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OVARIAN HORMONES, ADHD, RISK-TAKING, & IMPULSIVITY

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OVARIAN HORMONES, ADHD, RISK-TAKING, & IMPULSIVITY

DISSERTATION

A dissertation submitted in partial fulfillment
of the requirements for the degree of Doctor of Philosophy
in the College of Arts and Sciences at the University of Kentucky

By
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2016

ABSTRACT OF DISSERTATION

OVARIAN HORMONES, ADHD, RISK-TAKING, & IMPULSIVITY

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly impairing disorder of inattention, hyperactivity, and impulsivity that is more frequently diagnosed in males versus females at a ratio of 3:1. However, females with the disorder become highly impaired during adolescence, perhaps due to the onset of cycling ovarian hormones at puberty. The present study empirically assessed the role of the major female sex hormones, estrogen and progesterone, in the presentation of ADHD symptoms, impulsivity, and associated risk-taking behaviors (e.g., risky sex, substance use and abuse) in a non-clinical sample of young adult women. 32 healthy young adult women who were screened for hormonal conditions and medication use completed an initial laboratory visit during which measures of impulsivity and ADHD symptoms were collected. Each morning for 35 subsequent days, participants' hormones were measured via passive drool saliva samples, and participants responded to a brief online survey regarding substance use and sexual behaviors for the last 24 hours. Each evening, participants completed online questionnaires regarding ADHD symptoms. Results showed that ADHD symptoms were most pronounced when estrogen was low; this association manifested (1) between women, with lower average estrogen across the entire cycle predicting higher ADHD symptoms, and (2) within women, with lower-than-average levels of estrogen during periods of higher-than-average progesterone predicting higher ADHD symptoms two days later, consistent with a post-ovulatory, luteal phase effect of estrogen. Moderation analyses revealed that these within-person effects of ovarian hormones were significant *only among women with high negative or positive urgency* (emotion-related impulsivity) or *high sensation seeking*. With regard to alcohol use, within-person results were somewhat different; higher-than-average within-person estrogen was associated with higher likelihood of drinking and binge drinking on the following day, and this was true only during periods of lower-than-average progesterone, consistent with a pre-ovulatory, follicular phase effect of estrogen. These results have implications for the conceptualization of ADHD and associated risk-taking behaviors such as drinking, including personalization of treatment approaches for women.

KEYWORDS: ADHD, Estrogen, Progesterone, Menstrual Cycle, Ovarian Hormones

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OVARIAN HORMONES, ADHD, RISK-TAKING, & IMPULSIVITY

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CHAPTER ONE: INTRODUCTION

Background

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common and highly impairing childhood neurodevelopmental disorder (APA, 2013; Bernfort, Nordfeldt, & Persson, 2008; Pelham, Foster, & Robb, 2007, Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) that often persists into adolescence and adulthood (Faraone & Biederman, 2005; Kessler et al., 2006). The prevalence rate of ADHD in adults is thought to be between 3 and 5% (Faraone & Biederman, 2002; 2005; Kessler et al., 2006; Wilcutt, 2012). Adults with ADHD are at an increased risk for engaging in behaviors with negative outcomes and high societal cost, such as substance abuse, promiscuous sexual activity, and increased vehicular accidents, and are at increased risk for anxiety and mood disorders (Bauermeister et al., 2007; Barkley, 2006; Hosain, et al., 2012; Loe & Feldman, 2007; Flory, Molina, Pelham, Gnagy, & Smith, 2006; Wehmeier, Schacht, & Barkley, 2010). One of the most noted features of ADHD is that it is more frequently diagnosed in male children at a ratio of 3:1; yet females with the disorder are often particularly highly impaired beginning during adolescence and into adulthood (Lahey, et al. 1994), exhibiting such negative outcomes as poor self esteem, increased rates of anxiety and depression, and unplanned pregnancies (Biederman et al., 1999; Hosain, et al., 2012; Quinn, 2005, Robison et al., 2008). Further, there appear to be sex differences in symptom expression such that males with ADHD are more likely to exhibit hyperactivity-impulsivity and comorbid disruptive behavior disorders during childhood, while females with ADHD are more likely to exhibit inattention and comorbid depression during adolescence (Gaub & Carlson, 1997; Gershon & Gershon, 2002).

Yet, mechanisms of sex differences in symptom expression and comorbidity remain unknown, despite the fact that changes in sex, or gonadal hormones, during the prenatal period and adolescence may likely play a role. Initial work, in fact, suggests a role for prenatal testosterone exposure and ADHD (Martel, 2009; McFadden et al., 2005; Roberts & Martel, 2013). Such work suggests that known markers of symptoms and pathways to ADHD such as cognition and traits can help shed light on hormonal mechanisms. The current project focuses on ADHD symptoms, specific markers of disorder including cognition (executive function), risk-taking (drug abuse), and impulsivity (urgency), and circulating hormones during adolescence and young adulthood as a particularly understudied and yet critically important developmental risk factor for ADHD. The only existing work on hormonal associations with ADHD symptoms in adulthood relied on case studies which suggest that ADHD symptoms may fluctuate across the menstrual cycle, worsening the week before menstruation (when both estrogen and progesterone are declining; Quinn, 2005) and with symptom relief during pregnancy, a time of dramatically increased estrogen and progesterone (Nadeau & Quinn, 2002). Yet, no work to date has directly examined hormone levels themselves and their relationship to ADHD symptoms in groups of women, the goal of the current project.

Ovarian Hormonal Effects

Given that females with ADHD exhibit striking impairment beginning during adolescence, dramatic rises and fluctuations in sex hormones at puberty might play a role in this phenomenon. Beginning just before puberty, which typically occurs between 9 and 14 in human females (Norman & Litwack, 1997), both estrogen (E2) and progesterone (P4) rise and then begin to fluctuate across the monthly female reproductive cycle, as

shown in Figure 1 (Norman & Litwack, 1997). Generally speaking, in a typical 28-day cycle, E2 and P4 are both low during the week or so following the onset of menstruation, known as the early follicular phase. While P4 remains low throughout the remainder of the follicular phase, about eight days after the onset of menses, E2 begins rising steadily, reaching its peak around ovulation (occurring, on average, around 14 days prior to the onset of the next menses), alongside a more notable peak in lutenizing hormone, which marks the beginning of the luteal phase (Mishell et al., 1971; Norman & Litwack, 1997; see Figure 1). Notably, most variation in cycle length is attributable to the follicular phase of the menstrual cycle, with the luteal phase demonstrating much greater stability (~14 days). For example, stress can lengthen the follicular phase of the cycle, while the luteal phase of the cycle is much more consistent in length (Fehring, Schneider, & Raviele, 2006; Norman & Litwack, 1997).

This second half of the cycle (after ovulation) is called the luteal phase. Immediately following ovulation, E2 first declines rapidly before exhibiting a second smaller rise along with increasing P4 levels, which reach an all time high around mid-luteal phase. At the end of the luteal phase, both E2 and P4 decline rapidly a few days before the onset of the next menses (Norman & Litwack, 1997). Yet, it cannot be stressed enough that this typical pattern can vary greatly within women and between women on a month-to-month basis (Treloar, Boynton, Behn & Brown, 1967). For example, women exhibit striking variability in their levels of E2 and P4, as well as in the length of their cycle, even from month to month (Chatterton et al., 2005; Fehring, Schneider, & Raviele, 2006). In addition, individual women exhibit striking variation in their levels across the menstrual cycle with inter- and intra-person variation in the

magnitude of surges and declines (Chatterton et al., 2005). Further, after puberty, the menstrual cycle can take several years to become the fairly regular average of 28 days it is for most adult females (Norman & Litwack, 1997; Treloar, Boynton, Behn & Brown, 1967).

Cyclical hormonal patterns and levels change across development. Before puberty, gonadal hormones including E2 and P4, as well as testosterone, remain fairly low and static (Norman & Litwack, 1997). However, as puberty approaches, levels of gonadal hormones rise and, in women, begin to fluctuate in the cyclical manner described above (Norman & Litwack, 1997). Yet, this regular pattern often does not stabilize for several years. Furthermore, pregnancy, menopause, endocrine disease, use of oral contraceptives, use of steroid medication, body mass index, and even stress can impact hormone levels (Dobson & Smith, 2000; Gaspard et al., 1983; Lukanova et al., 2004; Nelson, 2011; Norman & Litwack, 1997; Pastor, Griffin-Korf, Aloi, Evans, & Marshall, 1998; Van der Vange, Blankenstein, Kloosterboer, Haspels, & Thijssen, 1990; Weiner, Primeau, & Ehrmann, 2004).

Yet, hormone levels and the more typical study of phase effects appear to be strikingly important for understanding female mood (which has been heavily studied; Eisenlohr-Moul, DeWall, Girdler & Segerstrom, 2015; Nelson, 2011; Payne, 2003; Steiner, Dunn, & Born, 2003; Vesco, Haney, Humphrey, & Nelson, 2007; Walf & Frye, 2006; Weiner, Primeau, & Ehrmann, 2004), as well as other affective processes, including impulsivity (Klump et al., 2014; Rosenblitt, Soler, Johnson and Quadagno, 2001). Yet, perhaps because of the complexity of such effects, hormonal influences on

these constructs remain relatively understudied and have never been directly studied in relation to ADHD in particular (Nussbaum, 2012).

