group to report drowsiness, headaches, and reduced alertness. In addition, the study provides supporting evidence for caffeine as a reinforcer (even in the absence of withdrawal) in that the caffeine-deprived group were more likely to consume more coffee when given the opportunity compared to the non-deprived caffeine group. Therefore, for moderate caffeine users, the avoidance of withdrawal symptoms (e.g., drowsiness and headaches) is the likely mechanism underlying the reinforcing effects of caffeine.

Physical dependence on caffeine plays an important role in maintaining daily caffeine consumption (Garrett & Griffiths, 1998; Hughes et al., 1993; Yeomans, Spetch, & Rogers, 1998). Chronic caffeine use can also increase the risk for developing caffeine tolerance (Griffiths & Munfold, 1996; Griffiths et al., 2003). Higher dose of caffeine (750-1200 -mg/day spread through out the day) is more likely, compared to lower dose (under 300 --mg/day), to produce dependence. Caffeine partially meets the primary criteria for drug dependence according to Gupta & Gupta (1999) because (1) it is a psychoactive drug, (2) some caffeine consumers experience difficulty abstaining (as

suggested in Griffiths & Mumford, 1996), and (3) it has reinforcing properties. Physical dependence on caffeine has also been evidenced by time-limited (typically within 30-60 minutes) withdrawal symptoms at termination or reduction of the usual caffeine dose (Griffiths et al., 2003; Juliano & Griffiths, 2004; Oliveto, Liguori, Carpenter, & Howard, 1998; Strain et al., 1994). For example, symptoms like, headache (77 %), fatigue (84%), decreased alertness (71%), decreased energy (75%), drowsiness (78%), difficulty concentrating (67%), decreased contentedness/well-being (61%), decreased desire to socialize (54%), and flu-like feelings (53%) have been validated based on the indicated percentage of studies with significant findings (Juliano & Griffiths, 2004). In sum, empirical data demonstrate that caffeine is a psychoactive drug that has properties for increasing tolerance and the risk of dependence.

In order to assess caffeine dependence in the general population, 162 randomly-selected caffeine users were assessed via structured-telephone interviews about their caffeine consumption during the past year. Participants were asked generic DSM-IV criteria in order to assess dependence. The authors found that 56% of the sample endorsed strong desire or unsuccessful attempts to stop use, 50% report spending a great deal of time with the drug, 28% use more than intended, 14% use despite knowledge of harm, and 24% met DSM-IV criteria for withdrawal. At least 1% would forgo enjoying activities to use (Hughes et al., 1998). In another community-based study, researchers demonstrated that (of 11,112 persons), 61% reported daily caffeine intake and 11% of those reported symptoms upon abstinence of use. In sum, both empirical and survey data demonstrate that caffeine is a psychoactive drug that has properties for increasing tolerance and the risk of dependence.

As mentioned, caffeine withdrawal has been documented in the literature for over 170 years (Juliano & Griffiths, 2004). Following the initial study by Dreisbach and Pfeiffer (1943), Smith and Tola (1998) also suggested the following withdrawal symptoms: throbbing headache, nausea, vomiting, and drowsiness, disinclination to work, mental depression, and yawning, and symptoms of stress. Likewise, Evans and Griffiths (1999) collected mood ratings using previously reported withdrawal symptoms along with mood scores from the Profile of Mood States (POMS). The withdrawal scale used asked participants to rate their present mood on a 4-point scale from “not at all” (0) to “very much” (3) on each of the 26 symptoms that have been validated (e.g., irritable/cross/grumpy; see table below). In sum, the mentioned symptoms will manifest beginning 12 to 24 hours after abstinence and gradually disappear (Gupta & Gupta, 1999; Juliano & Griffith, 2004).

Validation for the mentioned symptoms appears in a review by Juliano & Griffiths (2004). The authors critically examined 57 experiments (of those 42 double-blind trials) and 9 survey studies identified a total of 49 symptom categories. Of interest, the following symptoms are considered valid symptoms of withdrawal because they appear in more than half of the experiments assessed. The ten most predominate symptoms include headache (77 %), fatigue (84%), decreased alertness (71%), decreased energy (75%), drowsiness (78%), difficulty concentrating (67%), decreased contentedness/well-being (61%), and decreased desire to socialize (54%), flu-like symptoms (53%). Other symptoms frequently recorded by the studies included in the review were nausea-vomiting, depressed mood, and muscle pain-stiffness.

Signs and symptoms of caffeine withdrawal can occur at different severity levels ranging from mild to extreme. Withdrawal symptoms typically appear approximately 12 to 24 hours after abstinence and gradually disappear (Gupta & Gupta, 1999; Juliano & Griffith, 2004). At its worst, caffeine withdrawal has been repeatedly documented to produce clinically significant distress or impairment in daily functioning and, on rare occasions, to be totally incapacitating. For example, in one double-blind study with individuals from the general community, 52% of individuals from the general community with an average caffeine intake of 260 -mg/day reported moderate to severe headache, and 8-11% showed abnormally high scores on standardized depression, anxiety and fatigue scales (Hughes et al., 1998). In another double-blind study, 45% of individuals experienced a diffuse, throbbing headache, with almost a third also reporting nausea and sickness (Dews et al., 1999).

Based on the literature review, it was proposed that research criteria for caffeine-withdrawal diagnosis require abrupt abstinence of caffeine use or reduction in the amount of caffeine use, closely followed by three or more of the following: headache, fatigue, or drowsiness, dysphoric mood, depressed mood, or irritability; difficulty concentrating; and flu-like somatic symptoms, nausea, vomiting, or muscle pain-stiffness (Juliano & Griffiths, 2004). Evidence of the pharmacologically based effects (Couturier, Laman, Duijn, & Juijn, 1997; Jones, Herning, Cadet, Griffiths, 2000; Griffiths & Mumford, 1995; Silverman et al, 1992) of caffeine withdrawal and the addition of published studies provide support for the syndrome (Juliano & Griffiths, 2004).