Ovarian Hormonal Associations with Problems Related to ADHD

The fact that circulating hormone levels are dramatically understudied in relation to ADHD symptoms in females is particularly surprising given their known roles in associated processes such as executive function (EF), risk-taking, and response to psychostimulants. Deficits in executive function (e.g. problem-solving to achieve a future goal, including working memory, inhibition) are commonly associated with ADHD, occurring in at least 50% of individuals with an ADHD diagnosis (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Higher levels of both E2 and P4 have been individually linked to enhanced EF and attention (e.g., Davis & Nolen-Hoeksema, 2000; Hatta & Nagaya, 2009; Segerstrom, Roach, Evans, Schipper, & Darville, 2010). Several aspects of EF appear to be improved when E2 and P4 levels are high (Gogos, 2013; Howard, Gifford, & Lumsden, 1988; Jacobs & D'Esposito, 2011; Lord & Taylor, 1991; Rosenberg & Park, 2002; Segal, 2012; Vranic´ & Hromatko, 2008; Solís-Ortiz & Corsi-Cabrera, 2008; Solis-Ortiz, Guevara, & Corsi- Cabrera, 2004). For example, a study of naturally cycling young adult women (age 18-28), suggested a positive association between the follicular phase (when E2 is typically high) and executive functions that are "typical female" strengths. More specifically, women in the follicular phase demonstrated better performance on tasks of verbal implicit memory and verbal fluency, but worse performance on tasks involving mental rotations and perceptual priming (Maki, Rich & Rosenbaum, 2002). Thus, E2 appears to facilitate most types of EF.

Studies also demonstrate worsening memory and sustained attention during menopause (Frankiewicz & Cutler, 2000; Schmidt et al., 1996), a period characterized by a significant decrease in and destabilization of ovarian hormones. Likewise, a study in post-menopausal elderly women demonstrated that low doses of E2 might improve brain function efficiency during the tasks of sustained attention (Stevens, Clark & Prestwood, 2005). Finally, experimental administration of either E2 or P4 following pharmacological hormone suppression normalizes neural activity associated with executive functioning (Berman et al., 1997). Thus, overall, results are consistent with the idea that high levels of E2 are associated with better EF, including working memory and attention, two EFs that appear to be related to symptoms of ADHD.

In addition to the higher prevalence of EF deficits, individuals with ADHD also engage in higher levels of risk-taking than their peers (which in adulthood often manifests as substance abuse and risky sexual behaviors (Barkley, Murphy, & Fischer, 2010; Biederman et al., 2002; Disney et al., 1999; Wilens, Spencer, & Biederman, 1995). In some studies, cyclical "lows" of both E2 and P4 (measured via cycle phase and hormone levels) appear related to increased risk for alcohol and tobacco abuse (Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Evans & Levin, 2011; Epstein et al., 2006; Franklin et al., 2004, 2008; Pastor & Evans, 2003; Schiller, Saladin, Gray, Hartwell, & Carpenter, 2012). Yet, the subjective effects of stimulants (e.g. cocaine, methamphetamine) appear to have the opposite pattern of association with hormones, such that women report greater subjective effects of stimulants during the follicular phase (when E2 is rising and P4 is at low, at almost undetectable levels) compared to the luteal phase, when P4 is high and E2 is moderate (Sofuoglu, Dudish-Poulsen, Nelson, Pentel &

Hatsukami, 1999; Terner & de Wit, 2006). Pre-treatment with E2 also increases some of the subjective effects of stimulant medications (Justice & deWitt, 1999; 2000, White, Justice & de Wit, 2002), whereas high levels of P4 and administration of P4 attenuate the subjective effects of stimulants, minimizing the effects of E2 on stimulant effects during the luteal phase (Evans, 2007; Justice & deWitt, 1999). In line with hormonal effects on alcohol and nicotine use, lower E2 has also been associated with increased risk-taking as measured by monetary risk tasks, trust of strangers during an investment game, and measures of real-life risky behaviors, all of which demonstrated that women were less cautious (i.e., took more risks) during phases when levels of E2 were low, as measured by counting cycle days (Ball et al., 2013; Broder & Hohmann, 2003; Kaighobadi & Stevens, 2013).

Taken together, these studies suggest that low levels of E2 may be risky for increased use of and cravings for substances such as alcohol. Yet, the effects of other stimulants (e.g. cocaine, amphetamines) appear to be enhanced by E2 such that they are more rewarding to utilize when E2 is high and P4 is low (i.e. the follicular phase). Due to the higher incidence of risk-taking and substance use among women with ADHD, it is possible that women at risk for the disorder have lower average levels of E2 that put them at risk for use of alcohol. Thus, lower average E2 may represent a pathway to both substance use and ADHD symptoms in some women.

ADHD Heterogeneity

Recent theory of ADHD defines it as a disorder of disinhibition (Barkley, 1997; Nigg, 2001), and impulsivity is a core component based on ADHD diagnostic criteria. Yet, one of the most striking features of the disorder is its heterogeneity, which is

currently described using three subtypes, or presentations. Likewise, recent theory of ADHD suggests multiple pathways to the disorder (Nigg, Goldsmith, & Sachek, 2004; Sonuga-Barke, 2005), with continuous symptom dimensions perhaps best supported (Haslam et al., 2006; Larsson, Anckarsater, Råstam, Chang, and Lichtenstein, 2012; Marcus & Barry, 2011). In adulthood, one potentially particularly promising way of doing this is by focusing on impulsivity, which seems to be particularly prominent in adulthood (Barkley, Murphy, & Fischer, 2010). Notably, conceptualization of impulsivity has advanced in recent years (Lynam, Smith, Whiteside, & Cyders, 2006; Smith et al., 2007).

A handful of studies on such conceptualizations of impulsivity in adults with ADHD suggest associations with Lack of Perseverance (inability to remain with a task through completion), Negative Urgency (negative affect-driven rash action), and Lack of Planning (action without careful thinking; Miller et al., 2010; Pedersen et al., 2016; reviewed by Berg, Latzman, Bliwise, & Lilienfeld, 2015). Sensation Seeking (tendency to seek adventure) may be more specifically associated with hyperactivity-impulsivity (Lopez et al., 2015). Further, Urgency, Sensation-Seeking, and Lack of Planning appear to explain associations between ADHD and substance use (Pedersen et al., in press; Roberts et al., 2014). These studies suggest that trait impulsivity appears to be related to ADHD, and those who are high in certain forms of trait impulsivity may be more likely to experience risk-taking behaviors (e.g., substance use). According to an interactional perspective on personality (Endler & Parker, 1992), impulsive action (i.e. risk taking behaviors) are dependent on an individual's personality in addition to interactions with other factors, including social, environmental or biological factors (Endler & Parker,

1992). Therefore, studies examining hormonal associations with ADHD in young adult women may need to pay particular attention to impulsivity as a moderator of hormonal effects since these effects may interact and effects may be particularly striking for young women high in trait impulsivity.

Goals of the Present Study

To recap, although lower E2 appears to be associated with worse EF and more risk taking (e.g., substance use), no empirical work to date has directly examined the role of circulating E2 in relation to ADHD symptoms and associated markers. Further, specific types of trait impulsivity may help explain heterogeneity within ADHD in adults; yet, thus far, these ideas have not been examined.

The present study sought to examine the association between ovarian hormone levels**,** ADHD symptoms, and risk-taking behaviors (i.e., substance use), and to explore whether associations between ovarian hormones and ADHD symptoms and risk-taking behaviors are moderated by trait impulsivity. Based on prior work suggesting that higher E2 has positive effects on EF and decreases risk for more common forms of substance use (i.e., alcohol), it was hypothesized that, 1) between-women, lower average E2 across the entire menstrual cycle (i.e. higher overall recent exposure to E2) would be associated with greater ADHD symptoms and risky behaviors, 2) lower-than-average (within-person) levels of E2 would be associated with increases in ADHD symptoms and risky behaviors, and that 3) lower-than-average (within-person) levels of E2 would be more strongly associated with increased ADHD symptoms and risk-taking for those with higher levels of trait impulsivity. Additionally, given the potential for interactive effects of E2 and P4 (Klump et al., 2008; 2013; Eisenlohr-Moul et al., 2015), P4 was included as

an exploratory variable, and examined as a moderator of E2 effects. Finally, phase effects were also examined in order to more easily compare study results to previous studies that utilized cycle phase.

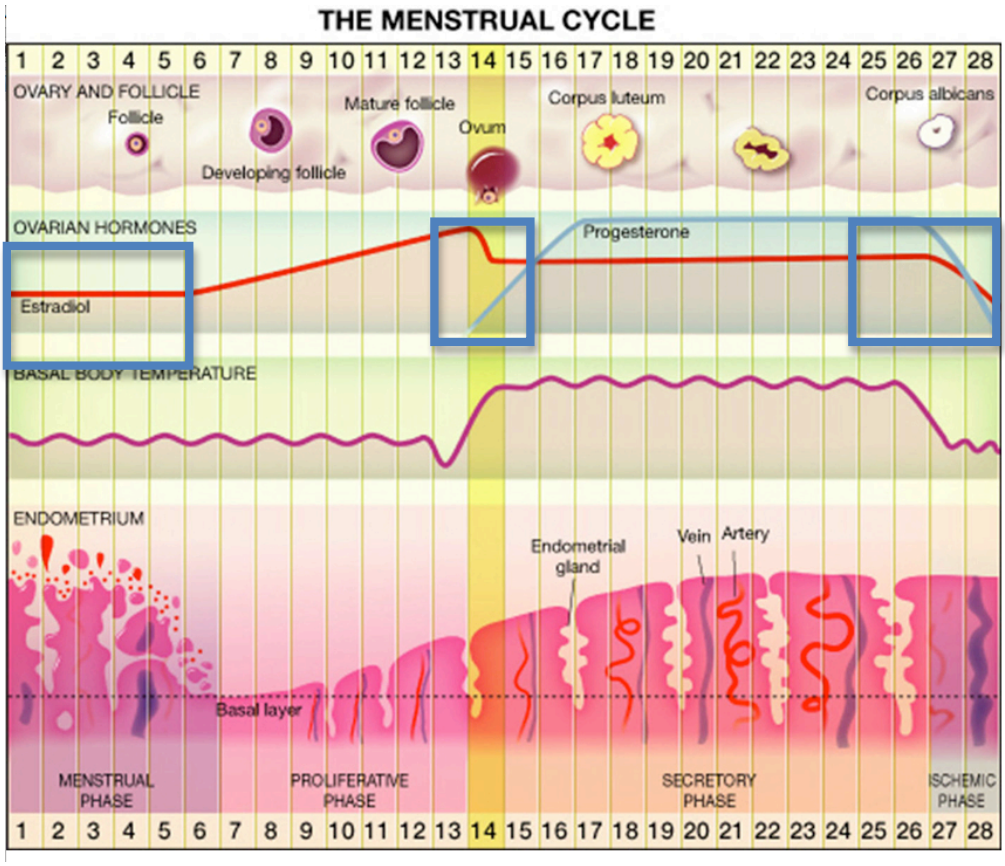


Figure 1. Typical representation of expected E2 and P4 levels across the cycle (Haimov-Kochman & Berger, 2007). The boxes indicate periods of the cycle hypothesized to exhibit increases in ADHD symptoms and risk-taking behaviors.

CHAPTER TWO: METHODS

Overview of Study Design

The study design was short-term longitudinal. Participants completed a screening visit to determine study eligibility. The women eligible to participate in the current project subsequently completed 35 sequential days of in-home data collection lasting 30-45 minutes each day. Hormones were assayed every other day, resulting in an average of 17 observations per woman.

Participants

Participants were a non-clinical sample of 32 naturally-cycling young women between the ages of 18 and 22 (M = 19.43, SD = 1.38) that were undergraduates recruited from the University of Kentucky Psychology Department subject pool and young women from the community recruited via posted flyers. The participants' ethnic background broadly matched that of the surrounding community; 70.6% of the sample identified as Caucasian, 17.6% as African American, and 11.8% as another ethnic minority.

Procedure

Screening and Initial Lab Visit. All participants completed one in-lab screening visit where they provided informed consent via IRB-approved procedures. The 32 eligible females completed 35 sequential days of follow-up data collection at home. Study eligibility was assessed at the initial screening visit. All participants completed the Screening and Medical History Form (detailed below), and a measure of study eligibility, with a trained study staff member. Participant's height and weight were also measured since body mass index has been demonstrated to have an effect on circulating levels of sex-steroid hormones (Lukanova et al., 2004; BMI *Mean* = 24.37, SD = 6.33). Finally,

participants completed measures of trait impulsivity, ADHD symptoms, and executive functioning at this initial visit (detailed below).

To be eligible for the study, participants had to be female and between 18 and 24. Exclusionary criteria included primary sensorimotor handicap, neurological disorder (e.g., seizure disorders, brain tumor, cerebral palsy, hydrocephalus, head injury with loss of consciousness), known pervasive developmental disorder (i.e., autism, Asperger's, Rett's, childhood disintegrative disorder), reported psychosis (i.e., schizophrenia, hallucinations, delusions), diagnosed intellectual disability, known hormonal abnormalities (e.g., Polycystic Ovarian Syndrome, thyroid conditions), including irregular cycles (i.e., cycles shorter than 21 days or longer than 35 days or fluctuating by more than 10 days across cycles, per self report), and current medical use of hormonal preparations (e.g., oral contraceptives, steroid-based medications), psychostimulants, or antipsychotic medications. Other medication use was measured in an open-ended manner; three women reported using prescribed Selective Serotonin Reuptake Inhibitors (SSRIs). However, SSRI use was not associated with outcomes or average hormone levels across the cycle (all p's < .34). Participants who met study exclusionary criteria were invited to complete the 35-day study. Forty-eight women were eligible and began data collection. However, 23% (*N*=11) discontinued participation during the study and 10% (*N*=5) completed less than 50% of data collection, leaving a final sample size with usable data of 32 women.

Eligible and interested female participants were sent home with a packet of data collection materials so they could collect data every day for the following 35 days. Detailed instructions on at-home data collection were provided verbally and in writing,

and participants were provided with the telephone number and email address of a trained research assistant in case they had any questions. They also provided a telephone number and email address so that they could receive daily reminders about data collection and links to morning and evening surveys throughout the 35 days. Every morning, participants provided saliva samples (described below), and responded to a short questionnaire about psychotropic medication use and food intake. All participants reported taking some form of medication over the course of the study. The most common included over-the-counter medications for pain, gastrointestinal distress, cold and flu, and allergies. None of the participants reported eating immediately upon waking, suggesting that saliva collection directions were followed.

At this time, participants also completed a measure of drinking, described below. In the evening after 5pm, they were instructed to follow an email link to a secure website to complete 30-45 minutes of questionnaires (described below) which are time- and date-stamped so accuracy of data collection could be monitored. Timestamps suggested that data were collected appropriately (e.g. morning surveys completed in morning and evening surveys completed same-day after 5pm). At the end of the 35 days, study staff contacted participants and arranged for a time for them to return their frozen saliva samples to the laboratory for storage in an -80 degree freezer. Participants who completed any data collection received $50 compensation, those who completed >50% of the data received $75, and those who completed all data collection received $100. Following the end of data collection, saliva samples were sent in bulk to the Center for Clinical and Translational Science (CCTS) on the University of Kentucky campus for at-cost assaying with well-established and reliable assays (described below).

Measures

ADHD Symptoms. Participants completed the *Current ADHD Symptoms Scale (CSS): Self-report,* a symptom checklist for ADHD, Oppositional-Defiant Disorder (ODD), and Conduct Disorder (CD) symptoms and associated impairment (Barkley & Murphy, 2006) at the screening visit and for the next consecutive 35 days. Symptom counts were used for analysis rather than diagnosis, as the sample was community-recruited and research indicates that ADHD is best represented as a continuum (vs. category; Barkley, 2006; Haslam et al., 2006; Marcus & Barry, 2011). Second reporter responses for childhood symptoms were received for 34% of participants (*N*=11), and indicated that only one participant experienced a clinically significant number of ADHD symptoms (5 inattentive and 3 hyperactive-impulsive symptoms) during childhood. Second reporter responses for current symptoms were received for 41% of participants (*N*=13) and reports of both childhood and adult symptoms were received from 28% of participants (*N* =9). Based on self and second reporter responses, none of the participants met DSM-5 criteria for ADHD. Total possible daily (state) reported ADHD symptoms ranged from 0 to 18 (M = .52, SD = 1.40; α = .80). Total possible Hyperactive-Impulsive symptoms ranged from 0 to 9 (M = .32, SD = .66; α = .66), and possible Inattentive symptoms ranged from 0 to 9 (M = .20, SD = .65; α = .72). Data screening revealed that symptoms were right skewed so log transformations were carried out and were successful in producing normal residuals for all analyses.

Impulsivity. At the initial visit, participants completed the *UPPS-P Trait Impulsivity Scale*, a 59-item questionnaire that assesses five components of trait impulsivity (i.e. Positive Urgency [positive affect-driven rash action], Negative Urgency

[negative affect-driven rash action], Lack of Planning [action without careful thinking], Lack of Perseverance [inability to remain with a task through completion], and Sensation Seeking [tendency to seek adventure; Whiteside & Lynam, 2001]). The scale has demonstrated reliability and validity for use in assessing young adults (Lynam et al., 2006; Cyders et al., 2007). In the current sample, Lack of Perseverance exhibited fair reliability ($\alpha = .56$) and Lack of Premeditation, Negative Urgency, Positive Urgency and Sensation Seeking exhibited good reliability ($\alpha = .82$-$.93$).