How does caffeine withdrawal symptoms compare to other commonly used drugs like nicotine, alcohol, and cocaine (Medical Encyclopedia, 2007)? Withdrawal symptoms

associated with nicotine are intense craving for nicotine, tension, irritability, headaches, difficulty concentrating, drowsiness and trouble sleeping, and increased appetite and weight gain. Those associated with alcohol are headache, sweating, nausea and vomiting, loss of appetite, insomnia, pallor, rapid heart rate, dilated pupils, clammy skin, tremor of hands, and for severe cases, fever, convulsions, blackouts, agitation, and visual hallucinations. Withdrawal symptoms for cocaine includes depressed mood, fatigue, generalized malaise, vivid and unpleasant dreams, agitation and restless behavior, slowing of activity, and increased appetite.

Effects of Caffeine Withdrawal on Mood and Psychomotor Performance

The following section highlight studies recently conducted showing not only mood and somatic effects of caffeine but also impaired psychomotor performances (e.g., reduced function on tasks requiring visual vigilance, reaction speed, character recognition, and complex problem solving; Christopher et al., 2005; James, 1998; Juliano & Griffiths, 2004; Rogers et al., 2005; Warburton et al., 2001). In order to ensure that the mentioned tasks are sensitive to detecting the effect of caffeine administration on mood and psychomotor performances, Christopher and colleagues (2005) examined 68 participants and found that caffeine administration enhanced performance on categoric search tasks, repeated digits vigilance task, and alertness. They found limited support for focused attention task and simple reaction time task.

James (1998) examined objective indices of performance, and self-reported mood, headache, and sleep in 36 healthy male and female habitual moderate caffeine consumers. The study used character-recognition task—contained components designed to measure performance in terms of information transfer and short-term memory and mood

measures. The author found significant impairment on psychomotor tasks when caffeine was withdrawal abruptly following habitual use. Caffeine withdrawal was associated with increases in the frequency and severity of headache. The occurrences of headache are often attributed to the restriction of cerebral blood flow due to abrupt abstinence of caffeine intake by other researchers (Couturier, Laman, Duijn, & Juijn, 1997; Jones, Herning, Cadet, Griffiths, 2000; Griffiths & Mumford, 1995; Silverman et al, 1992). Studies suggested that caffeine acts as a vasoconstrictor on cerebral blood vessels, therefore it is not surprising that abrupt abstinence of intake frequently causes headaches in habitual consumers.

Rogers et al. 2005, examined withdrawal symptoms in college students with moderate to moderate-high daily caffeine intake. In addition, the authors evaluated the effect of sleep deprivation in caffeine withdrawal (e.g., participants were allowed only 5 hours of sleep before the testing day). The authors found that ratings of mood and other feelings also showed marked negative effects of overnight caffeine withdrawal (ONW), with ONW participants reporting heightened feelings of tension, light-headedness, and jitteriness, more headache, and lower clear-headedness, and energy than the limited time withdrawal (LTW) participants. There was no difference in terms of psychomotor performance and blood pressure or heart rate. The present study provides additional support of negative effects of mood and cognitive performance associated caffeine abstinence. Impairments were seen in the following areas: cognitive performance and the perception that the cognitive tasks were more difficult and tiring to perform, greater headache, reduced alertness, and clear-headedness, and an increased feeling of light

headedness. In sum, cognitive performance was found to be affected adversely by acute caffeine withdrawal.

Hewlett & Smith (2006) conducted a study comparing consumers with non-consumers. The authors measured mood and somatic symptoms and cognitive performance in 176 participants (56 non-consumers) using overnight abstinence paradigm. The authors found similar effects of abstinence on mood (e.g., decreased alertness; Rogers et al., 1995). On the contrary, there was limited support for the effect of caffeine withdrawal on performance. The authors found that habitual consumers did not perform as well on tasks of verbal reasoning and focused attention choice reaction time compared to non-consumers during withdrawal. There were no differences detected on performance of tasks relating to memory including, short-term, semantic, delayed recognition, and free recall. Consistent with much of the literature on withdrawal, the present study did not find differences on memory and free recall tasks. The most robust effects were demonstrated on simple reaction time and sustained attention tasks (Smith et al., 1999; Warburton et al., 2001).

In sum, caffeine abstinence can lead to mood changes (e.g., headaches, decreased alertness and depressed moods), and impairment on cognitive performances involving time reaction, sustained attention, and vigilance tasks (Juliano & Griffiths, 2004; Stafford et al., 2007). In addition, complex problem solving and verbal reasoning is also affected. There appears, however, a lack of support for the effect of withdrawal on tasks involving memory. It remains unclear whether sex-differences will emerge in findings relating to memory function (Rubinow et al., 2007).

Rogers and colleagues (2005) provide additional support of negative effects of withdrawal and cognitive performance associated caffeine abstinence. Impairments were seen in the following areas: cognitive performance and the perception that the cognitive tasks were more difficult and tiring to perform, greater headache, reduced alertness, and clear-headedness, and an increased feeling of light headedness. In sum, cognitive performance was found to be affected adversely by acute caffeine withdrawal. In addition, Hewlett & Smith (2006) compared consumers with non-consumers and found that habitual consumers did not perform as well on tasks of verbal reasoning, focused attention, and choice reaction time compared to non-consumers during withdrawal. In sum, caffeine abstinence can lead to mood changes (e.g., headaches, decreased alertness and depressed moods), and impairment on cognitive performances involving time reaction, sustained attention, and vigilance tasks (Juliano & Griffiths, 2004; Stafford et al., 2007). In addition, complex problem solving and verbal reasoning is also affected. There appears, however, a lack of support for the effect of withdrawal on tasks involving memory.

Caffeine Processes across the Menstrual Cycle

Caffeine (1,3,7-methylxanthine) acts primarily as an antagonist of adenosine A1 and A2 receptors to produce its basic biological effects. The downstream impact of adenosine receptor inhibition is reflected in a number of biological substrates, including some of those involved in regulating the menstrual cycle. The effects of drugs may vary across the menstrual cycle for several reasons, including cycle-related variations in basal mood states or physiology, interactions between drugs and circulating ovarian hormones (i.e. estrogen, progesterone, luteinizing hormones (LH) and follicle stimulating hormone

(FSH; Turner & Wit, 2006). In particular, elimination of the drug is approximately 25% slower during the luteal phase of the menstrual cycle when progesterone levels are highest, as compared with the follicular phase, when both progesterone and estradiol levels are lower (Balogh et al., 1987; Institute of Medicine, 2001; James, 1997). While this finding is consistent across studies, it remains unclear why progesterone level affects caffeine elimination rates.