Risk-taking Behaviors. Each morning, participants reported detailed information about sexual behaviors (new sexual partners), drug use (marijuana and other recreational drugs), and the number of units of alcohol that they had consumed in the past 24 hours using an adaptation of the Timeline Followback Interview (Sobell & Sobell, 1992; 1994). This interview has good reliability and validity in this population (Tonigan, Miller, & Brown, 1997) and for this purpose (Del Boca, Darkes, Greenbaum, & Goldman, 2004). Due to the limited frequencies of drug use (17 reports, .4% of days) and risky sex (3 reports, .01% of days) in the sample, it was not possible to examine these outcomes. Units of alcohol were defined as one shot, one beer, or one glass of wine. Two daily binary outcomes were defined from this response: first, whether or not the woman drank alcohol at all, and second, whether the woman drank 4 or more drinks (binge drinking). Although binge drinking has been defined in a variety of ways, this corresponds to the definition provided by the CDC (http://www.cdc.gov/alcohol/fact-sheets/binge-drinking.htm). Because drinking was expected to follow a weekly cycle in which alcohol use is substantially higher on Thursday through Saturday, with intermediate levels of drinking on Sunday, and much lower levels of drinking Monday through Thursday (Del

Boca, Darkes, Greenbaum, & Goldman, 2004), day of week was also examined in analyses involving drinking utilizing a dichotomous predictor of weekend status (where Thursday through Sunday = 1).

17β-Estradiol and Progesterone. Saliva samples were collected via passive drool by participants in the morning thirty minutes after waking and were subsequently frozen. Participants were instructed not to eat, drink, brush teeth, or smoke before saliva collection. No participant reported violation of this morning protocol in daily diaries. Samples from every other day were analyzed due to cost. Serum E2 (pg/mL) and P4 (pg/mL) were determined using enzyme immunoassay kits available through Salimetrics and assayed through campus Clinical Center for Translational Science. For E2, the Salimetrics 17β-Estradiol immunoassay kit had a sensitivity of 0.1 pg/mL and high precision (% coefficient of variation ranging from .7 to 14.5). For P4, the Salimetrics immunoassay kits had a sensitivity of 5 pg/mL (from 0) and precision of percent coefficient of variation between 1.05 and 14.8. All participants showed peak P4 levels consistent with an ovulatory cycle (Howards et al., 2009). Finally, E2 and P4 generally showed expected trajectories across the menstrual cycle such that E2 demonstrated a midcycle peak and secondary peak during the midluteal phase, and P4 was low during the follicular phase and peaked during the luteal phase.

Menstrual Cycle Phase Coding. First, we coded the follicular, midluteal, and premenstrual phase menstrual cycle days using methods described by Edler, Lipson, & Keel (2007). The first day of menses was coded as 1; from this day 1, cycle day was counted backward to -15, and forward to +10. There was no day 0. Cycle phases were coded as Follicular (days +3 to +7), Midluteal (-9 to -5) and Premenstrual (-3 to +1). In

addition to these traditional menstrual cycle coding methods, we created an additional cycle phase variable to further differentiate pre-ovulatory and post-ovulatory phases. To create this variable, we identified four pre-E2 peak and four post-E2 peak days: after identifying the ovulatory E2 peak, the day of the ovulatory E2 peak and the three days prior comprised the "preovulatory" phase, while the four days after the ovulatory peak comprised the "postovulatory" phase. Therefore, five total phases were coded, with no overlap: Follicular, Preovulatory, Postovulatory, Midluteal, and Premenstrual.

Analytic Plan

Operationalization of Predictor and Outcome Variables. Each participant had two E2 variables and two P4 variables: (1) Between-Person Variables: the person's average levels of E2 and P4 across all samples ("trait" variance in each hormone across one menstrual cycle) and (2) Within-Person Variables: the standardized deviation of today's E2 and P4 values from a woman's average levels of E2 and P4 across all samples (i.e., today's hormone value minus the "person average" for that hormone, divided by the person's standard deviation for that hormone; see Klump et al., 2008). The latter standardized deviation reflects fluctuations in E2 and P4 relative to the person's own average level and one's own typical degree of variability and was the central within-person predictor. Hormones were also *lagged* such that hormonal predictors of today's ADHD outcomes represented hormone levels two days ago, and hormonal predictors of today's drinking outcomes (analyzed in the subsample of 22 women reporting drinking any alcohol) represented levels one day ago. We made this decision because participants responded to questions about their drinking "over the last 24 hours" during morning

surveys and to questions about ADHD symptoms and impulsivity about "today" during evening surveys. All continuous between-person predictors were standardized.

Multilevel Logistic Models. Data were analyzed using multilevel models in SAS PROC MIXED and SAS PROC GLIMMIX in which repeated daily measures (outcomes, hormones) were nested within women. Multilevel models utilize all available data with no listwise deletion and accommodate missing data using maximum likelihood estimation. In daily models, day-level hormonal predictors were person-standardized around each woman's average and standard deviation to isolate the within-person component and create a averageingful scale for estimates.

To evaluate the unique contributions of between- and within-person variance in ovarian hormones to ADHD symptoms, normal multilevel models were utilized predicting daily outcomes (ADHD symptoms and drinking) in SAS PROC MIXED. In each of these multilevel models, predictors were: 1) standardized BMI as a person-level covariate, 2) one's average E2 (across all observations), 3) one's average P4 (across all observations), 4) person-standardized E2 two days before the outcome, 5) person-standardized P4 two days before the outcome, and 6) the interaction of person-standardized E2 and P4. Both between-person predictors (one's average E2 and P4) and within-person predictors (person standardized E2 and P4 at the current assessment point) were entered into the same model (see tables 3.1-3.5).

In order to explore whether person-standardized ovarian hormones (fluctuations relative to one's individual average and SD) were more strongly associated with daily ADHD symptoms for those with higher trait levels of impulsivity, multilevel regression models were again utilized predicting each outcome from 1) standardized BMI as a

covariate, 2) one's average levels of E2 and P4 (as a control variables), 3) person-standardized recent E2 and P4, and 4) their interaction, 5) trait levels of impulsivity, and 6) the interactions of all hormone variables with trait impulsivity.

Drinking outcomes were analyzed in logistic multilevel models in SAS PROC GLIMMIX. Daily drinking outcomes were predicted from 1) standardized BMI and legal drinking status (0 = Underage 1 = Legal Age) as person-level covariates, 2) dichotomous weekend status (Thursday-Sunday = 1; Monday-Wednesday=0, 3), average E2 and P4 (across all observations), 4) yesterday's person-standardized levels of E2, 5) yesterday's person-standardized levels of P4, 6) their interaction, and 7) the two- and three-way interactions of steroid levels with weekend status.

Statistical Power. For all analyses, power was adequate (.8) to detect moderate effect sizes (*d* =.07-.09; Klump et. al., 2013) based on the current sample size (*N* =32). In order to reach power to detect small effect size (*d*=.02), 2000 observations from 145 women would be needed. For ADHD outcomes (full sample; normal multilevel models), intraclass correlation coefficients for both daily hyperactive/impulsive symptoms (ICC = .27) and daily inattentive symptoms (ICC = .36) indicated that the majority of the variance in ADHD symptoms was at the within-person level, leading to an adjusted *N* of 95 observations for the hyperactive/impulsive outcome, and an adjusted *N* of 76 observations for the inattention outcome. The smallest detectible effect sizes, assuming a normally distributed outcome, for a cross-level interaction predicting daily hyperactivity/impulsivity (*f squared* = .091) and daily inattention (*f squared* = .085) indicated sufficient power to detect conventionally small-to-medium interactive effects of UPPS traits and within-person hormone variables.

For drinking outcomes, intraclass correlation coefficients for both daily drinking (ICC = .15) and daily binge drinking (ICC = .23) also indicated that the majority of the variance in drinking was at the within-person level, leading to an adjusted *N* of 140 observations for the daily drinking outcome, and an adjusted *N* of 95 observations for the daily binge drinking outcome. Detectible ranges of effect sizes (in this case, odds ratios) in logistic models predicting drinking (ORs below .58 and ORs above 1.71) and binge drinking (ORs below .51 and ORs above 1.94) indicated sufficient power to detect conventionally small-to-medium main effects of a within-person hormonal predictor in a model in which other predictors account for 25% of the variance in drinking.

CHAPTER THREE: RESULTS

Descriptive Analyses

The full sample (*N*=32) included 1058 response days, with 476 outcome days included in analyses (i.e., days with nonmissing lagged hormonal predictors). 22 women in the sample reported alcohol use with similar demographics as the full sample. The subsample included 707 total days, with 352 outcome days included in analyses (i.e., days with non-missing lagged hormonal predictors). Among women who reported drinking, there were 97 total daily drinking reports (13.7% of days range = 0-15 days of drinking) and 31 binge drinking reports (4.3% of days).

Association of Hormone Averages, Trait Impulsivity & Trait ADHD Symptoms

Despite the small degree of between-person variance noted in ADHD symptoms, spearman rank partial correlations examined the associations of average ADHD symptom reports with average levels of E2 and P4 across the data collection period (controlling for both age and BMI). Higher total exposure to E2 and P4 were associated with *lower*

average inattention. E2 exposure, but not total P4 exposure, was associated with lower average hyperactivity/impulsivity. Average E2 was uncorrelated with any impulsivity measures, but total P4 exposure was negatively associated with Positive Urgency, Sensation Seeking, and Lack of Premeditation.