A Theoretical Model

In consideration of limitations of the proposed research area, a theoretical model for understanding the effects of caffeine on the hormonal physiology of the menstrual cycle is posited in order to understand the effects of this powerful stimulant in the central nervous system. The central neurotransmitter adenosine is a purine nucleoside formed through the combination of adenine and D-ribose. Adenosine is one of the four major components of DNA and RNA that acts to inhibit a range of central synapses, thereby decreasing the rate of firing of central neurons and acting to inhibit glutamateric transmission and dopamine release. One result is the downregulation of estrogen receptors. Caffeine is an adenosine antagonist, which binds to adenosine receptors, thereby reducing the inhibitory effects of the neurotransmitter, resulting in increased excitation of the affected neural systems (Phillis, 1986). Since the central nervous system is responsible for the production of steroid hormones (e.g., estradiol and progesterone), the depressant action of adenosine may be influenced by the presence of estradiol and progesterone.

Progesterone accumulates in several areas of the central nervous system (CNS), including the cerebral cortex. Concentration of progesterone during the luteal phase can

increase up to 40% compared to the follicular phase of the cycle (Phillis 1991). This drastic increase in progesterone production is responsible for changes in mood symptoms such as irritability and depression (e.g., in women with premenstrual syndrome, PMS, or premenstrual dysphoric disorder, PMDD, (Backstrom et al., 1983; Laessle et al., 1990).

Because progesterone inhibits the reuptake of adenosine into cerebral cortical nerve endings, it significantly enhances the level of adenosine concentrations in the extracellular space, therefore allowing adenosine to function more freely.

Administration of progesterone in rats depressed the spontaneous firing of cerebral cortical neurons and prolonged the mean duration of adenosine-evoked inhibitors by 56% (Phillis, 1985). Progesterone potentiates the action of adenosine (Phillis, 1986), by inhibiting its reuptake into nerve and glial cells. This action creates higher concentrations of adenosine in extracellular space allowing for greater experiences of fatigue and depression associated with the initial luteal phase of the cycle (Phillis, 1989). Since caffeine facilitates the actions of adenosine leading to sedative-type experiences and caffeine is able to counteract such effects, it becomes a somewhat essential component for alleviating withdrawal experiences (e.g., depression) associated with the luteal phase. As such, the abstinence of caffeine during the luteal phase may involve greater impairment on psychomotor tasks and increased withdrawal experiences.

On the contrary, research indicates that estradiol increases firing of only some neurons (~9% compared to 42% attributable to progesterone; Phillis et al., 1985), resulting in only a weak ability to inhibit adenosine transport (Phillis, 1991). So estradiol is much like caffeine in that it feebly antagonizes the inhibitory actions of adenosine (Fenster et al., 1999). Phillis (1991) suggests that although estradiol concentration in

extracellular fluid of the brain are unlikely to reach levels at which the activity of the adenosine transporter is compromised, they may be sufficient to antagonize the actions of endogenously released adenosine, exerting caffeine-like stimulating action on the CNS. Such action could account for positive emotions attributed to the follicular phase of the cycle. It is also plausible that caffeine consumption during the follicular phase adds to the effects of rising levels of estradiol, since there is evidence that certain constituents of coffee may be estrogenic (Kitts, 1987). Lucero and colleagues (2001) also demonstrated that early follicular estradiol levels increase corresponding to level of caffeine consumption in women and that higher level of caffeine intake was associated with greater increases in the levels of estradiol (Lucero et al., 2001). (2) The follicular phase is characterized by significant increases in estradiol and is often associated with more positive emotions compared to the luteal phase (Backstrom et al., 1983). The addition of low to moderate doses of caffeine also enhances positive affect (James, 1997). Hence, the additive effect of estradiol and caffeine during the follicular phase should lead to more positive mood experiences and better performances on psychomotor tasks.

The effects of caffeine vary across the menstrual cycle (Lucero et al., 2001; Turner & Wit, 2006). During the menstrual cycle, progesterone is associated with feelings of fatigue and depression while estradiol with feelings of well-being (Phillis, 1991) and improvements on psychomotor tasks (James, 1997). Likewise, the presence of these reproductive hormones interact with caffeine; whereby, caffeine alleviates the degree of influence that progesterone has on mood and augments the effects of estradiol on mood and psychomotor performances. Of interest, is the phase-differentiated effects of caffeine abstinence. Caffeine has been shown to enhance performances on select

psychomotor tasks (Juliano & Griffiths, 2004; 2005; Rogers et al., 2005; Smith et al., 2007). Caffeine abstinence yields negative affect on withdrawal symptoms and psychomotor performances (Christopher, Sutherland, & Smith, 2005; James, 1998; Juliano & Griffiths, 2004; Rogers et al., 2005; Warburton et al., 2001). The theory posited suggests phase-differentiated interactions between caffeine and the menstrual cycle. Therefore, differential caffeine withdrawal experience during the menstrual cycle is also warranted. More specifically, caffeine abstinence may lead to differences in the severity of withdrawal symptoms experienced and in the level of impairment on psychomotor performances during the follicular and during the luteal phase. Possible reasons for such difference include: (1) the luteal phase is characterized by a higher baseline in mood and somatic symptoms and sedated neurological activities than the follicular phase; (2) the presence of estradiol alone improves psychomotor functioning (James, 1997) and (3) mood/somatic symptoms (Phillis, 1991).

Appendix B: Participant Screening Form

Screening Number: _____

Age:

Marital Status

- 1 = Single
- 2 = Married and living with spouse
- 3 = Separated married not living with spouse
- 4 = Divorced

Do you take oral contraceptives?

YES NO

Are you pregnant?

YES NO

Do you take any medication regularly?

YES NO

If you do take medication regularly, state what kind and how much.

How much COFFEE (CUPS) do you drink daily?

How much TEA (CUPS) do you drink daily?

How many COLA DRINKS (CANS) do you drink daily?

Please indicate if you take NODOZ on a regular basis.

YES NO

Please indicate if you take VIVARIN on a regular basis.

YES NO

Please indicate if you take ANACIN on a regular basis.

YES NO

Please indicate if you take A.S.A. COMPOUND on a regular basis.

YES NO

Please indicate if you take BROMO SELTZER on a regular basis.

YES NO

Please indicate if you take COPE on a regular basis.

YES NO

Please indicate if you take COUNTERPAIN on a regular basis.