Effects of E2 and P4 on ADHD Symptoms

The model included both between-person and within-person ovarian hormone variables as predictors of daily ADHD symptoms (Inattentive, Hyperactive-Impulsive, and total ADHD symptoms). In other words, three separate models were conducted in which these different symptom domains were independently predicted as a function of one's average levels of both E2 and P4 across the menstrual cycle, from women's person-standardized E2 and P4 fluctuations around their own average, and the within-person interaction of E2 and P4. Model effects reported throughout this manuscript were not substantially altered in significance or effect size when random effects of within-person hormonal predictors were added to the multilevel models. However, these random effects of within-person hormonal predictors did not significantly improve model fit (as evaluated using a likelihood ratio test) and were therefore dropped from the models. Results of this model are presented in Table 3.1 and are summarized in the paragraphs that follow.

There was just one significant between-person effect of average hormones on ADHD symptoms. As hypothesized, lower average E2 across the month predicted higher average endorsement of daily hyperactive-impulsive ADHD symptoms across the month. *Within* a given person, person-standardized E2 and P4 interacted to predict daily total ADHD symptoms in total, including both inattention and hyperactivity-impulsivity. The

pattern of this interaction was identical across these three outcomes, and each of these interactions are depicted in Figure 3.1. When P4 was higher than usual, lower person-standardized E2 was associated with more current total ADHD symptoms (γ = -.08, *SE* = .03, *t*(393) = -2.77, *p* = .005; when P4 is +1 person-SD above the person average, a +1 person-SD above one's person average E2 corresponds to an average decease of .08 in ADHD symptoms), hyperactive/impulsive symptoms (γ = -.06, *SE* = .02, *t*(390) = -2.93, *p* = .003; when P4 is at +1 person-SD above the person average, a +1 person-SD above one's person average E2 corresponds to an average decrease of .06 in hyperactive/impulsive symptoms), and inattentive symptoms (γ = -.05 *SE* = .02, *t*(424) = -1.99, *p* = .049; when P4 is at +1 person-SD above the person average, a +1 person-SD above one's person average E2 corresponds to an average decrease of .05 in inattentive symptoms), consistent with a post-ovulatory, luteal phase effect of E2. The effects of person-standardized E2 were not significant when P4 was lower than usual (all *p's* > *.34).* Phase analyses showed similar results, in that inattentive symptoms were significantly higher during the postovulatory period than follicular phase (*p*= .03; see *Figure* 3.2). Although statistically significant, these unmoderated (average) hormonal effects are quite small when considered in light of the possible ranges of the outcomes (0-9 for each subscale and 0-18 for the total score).

Moderation of Hormone Effects by Trait Impulsivity

Negative and Positive Urgency. Both Positive and Negative moderated average E2 and the interaction between recent E2 and P4 predicting ADHD outcomes. There was a significant interaction between both types of Urgency and average levels of E2 predicting all ADHD symptoms outcomes and between both types of Urgency and the

interaction of recent levels of E2 and P4 predicting ADHD outcomes; each of these interactions took the same form, which are depicted in Figures 3.3 through 3.7. However, further examination revealed that these effects were significant only for those women who were high in either Positive or Negative Urgency (all p's < .016). Results of analyses probing these interactions revealed that, at high levels of Positive or Negative Urgency, lower average E2 across the cycle was associated with increased ADHD symptoms. None of these effects of E2 were significant among women low in Negative Urgency (all p's > .39) or low in Positive Urgency (all p's > .59).

To further decompose these three-way interactions, we tested the simple effects of recent E2 on each outcome at both lower-than-average (-1 person-SD below the person average of P4) and higher-than-average (+1 person-SD above the person average of P4) P4 among women high (+1 SD) in trait Urgency. The simple effects of lower-than-average E2 leading to higher ADHD symptoms were significant only at higher-than-average P4 (e.g., the luteal phase; all p's < .025). This was true for both Negative and Positive Urgency. At lower-than-average P4 (i.e., the follicular phase) among women with high Positive or Negative Urgency, simple effects of recent E2 were not significant (all p's < .27).

Phase analyses revealed that for those high in Negative Urgency, inattentive symptoms peaked in the post-ovulatory phase relative to the follicular, pre-ovulatory midluteal phase and premenstrual phases (see Figure 3.8). Similarly, for those high in Positive Urgency, inattentive and hyperactive-impulsive symptoms peaked during the postovulatory phase (see Figure 3.9).

Sensation Seeking. There were no significant interactions between Sensation Seeking and average levels of E2 or P4 predicting any ADHD symptoms outcomes. However, there were significant interactions between Sensation Seeking, Recent E2, and Recent P4 predicting all ADHD symptoms; each of these interactions are presented in Figure 3.10. The two-way interaction between recent E2 and recent P4 was significant only among women who were high (+1 SD) in Sensation Seeking. The three-way interaction was explored in the same manner described above.

The simple effects of lower-than-average E2 leading to higher ADHD symptoms were significant only at higher-than-average P4 (e.g., the luteal phase) among women with high Sensation Seeking. At lower-than-average P4 (i.e., the follicular phase) among women with high Sensation Seeking, simple effects of recent E2 were not significant (all p's < .15).

Phase analyses revealed a decrease in inattentive and hyperactive-impulsive symptoms during the pre-ovulatory phase for those high or low in Sensation Seeking; however, symptoms were lowest during the premenstrual phase than any other phase. There was also a peak in symptoms during the post-ovulatory phase for those high in Sensation Seeking (see Figure 3.11).

Lack of Premeditation and Lack of Perseverance. Lack of Premeditation did not moderate any hormone effects on ADHD symptoms. Lack of Perseverance moderated just one effect; among women high in Lack of Perseverance (+1 SD above sample average), higher average E2 was associated with lower hyperactive/impulsive symptoms (γ = -.22 SE = .07, $t(30)$ = -3.11, p = .004); the effect of average E2 was not significant among women with low Lack of Perseverance (-1 SD below sample average).

Phase analyses revealed a significant decrease in inattentive symptoms during the premenstrual phase and a peak in symptoms during the post-ovulatory phase for those high in Lack of Premeditation (see Figure 3.13).

Effect Size of Trait Moderators. Results of follow-up probing analyses reveal that women with high sensation seeking, positive urgency, or negative urgency, when P4 is +1 person-SD above the person average, experience a change of roughly .10-.20 (one tenth to one twenthieth) of an ADHD symptom with a 1 person-SD change in E2.

Effects of E2 and P4 on Alcohol Use

The second set of models focused on hormone variables as predictors of alcohol use in the subsample of 22 women. For the multilevel model on this subsample, hormone predictors and covariates were the same as above, but also included the covariate of legal drinking status and the dichotomous predictor of weekend status (where Thursday through Sunday = 1) Results of this model are presented in Table 3.7 (alcohol use), and are summarized in the paragraphs that follow.

There were no significant between-person correlations of an individual's proportion of drinking days and their average levels of E2 or P4 (all *p's* < .45 in full sample; all *p's* < .36 in drinking subsample). However, within-person results of models predicting both daily drinking and daily binge drinking from person-standardized E2 and P4 levels (one day prior to drinking outcome), and interactions of E2 and P4 with weekend status are presented in Table 3.7. Significant interactions are depicted in Figure 3.14 and are further characterized using simple slope analyses at the bottom of Table 3.7. There were significant three-way interactions between weekend status, E2, and P4 predicting both drinking and binge drinking. Hormones were predictive of drinking

outcomes only on weekend days. Simple slope analyses, presented at the bottom of Table 3.7, indicated that higher-than-average E2 on weekend days predicted a greater likelihood of drinking and binge drinking; these effects of E2 were strongest when P4 was lower than usual, and were attenuated but still significant when P4 was higher than usual. A one person-SD elevation above the person average of E2 was associated with a 26% increase in the probability of drinking, and was associated with a 125% increase in the probability of *binge* drinking when P4 was 1 person-SD *below* the person average. A similar elevation of E2 was associated with a 19% increase in the probability of drinking and a 27% increase in the probability of *binge* drinking when P4 was 1 person-SD *above* the person average. Thus, elevated P4 attenuated the effects of E2 elevations on increased drinking on weekend days. Extrapolating the size of the effects reported in Table 3.2, indicates that ovulation is associated with a 657% increase in odds of binge drinking on the weekend (Odds Ratio = 7.57 for a 2.5 person-SD elevation in E2 above one's person average, at 1-SD below the P4 person average). Phase analyses were in line with these results, showing a peak in drinking during the pre-ovulatory phase, when E2 is increasing dramatically (see Figure 3.15).

Table 3.1

Main Effects of Between- and Within-Person Ovarian Hormones on Daily Outcomes

	Outcome (Range of Scale)		
Parameter	ADHD Sx (0-18)	Hyper/Imp Sx (0-9)	Inattentive Sx (0-9)
Intercept	.19 (.15)	.09 (.10)	.11 (.10)
BMI	.003 (.01)	.002 (.004)	.003 (.004)
Average E2	-.08 (.04)	**-.06* (.03)**	-.05 (.03)
Average P4	-.004 (.04)	.02 (.03)	-.02 (.03)
Recent E2	-.04 (.02)	**-.03* (.01)**	-.01 (.02)
Recent P4	.02 (.03)	**.03* (.02)**	-.001 (.02)
Recent E2 X P4	**-.05* (.02)**	**-.03* (.01)**	**-.04* (.02)**

Note. $^{**}p < .01$, $^{*}p < .05$. Recent E2 and P4 are person-standardized values from two days prior to the outcome, calculated as today's hormone value minus the woman's average value for that hormone across the entire cycle, divided by the woman's standard deviation for that hormone across the entire cycle. BMI, Average E2, and Average P4 are sample-standardized.