YES NO

Please indicate if you take EXCEDRIN on a regular basis.

YES NO

Please indicate if you take EMPIRIN COMPOUND on a regular basis.

YES NO

Please indicate if you take FEMICIN on a regular basis.

YES NO

Please indicate if you take MEDACHE on a regular basis.

YES NO

Please indicate if you take MIDOL on a regular basis.

YES NO

Please indicate if you take PAC on a regular basis.

YES NO

Please indicate if you take SAL-FAYNE on a regular basis.

YES NO

Please indicate if you take STANBACK on a regular basis.

YES NO

Please indicate if you take TRIGESIC on a regular basis.

YES NO

Do you smoke cigarettes?

YES NO

If you do, how many cigarettes do you smoke daily?

What brand do you smoke?

Have you ever experience adverse (highly unpleasant or problematic) reactions to caffeine?

YES NO

If yes, please indicate when.

If yes, please indicate how many times this has happened.

Describe your symptom(s).

What did you consume (e.g., chocalate bar, Starbucks coffee, caffeine pill, etc.)?

Have you or any member(s) of your family been diagnosed with depression?

YES NO

If yes, please indicated who and the date of the diagnosed?

Are you lactose-intolerant?

YES NO



Caffeine Menstrual

During the last 4 weeks, how much have you been bothered by STOMACH PAIN?

- 1. Not bothered
- 2. Bothered a little
- 3. Bothered a lot

During the last 4 weeks, how much have you been bothered by BACK PAIN?

- 1. Not bothered
- 2. Bothered a little
- 3. Bothered a lot

During the last 4 weeks, how much have you been bothered by PAIN IN YOUR ARMS, LEGS, OR JOINTS (KNEES, HIPS, ETC.)?

- 1. Not bothered
- 2. Bothered a little
- 3. Bothered a lot

During the last 4 weeks, how much have you been bothered by MENSTRUAL CRAMPS OR OTHER PROBLEMS WITH YOUR PERIODS?

- 1. Not bothered

2. Bothered a little

3. Bothered a lot

During the last 4 weeks, how much have you been bothered by PAIN OR PROBLEMS DURING SEXUAL INTERCOURSE?

1. Not bothered

2. Bothered a little

3. Bothered a lot

During the last 4 weeks, how much have you been bothered by HEADACHES?

1. Not bothered

2. Bothered a little

3. Bothered a lot

During the last 4 weeks, how much have you been bothered by CHEST PAIN?

1. Not bothered

2. Bothered a little

3. Bothered a lot

During the last 4 weeks, how much have you been bothered by DIZZINESS?

1. Not bothered

2. Bothered a little

3. Bothered a lot

During the last 4 weeks, how much have you been bothered by FAINTING SPELLS?

- 1. Not bothered
- 2. Bothered a little
- 3. Bothered a lot

During the last 4 weeks, how much have you been bothered by FEELING YOUR HEART POUND OR RACE?

- 1. Not bothered
- 2. Bothered a little
- 3. Bothered a lot

During the last 4 weeks, how much have you been bothered by SHORTNESS OF BREATH?

- 1. Not bothered
- 2. Bothered a little
- 3. Bothered a lot

During the last 4 weeks, how much have you been bothered by CONSTIPATION, LOOSE BOWELS, OR DIARRHEA?

- 1. Not bothered
- 2. Bothered a little
- 3. Bothered a lot

During the last 4 weeks, how much have you been bothered by NAUSEA, GAS, OR INDIGESTION?

- 1. Not bothered
- 2. Bothered a little

- 3. Bothered a lot

Over the last 2 weeks, how often have you been bothered by LITTLE INTEREST OR PLEASURE IN DOING THINGS?

- 1. Not at all
- 2. Several days
- 3. More than half the days
- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by FEELING DOWN, DEPRESSED, OR HOPELESS?

- 1. Not at all
- 2. Several days
- 3. More than half the days
- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by TROUBLE FALLING OR STAYING ASLEEP, OR SLEEPING TOO MUCH?

- 1. Not at all
- 2. Several days
- 3. More than half the days
- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by FEELING TIRED OR HAVING LITTLE ENERGY?

- 1. Not at all

- 2. Several days
- 3. More than half the days
- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by POOR APPETITE OR OVEREATING?

- 1. Not at all
- 2. Several days
- 3. More than half the days
- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by FEELING BAD ABOUT YOURSELF, OR THAT YOU ARE A FAILURE, OR HAVE LET YOURSELF OR YOUR FAMILY DOWN?

- 1. Not at all
- 2. Several days
- 3. More than half the days
- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by TROUBLE CONCENTRATING ON THINGS, SUCH AS READING THE NEWSPAPER OR WATCHING TELEVISION?

- 1. Not at all
- 2. Several days
- 3. More than half the days

- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by MOVING OR SPEAKING SO SLOWLY THAT OTHER PEOPLE COULD HAVE NOTICED; OR THE OPPOSITE - BEING SO FIDGETY OR RESTLESS THAT YOU HAVE BEEN MOVING AROUND A LOT MORE THAN USUAL?

- 1. Not at all
- 2. Several days
- 3. More than half the days
- 4. Nearly every day

Over the last 2 weeks, how often have you been bothered by THOUGHTS THAT YOU WOULD BE BETTER OFF DEAD, OR OF HURTING YOURSELF IN SOME WAY?

- 1. Not at all
- 2. Several days
- 3. More than half the days
- 4. Nearly every day

In the last 4 weeks, have you had an ANXIETY ATTACK - SUDDENLY FEELING FEAR OR PANIC? Note: if you checked NO please scroll down to the question beginning with a *

- 1. No
- 2. Yes

Have you ever HAD AN ANXIETY ATTACK BEFORE?

- 1. No
- 2. Yes

Do some of these ANXIETY ATTACKS come suddenly out of the blue - that is, in situations where you do not expect to be nervous or uncomfortable?

1. No

2. Yes

Do these ANXIETY ATTACKS bother you a lot or are you worried about having another attack?

1. No

2. Yes

Thinking about your last bad anxiety attack, WERE YOU SHORT OF BREATH?

1. No

2. Yes

Thinking about your last bad anxiety attack, DID YOUR HEART RACE, POUND, OR SKIP?

1. No

2. Yes

Did you have chest pain or pressure?