Table 3.2

Interactive Effects of Trait Negative Urgency and Ovarian Hormone Predictors on Daily ADHD Symptoms

	Outcome (Scale)					
Parameter	Total ADHD SX		Hyperactive Sx		Inattentive Sx	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	0.22**	0.05	0.10**	0.03	0.15**	0.04
BMI	0.00	0.05	0.00	0.02	0.00	0.04
Average E2	-0.11	0.06	-0.06	0.03	-0.08	0.05
Average P4	-0.02	0.06	0.01	0.03	-0.03	0.05
Recent E2	-0.03	0.02	-0.03	0.01	-0.02	0.02
Recent P4	0.03	0.02	**0.04****	0.01	0.01	0.02
Recent E2 X Recent P4	**-0.06****	0.02	**-0.04****	0.01	**-0.04****	0.02
Trait Negative Urgency (NU)	**0.17****	0.06	**0.08***	0.03	**0.13***	0.05
NU X Trait E2	**-0.15***	0.06	**-0.09***	0.03	**-0.10***	0.05
NU X Trait P4	-0.09	0.08	-0.02	0.04	-0.09	0.06
NU X Recent E2	-0.02	0.02	-0.03	0.02	-0.02	0.02
NU X Recent P4	0.05	0.03	**0.05****	0.02	0.02	0.02
NU X Recent E2 X Recent P4	**-0.08****	0.02	**-0.04****	0.01	**-0.06****	0.02

Note. $**p < .01$, $*p < .05$. Recent E2 and P4 are person-standardized values from two days prior to the outcome, calculated as today's hormone value minus the woman's average value for that hormone across the entire cycle, divided by the woman's standard deviation for that hormone across the entire cycle. BMI, Average E2, Average P4, and Negative Urgency (NU) are sample-standardized.

Table 3.3

Interactive Effects of Trait Positive Urgency and Ovarian Hormone Predictors on Daily ADHD Symptoms

	Outcome (Scale)					
Parameter	Total ADHD SX		Hyperactive Sx		Inattentive Sx	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	**0.25****	0.04	**0.13****	0.02	**0.17****	0.03
BMI	-0.03	0.03	-0.01	0.02	-0.02	0.03
Average E2	**-0.18****	0.04	**-0.10****	0.03	**-0.13****	0.03
Average P4	0.05	0.04	**0.06***	0.03	0.01	0.03
Recent E2	-0.02	0.02	-0.02	0.01	0.00	0.02
Recent P4	0.02	0.02	**0.03***	0.01	-0.01	0.02
Recent E2 X Recent P4	**-0.05****	0.02	**-0.03***	0.01	**-0.04***	0.02
Trait Positive Urgency (PU)	**0.24****	0.04	**0.12****	0.03	**0.19****	0.03
PU X Average E2	**-0.23****	0.04	**-0.12****	0.03	**-0.17****	0.03
PU X Average P4	-0.02	0.04	0.03	0.03	-0.04	0.03
PU X Recent E2	0.00	0.02	-0.01	0.01	0.01	0.02
PU X Recent P4	0.03	0.02	**0.04***	0.02	0.01	0.02
PU X Recent E2 X P4	**-0.06****	0.02	**-0.03***	0.01	**-0.06****	0.02

Note. $^{**}p < .01$, $^{*}p < .05$. Recent E2 and P4 are person-standardized values from two days prior to the outcome, calculated as today's hormone value minus the woman's average value for that hormone across the entire cycle, divided by the woman's standard deviation for that hormone across the entire cycle. BMI, Average E2, Average P4, and Positive Urgency (PU) are sample-standardized.

Table 3.4

Interactive Effects of Trait Sensation Seeking and Ovarian Hormone Predictors on Daily ADHD Symptoms

	Outcome (Scale)					
Parameter	Total ADHD SX		Hyperactive Sx		Inattentive Sx	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	**0.21****	0.05	**0.11****	0.03	**0.14****	0.04
BMI	0.09	0.06	0.05	0.03	0.07	0.05
Average E2	-0.11	0.06	**-0.07***	0.03	-0.08	0.04
Average P4	0.07	0.06	0.07	0.03	0.03	0.05
Recent E2	-0.01	0.02	-0.02	0.01	0.00	0.02
Recent P4	0.01	0.02	0.03	0.01	-0.01	0.02
Recent E2 X Recent P4	**-0.05***	0.02	**-0.03***	0.01	**-0.04***	0.02
Trait Sensation Seeking (SS)	**0.17****	0.06	**0.10****	0.03	**0.13****	0.05
SS X Average E2	0.01	0.09	-0.02	0.05	0.01	0.07
SS X Average P4	-0.14	0.12	-0.02	0.07	-0.12	0.09
SS X Recent E2	-0.01	0.02	-0.01	0.01	-0.01	0.02
SS X Recent P4	0.03	0.02	**0.03***	0.02	0.02	0.02
SS X Recent E2 X P4	**-0.05***	0.02	**-0.03***	0.01	**-0.05****	0.02

Note. $^{**}p < .01$, $^{*}p < .05$. Recent E2 and P4 are person-standardized values from two days prior to the outcome, calculated as today's hormone value minus the woman's average value for that hormone across the entire cycle, divided by the woman's standard deviation for that hormone across the entire cycle. BMI, Average E2, Average P4, and Sensation Seeking (SS) are sample-standardized.

Table 3.5

Interactive Effects of Trait Lack of Premeditation and Ovarian Hormone Predictors on Daily ADHD Symptoms

	Outcome (Scale)					
Parameter	Total ADHD SX		Hyperactive Sx		Inattentive Sx	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	0.21**	0.06	0.12**	0.04	0.14**	0.05
BMI	0.00	0.06	0.01	0.03	-0.01	0.04
Average E2	-0.12	0.07	**-0.09***	0.04	-0.08	0.05
Average P4	0.00	0.08	0.05	0.05	-0.04	0.06
Recent E2	-0.01	0.02	-0.02	0.01	0.00	0.02
Recent P4	0.02	0.02	**0.03***	0.02	0.00	0.02
Recent E2 X Recent P4	**-0.05****	0.02	**-0.03***	0.01	**-0.04****	0.02
Trait Lack of Premed (LPM)	0.06	0.08	0.03	0.04	0.05	0.06
LPM X Average E2	-0.11	0.07	-0.06	0.04	-0.08	0.05
LPM X Average P4	-0.06	0.08	0.01	0.04	-0.08	0.06
LPM X Recent E2	0.00	0.03	-0.01	0.02	0.00	0.02
LPM X Recent P4	0.03	0.03	0.02	0.02	0.03	0.02
LPM X Recent E2 X P4	-0.03	0.02	-0.01	0.02	-0.03	0.02

Note. $^{**}p < .01$, $^{*}p < .05$. Recent E2 and P4 are person-standardized values from two days prior to the outcome, calculated as today's hormone value minus the woman's average value for that hormone across the entire cycle, divided by the woman's standard deviation for that hormone across the entire cycle. BMI, Average E2, Average P4, and trait Lack of Premeditation (LPM) are sample-standardized.

Table 3.6

Interactive Effects of Trait Lack of Perseverance and Ovarian Hormone Predictors on Daily ADHD Symptoms

	Outcome (Scale)					
Parameter	Total ADHD SX		Hyperactive Sx		Inattentive Sx	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	0.22**	0.06	0.10**	0.03	0.16**	0.05
BMI	-0.01	0.06	-0.01	0.03	0.00	0.05
Average E2	-0.08	0.06	-0.06	0.03	-0.05	0.05
Average P4	-0.01	0.07	0.02	0.03	-0.03	0.06
Recent E2	-0.03	0.02	-0.02	0.01	-0.01	0.02
Recent P4	0.01	0.02	0.03	0.01	0.00	0.02
Recent E2 X Recent P4	**-0.04***	0.02	**-0.02****	0.01	-0.03	0.02
Trait Lack of Persev (LPS)	0.12	0.07	0.05	0.04	0.10	0.06
LPS X Average E2	-0.17	0.09	**-0.13****	0.04	-0.10	0.07
LPS X Average P4	0.06	0.09	0.08	0.05	0.00	0.08
LPS X Recent E2	-0.01	0.03	-0.02	0.02	0.02	0.02
LPS X Recent P4	0.00	0.03	0.00	0.02	-0.02	0.02
LPS X Recent E2 X P4	-0.01	0.03	0.01	0.02	-0.01	0.02

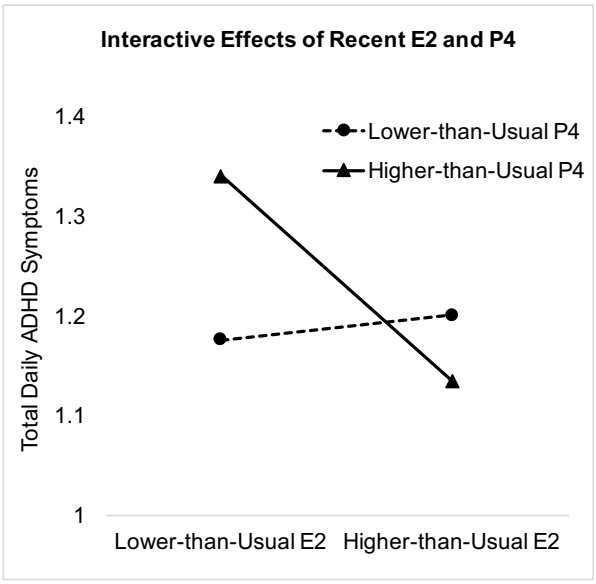
Note. $^{**}p < .01$, $^{*}p < .05$. Recent E2 and P4 are person-standardized values from two days prior to the outcome, calculated as today's hormone value minus the woman's average value for that hormone across the entire cycle, divided by the woman's standard deviation for that hormone across the entire cycle. BMI, Average E2, Average P4, and Trait Lack of Perseverance (LPS) are sample-standardized.