1. No

2. Yes

Did you sweat?

YES NO

Did you feel as if you were choking?

YES NO

Did you have hot flashes or chills?

YES NO

Did you have nausea or an upset stomach, or the feeling that you were going to have diarrhea?

YES NO

Did you feel dizzy, unsteady, or faint?

YES NO

Did you have tingling or numbness in parts of your body?

YES NO

Did your tremble or shake?

YES NO

Were you afraid you were dying?

YES NO

*Over the LAST 4 WEEKS, how often have you been bothered by feeling nervous, anxious, on edge, or worrying a lot about different things. Note: If you checked NOT AT ALL, scroll down to the next question beginning with a *

1 = Not at all

2 = Several days

3 = More than half the days

Over the LAST 4 WEEKS, how often have you been bothered by feeling restless so that it is hard to sit still?

1 = Not at all

2 = Several days

3 = More than half the days

Over the LAST 4 WEEKS, how often have you been bothered by getting tired very easily?

- 1 = Not at all
- 2 = Several days
- 3 = More than half the days

Over the LAST 4 WEEKS, how often have you been bothered by muscle tension, aches, or soreness?

- 1 = Not at all
- 2 = Several days
- 3 = More than half the days

Over the LAST 4 WEEKS, how often have you been bothered by having trouble falling asleep or staying asleep?

- 1 = Not at all
- 2 = Several days
- 3 = More than half the days

Over the LAST 4 WEEKS, how often have you been bothered by havign trouble concentrating on thins, such as reading a book, watching TV, etc.?

- 1 = Not at all
- 2 = Several days
- 3 = More than half the days

Over the LAST 4 WEEKS, how often have you been bothered by becoming easily annoyed or irritable?

- 1 = Not at all
- 2 = Several days

3 = More than half the days

*Questions about eating: Do you often feel that you can't control WHAT or HOW MUCH you eat?

YES NO

Questions about eating: Do you often eat, WITHIN ANY 2-HOUR PERIOD, what most people would regard as a unusually LARGE amount of food? Note: If you answered NO to either this or the previous question, please scroll down to the next question beginning with the *

YES NO

Questions about eating: has this been often, on average as twice a week for the last 3 months.

YES NO

In the LAST 3 MONTHS have you OFTEN MADE YOURSELF VOMIT in order to avoid gaining weight?

YES NO

In the LAST 3 MONTHS have you OFTEN TOOK MORE THAN TWICE THE RECOMMENDED DOSE OF LAXATIVES in order to avoid gaining weight?

YES NO

In the LAST 3 MONTHS have you OFTEN FASTED-NOT EATEN ANYTHING FOR AT LEAST 24-HOURS in order to avoid gaining weight?

YES NO

In the LAST 3 MONTHS have you OFTEN EXERCISED FOR MORE THAN AN HOUR SPECIFICALLY TO AVOID GAINING WEIGHT AFTER BINGE EATING?

YES NO

If you checked YES to any of the above methods to avoid gaining weight, were any as often, on average, as twice a weeks?

YES NO

Do you ever drink alcohol (including beer or wine)? Note: if you checked NO scroll down to the next question beginning with the *

YES NO

Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU DRANK ALCOHOL EVEN THOUGH YOU DOCTOR SUGGESTED THAT YOU STOP DRINKING BECAUSE OF A PROBLEM WITH YOUR HEALTH?

YES NO

Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU DRANK ALCOHOL, WERE HIGH FROM ALCOHOL, OR HUNG OVER WHILE YOU WERE WORKING, GOING TO SCHOOL, OR TAKING CARE OF CHILDREN OR OTEHR RESPONSIBILITIES?

YES NO

Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU MISSED OR WERE LATE FOR WORK, SCHOOL, OR OTHER ACTIVITIES BECAUSE YOU WERE DRINKING OR HUNG OVER?

YES NO

Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU HAD A PROBLEM GETTING ALONG WITH PEOPLE WHILE YOU WERE DRINKING?

YES NO

Have any of the following happened to you MORE THAN ONCE IN THE LAST 6 MONTHS: YOU DROVE A CAR AFTER HAVING SEVERAL DRINKS OR AFTER DRINKING TOO MUCH?

YES NO

If you checked off ANY problems on this page, how DIFFICULT have these problems made it for you to do your work, take care of things at home, or get along with other people?

1 = Not difficult at al

2 = Somewhat difficult

3 = Very difficult

4 = Extremely difficult

During the LAST 4 WEEKS, how much have you been bothered by WORRYING ABOUT YOUR HEALTH?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by YOUR WEIGHT OR HOW YOU LOOK?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by LITTLE OR NO SEXUAL DESIRE OR PLEASURE DURING SEX?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by DIFFICULTIES WITH HUSBAND/WIFE, PARTNER/LOVER OR BOYFRIEND/GIRLFRIEND?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by THE STRESS OF TAKING CARE OF CHILDREN, PARENTS OR OTHER FAMILY MEMBERS?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by STRESS AT WORK OR OUTSIDE OF THE HOME OR AT SCHOOL?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by FINANCIAL PROBLEMS OR WORRIES?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by HAVING NO ONE TO TURN TO WHEN YOU HAVE A PROBLEM?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by SOMETHING BAD THAT HAPPENED RECENTLY?

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

During the LAST 4 WEEKS, how much have you been bothered by: thinking or dreaming about something terrible that happened to you IN THE PAST (ie. your house being destroyed, a severe accident, being hit or assaulted, or being forced to commit a sexual act?)

1 = Not bothered at all

2 = Bothered a little

3 = Bothered a lot

In the last year, have you been hit, slapped, kicked or otherwise physically hurt by someone, or has anyone forced you to have an unwanted sexual act?

YES NO

What is the most stressful thing in your life right now?

Are you taking any medicine for anxiety, depression or stress?

YES NO

THIS SECTION ON IS FOR WOMEN ONLY: Questions pertaining to menstruation, pregnancy, and childbirth. Which best describes your menstrual periods?

1 = Periods are unchanged

2 = No periods because of pregnancy or recently gave birth

3 = Periods have become irregular or changed in frequency, duration or amount

4 = No periods for at least a year

5 = Having periods because taking hormone replacement (estrogen) therapy or oral contraceptive

During the week before your period starts, do you have a SERIOUS problem with your mood (ie. depression, anxiety, irritability, or anger)?