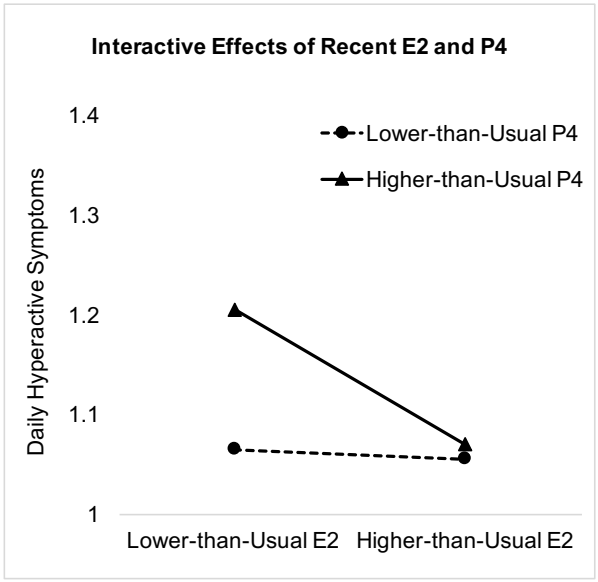
Table 3.7

Models Predicting Daily Alcohol Use from Weekend Status and Recent Ovarian Steroid Levels

Parameter	Outcome: Daily Alcohol Use		Outcome: Daily Binge Drinking (>=4 Drinks)	
	Estimate	*SE*	*Estimate*	*SE*
Intercept	-2.33**	0.40	**-4.72****	0.85
BMI	0.11	0.22	-.20	.65
Legal Drinking Status	**0.14***	0.06	0.02	.69
Weekend Status	**0.93***	0.37	**2.20***	0.71
Recent E2	**0.28***	0.12	**1.00****	0.33
Recent P4	-0.08	0.18	**0.37***	0.18
Recent E2 × Recent P4	-0.08	0.12	-0.05	0.22
Wknd × Recent E2	0.00	0.01	-0.33	0.59
Wknd × Recent P4	0.00	0.28	**-0.99****	0.38
Wknd × Recent E2 × Recent P4	**0.04****	0.01	**-0.12***	0.06
Simple Effects of Within-Person E2 Levels on the Weekend				
At Low P4	**0.23***	0.11	**0.81***	0.36
Odds Ratio (95% CI)	**1.25** (1.02 to 1.56)		**2.24** (1.11 to 4.55)	
At High P4	**0.17***	0.083	**0.24***	0.11
Odds Ratio (95% CI)	**1.18** (1.01 to 1.39)		**1.27** (1.02 to 1.57)	

Note. *$p < .05$, **$p < .01$, ***$p < .001$. All hormones are standardized within person and calculated as today's value minus one's person average, divided by one's person standard deviation. E2 = Estradiol, P4 = Progesterone. Low P4 = 1 standard deviation below the person average; High P4 = 1 standard deviation above the person average. Significant fixed effects are shown in bold.





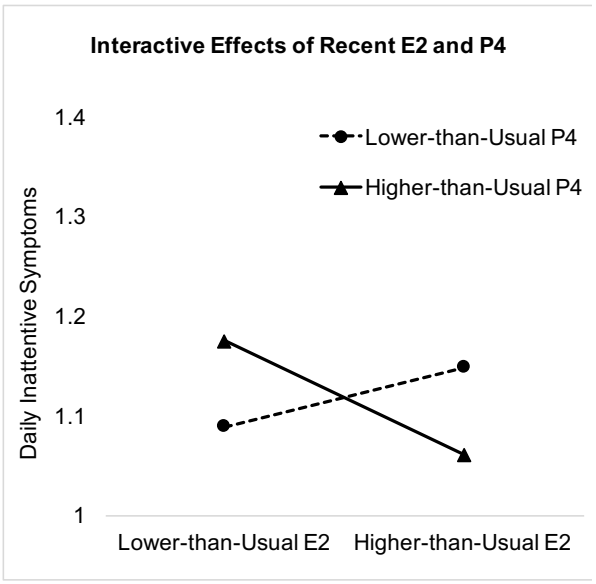
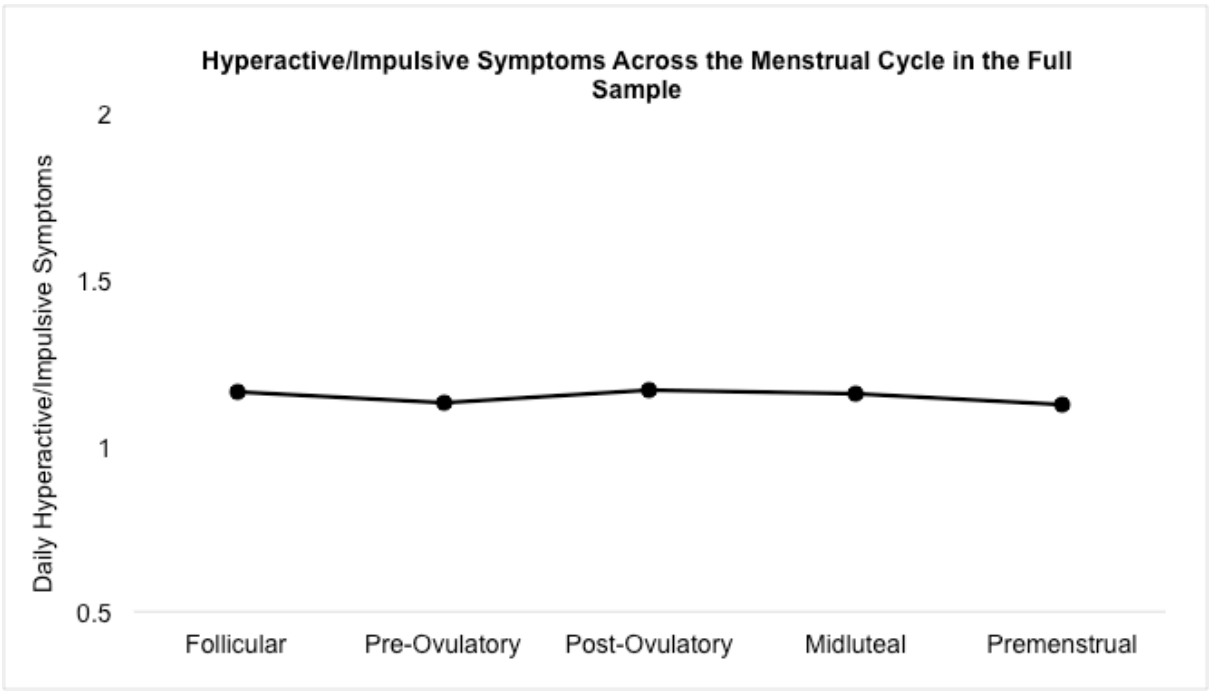


Figure 3.1. Interactive Effects of Person-Standardized Recent E2 and P4 on ADHD Symptoms in Women Across One Menstrual Cycle.