YES NO

If you answered YES to the previous question, do these problems go away by the end of your period?

YES NO

Have you given birth within the last 6 months?

YES NO

Have you had a miscarriage within the last 6 months?

YES NO

Are you having difficulty getting pregnant?

YES NO

Appendix D: Daily Diary



Menstrual Cycle Study

Please enter your screening ID

Have you had any of the following products today? [alcohol, coconut products, shellfish, medications (e.g., Tylenol, Advil, Excedrin), foods containing chocolate, and foods containing caffeine]

YES NO

If yes, please write down which products you consumed.

Please indicate whether your LH test was positive.

YES NO

Please indicate the number of times TODAY that you consumed REGULAR COFFEE. If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed INSTANT COFFEE. If you had a large drink at a coffee shop, count it as 2 drinks

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed DECAFFEINATED COFFEE. If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ESPRESSO (ONE SHOT). If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed CAFFE MOCHA (2 SHOTS). If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed CAFFE LATTE (2 SHOTS). If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANY OTHER ESPRESSO DRINK. If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed HOT CHOCOLATE (COCOA). If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANY OTHER COFFEE/COCOA TYPE DRINK. If you had a large drink at a coffee shop, count it as 2 drinks.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed COCA-COLA.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed DIET COKE.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed PEPSI-COLA.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed JOLT COLA.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed AFRI COLA.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANY OTHER COLA.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed MOUNTAIN DEW.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed DR. PEPPER.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed BARQ'S ROOT BEER.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANY OTHER SODA.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANY OTHER DECAFFEINATED DRINKS.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed GREEN TEA (MADE FROM A TEA BAG).

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed BLACK TEA (MADE FROM A TEA BAG).

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANY HERBAL TEA.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed BOTTLED ICED TEA.

0 1 2 3 4 5

Please indicate the number of servings of COFFEE FLAVORED ICE CREAM you consumed TODAY.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed COFFEE FLAVORED YOGURT.

0 1 2 3 4 5

Please indicate the number of servings of CHOCOLATE CANDY that you consumed. (Estimate the serving size consumed based on the serving size indicated on the package. Please round to the next whole number.)

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed NODOZ, MAXIMUM STRENGTH.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed NODOZ, REGULAR STRENGTH.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed EXCEDRIN, REGULAR.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed EXCEDRIN, PM.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed VIVARIN.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANACIN.

0 1 2 3 4 5

Please indicate the number of times TODAY that you consumed ANY OTHER DRUG WITH CAFFEINE.

0 1 2 3 4 5

Please rate how WELL-BEING you feel at present.

Not at all

A little

Moderately

Very much

Please rate how MOTIVATION TO WORK you feel at present.

Not at all

A little

Moderately

Very much

Please rate how ABLE TO CONCENTRATE you feel at present.

Not at all

- A little
- Moderately
- Very much

Please rate how ENERGY/ACTIVE you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how SELF-CONFIDENT you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how MUZZY (LACKING CLARITY/PRECISION THOUGHTS) you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how HEADACHE you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how DROWSY/SLEEPY you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how alert/attentive you feel at present.

- Not at all
- A little
- Moderate
- Very much

Please rate how talkative you feel at present.

- Not at all
- A little
- Moderate
- Very much

Please rate how IRRITABLE/CROSS/GRUMPY you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how DEPRESSED you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how ANXIOUS/NERVOUS you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how UPSET STOMACH you feel at present.

- Not at all
- A little
- Moderately

Very much

Please rate how CONFUSED you feel at present.

Not at all

A little

Moderately

Very much

Please rate how MUSCLE PAIN OR STIFFNESS you feel at present.

Not at all

A little

Moderately

Very much

Please rate how LETHARGY/FATIGUE/TIRED/SLUGGISH you feel at present.

Not at all

A little

Moderately

Very much

Please rate how CEREBRAL FULLNESS you feel at present.

Not at all

A little

Moderately

Very much

Please rate how JITTERY/SHAKY you feel at present.

Not at all

A little

Moderately

Very much

Please rate how LIGHT-HEADED/DIZZY you feel at present.

Not at all

A little

Moderately

Very much

Please rate how IMPAIRED WORK/THOUGHT RELATED ACTIVITIES you feel at present.

Not at all

A little

Moderately

Very much

Please rate how CRAVING FOR CAFFEINE-CONTAINING FOODS you feel at present.

Not at all

- A little
- Moderately
- Very much

Please rate how IMPAIRED VERBAL ABILITY you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how URGE TO DO TASK/WORK-RELATED ACTIVITIES you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how CONTENT/SATISFIED you feel at present.

- Not at all
- A little
- Moderately
- Very much

Please rate how FLU-LIKE you feel at present.

- Not at all
- A little
- Moderately
- Very much

Are you currently menstruating?

- YES NO

Please indicate the most appropriate score for the level of irritability/hostility you are experiencing (irritable, hostile, negative attitude, angry, short-fused, yelling, and screaming at others).

- Not irritable
- Uncertain
- Mild, occasional outbursts of anger and hostile behavior.
- Moderate, irritable behavior evident, frequent outbursts.
- Severe, affects most interactions between self and significant other.

Please indicate the most appropriate score for the level of tension you are experiencing (tense, restless, jittery, upset, highstrung, unable to relax).

- Not tense.
- Doubtful, trivial.
- Mild, occasional tension.
- Moderate, tense, jittery, unable to relax, restless behavior evident.
- Severe, constantly tense and upset.

Please indicate the most appropriate score for the level of efficiency you are experiencing (decreased efficiency, easily fatigued).

- No disturbance
- Doubtful, trivial.
- Mild, somewhat reduced efficiency.
- Moderate, easily fatigued, gets much less done than usual.
- Severe, fatigue causes serious interference with functioning.

Please indicate the most appropriate score for the level of dysphoria that you are experiencing (dysphoria--a state of feeling unwell or unhappy mood, distinguish from depression).

- Not dysphoric.
- Somewhat blue, sad.
- Mild dysphoric and labile mood, spontaneously occurring.
- Marked spontaneous emotional lability, occasional crying, feelings of loneliness.
- Severe, obvious and persistent.

Please indicate the most appropriate score for the level of motor coordination you are experiencing (clumsy, prone to accidents, lowered motor coordination).

- No disturbance.
- Doubtful, trivial.
- Mild clumsiness, feel awkward.
- Moderate, frequent.

- ❑ Severe, impairment in motor coordination, (e.g., unable to write properly, sew, or unable to drive).

Appendix E: Food Restriction Guidelines

At noon of the day before your scheduled visit, please restrain from the following foods:

1. Alcohol
2. Coconut products
3. Shellfish
4. Foods containing chocolate products and caffeine

****Please only consume fluids such as fruit juice, water, milk****

Appendix F: Participant Information Sheet

Incentives

You will receive a total of \$20.00 when you complete this study. In addition, you will receive 6-8 credits for your psychology course at the end of the experiment.

Study Overview

(1) *Orientation.* Our meeting today is the orientation. You will sign inform consent for your participation. This meeting will take approximately 90 minutes. You will learn how to use the midstream ovulation test kit, and access the surveys online. You will also be able to familiarize yourself with some computer tasks that you will do during the laboratory sessions of the study.

(2) *Daily Diaries.* You are to complete surveys online daily for approximately 60 days. We would like you to complete the questions as thoroughly as possible. Please continue to complete your entries at the **same time daily** until you receive an email from the researcher indicating otherwise.

What You Need Prior to Your Daily Diaries

1. Before you go to bed, remember to complete the ovulation tests first.

To Access the Daily Diaries

2. Go to: <https://cgi.umd.edu/survey/display?um/Caffeine2007>
3. Logon with your University Directory ID and Password (e.g., ID: hvo, password: soccer). Click **Submit Request**
4. This will take you right the questionnaire titled “Caffeine Menstrual”. Please fill-in a number for each of the questions on the first page.
5. Click **Next** at the bottom of the page to get to the next form.
6. *Please make sure you complete the entry about the same time every night.*
 - a. *If you miss one day, please complete 2 entries on this site the following day.*
7. Please be sure you complete all the questions on this site as accurately and as completely as possible.

(3) Laboratory Session

1. You will receive a call from the researcher about 4 days before you need to come in for this part of the study. You will have approximately a week to plan your visit.
2. At noon of the day before your scheduled visit, please restrain from the following foods (alcohol, coconut products, shellfish, and all foods containing chocolate products and caffeine; only allow to consume fluids such as fruit juice, water, milk)

3. During the visit, you will be asked to (1) provide a saliva sample, (2) complete your daily diaries online, and (3) do some computer tasks.

Questions and Concerns: Please send an email to Hoa at: hvo2005@yahoo.com.



Ovulation Midstream Tests

- Free Shipping!
- Confidential Packaging
- Maximum Expiry Dates
- *Accurate, Easy-to-Use!*

Instructions for LH Ovulation Midstream Test

INTRODUCTION

Luteinizing hormone in elevated quantities causes ovulation. During the menstrual cycle only a small amount of LH is made, but in the middle of the cycle LH briefly increases. This increase is called the "LH surge" and precedes ovulation. Conception is most likely to occur within thirty-six hours following the LH surge. The Midstream Urine LH Ovulation Test is specifically designed to detect your LH surge - the time when you are likely to ovulate.

DETERMINE WHEN TO START TESTING

To determine when to start testing, you must first determine the length of your menstrual cycle. The length of the menstrual cycle is the number of days from the first day of menstrual bleeding to the day before bleeding begins on the next period.

Determine the usual length of the menstrual cycle over the last few months. Then, refer to the Cycle Chart to determine on which day of the menstrual cycle to begin testing. If your cycle is less than twenty-one days or greater than forty days, consult a physician.

Cycle Chart

Your Cycle Length	Day to Begin Testing
21 days	Day 5
22 days	Day 6
23 days	Day 7
24 days	Day 8
25 days	Day 9
26 days	Day 10
27 days	Day 11
28 days	Day 12
29 days	Day 13
30 days	Day 14
31 days	Day 15
32 days	Day 16
33 days	Day 17
34 days	Day 18
35 days	Day 19

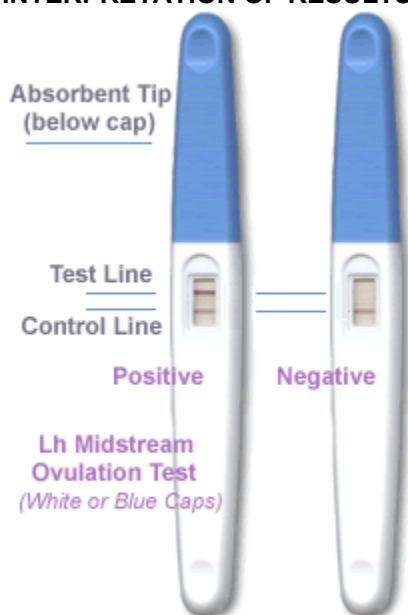
36 days	Day 20
37 days	Day 21
38 days	Day 22
39 days	Day 23

TEST PROCEDURE

Do **not** use first morning samples as LH is synthesized in your body early in the morning. It will not show up in urine until later in the day. The best time to test urine is between 11am and 8pm. Be sure to test at the same time each day. Also, reduce your liquid intake (and try not to urinate) around 2 to 3 hours before testing as a diluted liquid sample can hinder LH detection.

1. To begin testing, open the sealed pouch by tearing along the notch. Remove test kit from the pouch.
2. Hold the round end of cover with one hand. Use the other hand to pull out the test device and expose the absorbent tip.
3. Point the absorbent tip downward. Place the absorbent tip in urine stream for at least seven to ten (10) seconds to be thoroughly wet. NOTE: Do not allow urine to splash into the result window. To prevent urine from splashing the result window, during application, place your thumb over the interpretation window while holding the test in the urine stream.
4. Re-cap the device, lay flat on a table, and wait for color bands to appear. Depending on the concentration of LH, a positive result may be observed in as few as 40 seconds; however, to confirm negative results, the complete reaction time (5 minutes) is required. Do not read results after 10 minutes.

INTERPRETATION OF RESULTS



Lh Mid-Stream Test

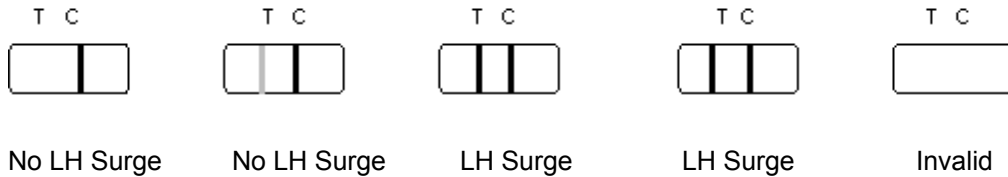
Negative - No LH Surge: Only one color band appears on the control (C) region or the test (T) band is much lighter than the control band. There is no LH surge.

Postive - LH Surge: If two color bands are visible and the test (T) band is equal to or darker than

the control (C) band, ovulate will probably take place within the next 24-48 hours.

Invalid: No visible band at all. The control band will not appear if an insufficient volume of specimen is added into the test kit. Proper procedures may not have been followed in performing the test. Repeat with a new test kit. Please consult above instructions and follow precisely.

*Important Note from Early-Pregnancy-Tests.com Regarding Invalid Test Results: The most common reason for an invalid test result with a midstream test is that urine has splashed into the interpretation window. This prevents liquid from properly “wicking” up the test and through the band of dye. Please note that invalid results can nearly always be avoided by placing your thumb over the interpretation window while holding the test in the urine stream.



QUESTIONS & ANSWERS

1) Should I restrict my diet before taking the test?

No, diet will not affect the test results.

2) Does alcohol, aspirin, or any other common drug affect the test?

No, but some hormonal medications can interfere with test results. If such medications are being taken or are suspected, seek professional advice from a physician to confirm the test results.

3) Should the test be used for contraception?

No, the test is not designed to prevent or help prevent conception and should not be used to do so.

4) Why is first morning urine not a good sample?

If first morning urine is used with the test, the first day of the LH surge may not be detected. The best time to collect the urine is between 10:00 A.M. and 8:00 P.M.. Always try to collect it at about the same time each day.

5) Today's control band is a different shade of red than yesterday's control band. Is this a concern?

No. Variations in the color of the control band will not affect the test result. Always compare the color of the test band to that of the control band of the same device on the day the test is performed. Do not compare bands from different devices.

6) Can test results be interpreted after five minutes?

No. Test results must be read at 5 minutes. Though a positive result should not change for several days, a negative result may change to a false positive within minutes after the end of the testing period, which would not be an accurate reading. It is always best to read the results at the 5 minute testing period and then discard the test to avoid confusion.

7) A pink background color and vertical streaking appeared in the result area during the testing period. Is this a concern?

No. Each urine sample will vary in its chemical makeup, as will the humidity of the air in testing chamber (room). Such variations in physical conditions can cause the vertical streaking and/or the pink-rose background color but will not affect the test results. As long as the control band appears within five minutes, the test is working properly.

STORAGE AND STABILITY

Store the test kit below 28°C; do not freeze. Refer to the expiration dates of the individual components for stability information.

WARNINGS AND PRECAUTIONS

1. The test kit is for in vitro (external) diagnostic use only.
2. Do not use beyond the expiration date.

Appendix G: Informed Consent Form

Project Title: Caffeine Abstinence during the Menstrual Cycle: An Evaluation of Mood and Psychomotor Effects of Withdrawal

By consenting, you indicate that you are over 18 years old, in good physical health, and wish to participate in a program of research being conducted by Dr. Barry Smith and Hoa T. Vo in the Department of Psychology at the University of Maryland, College Park, Maryland 20742.

Purpose & Procedures:

The purpose of this research is to examine the abstinence effects of foods across the menstrual cycle. Your participation in this research project is completely voluntary. However, if you choose to participate, you should note that the procedures involve completing about 60 days of diaries online. Your time commitment for this study will be approximately 90 minutes for the orientation, 5 minutes every morning (for about 60 days), and 2 hours in the lab. In sum, your total hour committed will be about 9 hours. Note that you will be awarded 6 extra credit points for your psychology course and will receive \$20.00 for your participation. You will also be given the opportunity to address concerns and questions about the project when your participation terminates.

Confidentiality:

All information collected in the study is confidential, and your name will not be revealed at any time. The data collected from you will be grouped with data collected from other participants and used for written research publications and presentations. Please note that your information may be shared with representatives of the University of Maryland, College Park or governmental authorities if you or someone else is in danger or if we are required to do so by law.

Benefits:

You should be aware that the experiment is not designed to benefit you personally, but that the investigators hope to learn more about food consumption across the menstrual cycle. You also should be aware that you are free to ask questions or to withdraw from participation at any time without penalty. Additionally, in the event that you do not complete the experiment, you should know that you will be awarded the appropriate amount of extra credit and money for your time invested in the project.

Risks:

You should be aware that you might experience some inconvenience due to the time commitment involved in this project. You may also experience temporary discomfort resulting from certain food restrictions (during 2 days throughout the study). In addition, you may find the content of the questionnaires, and the urine tests to be intrusive. Completion of questionnaires and the urine tests are completely voluntary. You may choose not to answer any or all questions without penalty. You will be asked to provide a saliva sample, which may or may not be used in the final analysis. You will be asked to complete some computer tasks online. You may find these tasks frustrating to complete. For example, one of the tasks asks you to respond rapidly by typing two alternating letters on the computer keyboard. In the event that you experience discomfort, discontinuation of the computer tasks will not be penalized.

Medical Care:

In the unlikely event of physical injury or negative psychological effects resulting from participation in this study, you should be aware that immediate medical or psychological treatment is available nearby at the UMD Counseling Center, the Psychology Clinic, and the Health Center at the University of Maryland. However, note that the University of Maryland does not provide any medical or hospitalization insurance coverage for participants in the research study, nor will the University of Maryland provide any compensation for any injury sustained as a result of participation in this research study except as required by law.

Rights of Research Participants: If you have questions about your rights as a research participant or you wish to report a research-related injury, you can contact: Institutional Review Board

Office, University of Maryland, College Park, Maryland, 20742; (e-mail) irb@deans.umd.edu; (telephone) 301-405-0678.

Contact Information

If you have further questions or concerns about this study, you may also contact the primary investigator:

Barry Smith, Ph.D.
smith@psyc.umd.edu
301-405-5860
University of Maryland College Park
1123D Biology/Psychology Bldg
College Park, MD 20742

Participant Printed Name: _____

Participant Signature: _____

Date: _____

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