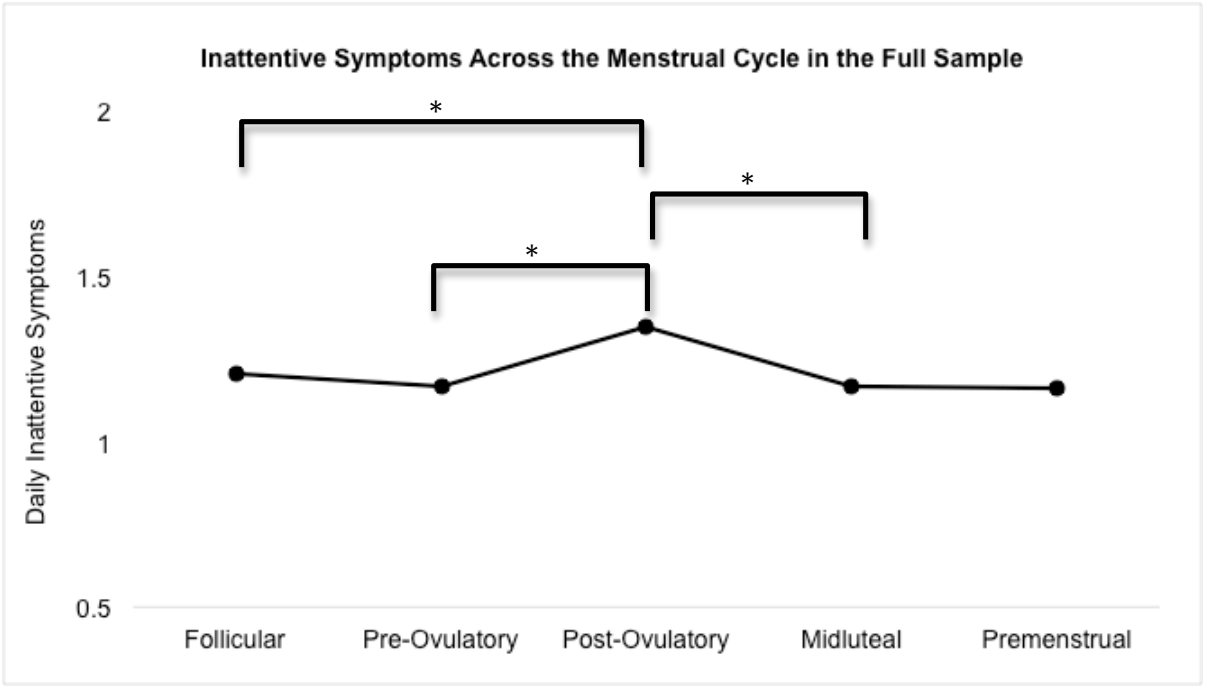
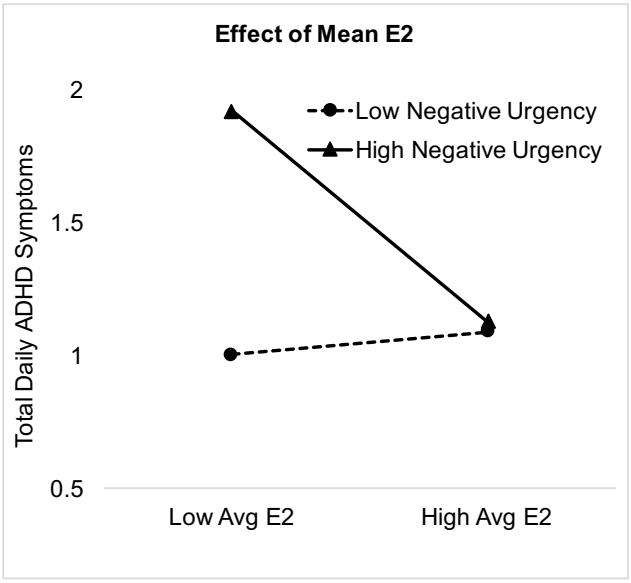
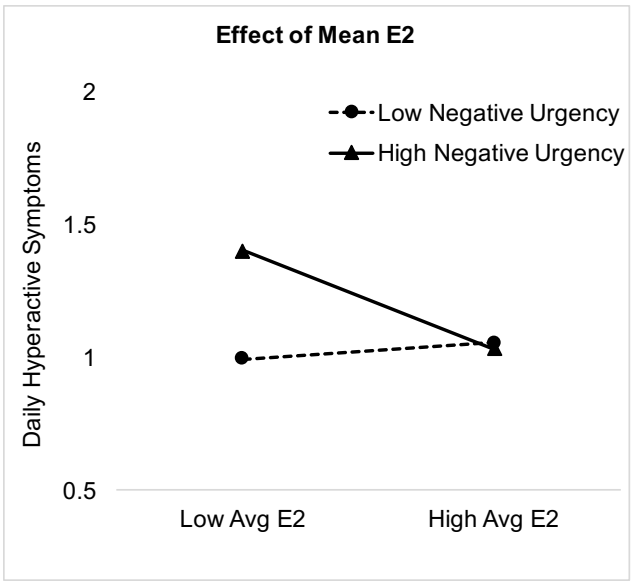


Figure 3.2. Phase analyses of Hyperactive-Impulsive Symptoms (TOP) and Inattentive Symptoms (BOTTOM). *Indicates a significant difference ($p < .05$) between phases.





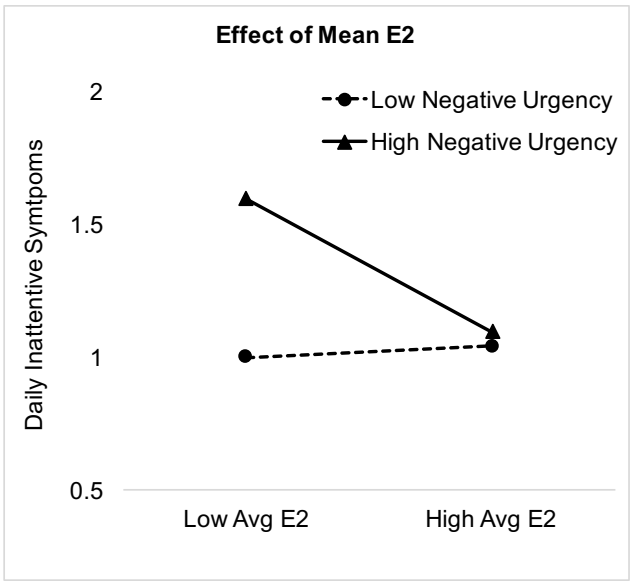


Figure 3.3. Interactive Effects of Trait Negative Urgency and Average E2 on Average Daily ADHD Symptoms in Women Across One Menstrual Cycle.

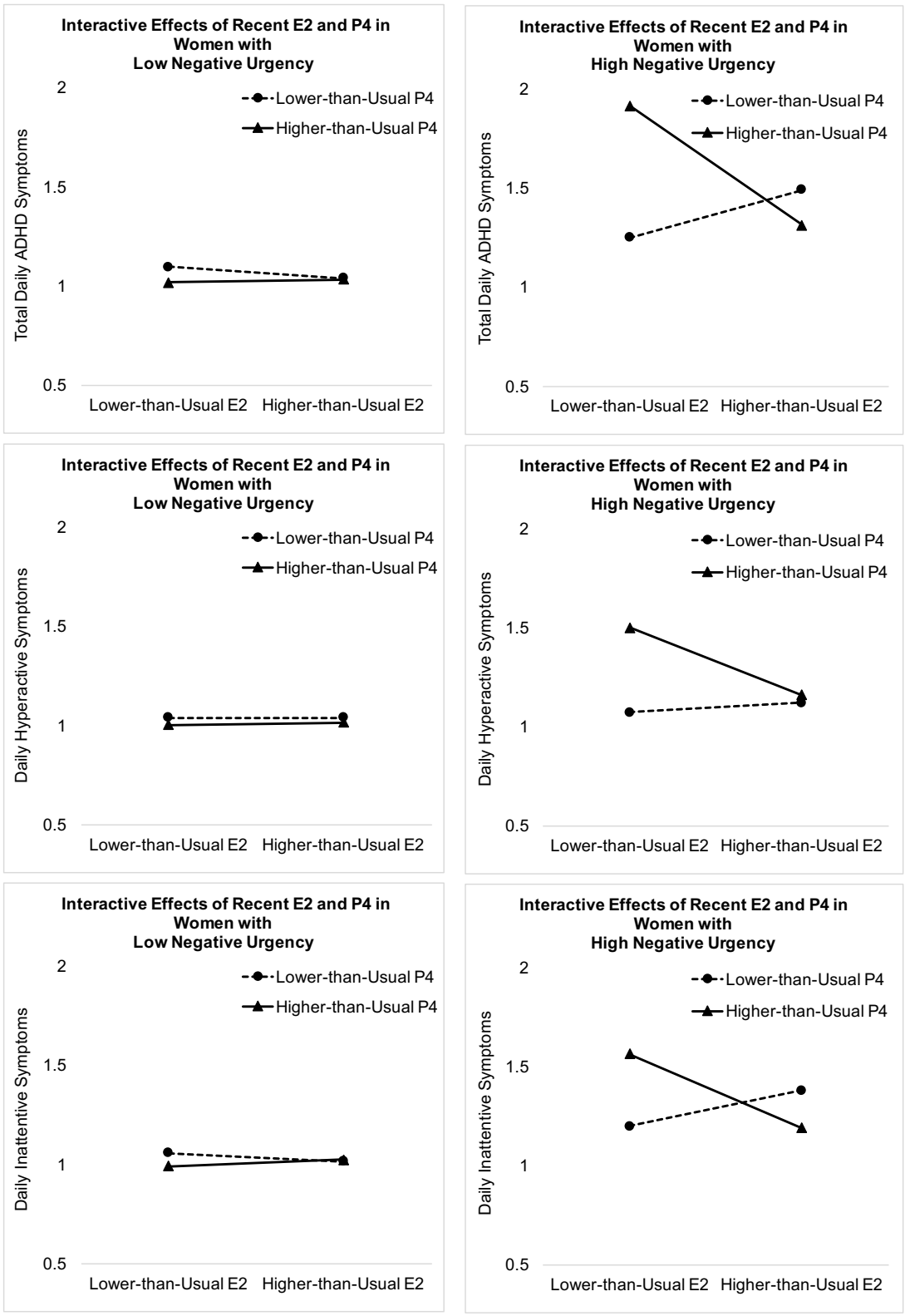


Figure 3.4. Interactive Effects of Trait Negative Urgency with Recent E2 and P4 (Person-Standardized) on Daily ADHD Symptoms in Women Across One Menstrual Cycle.

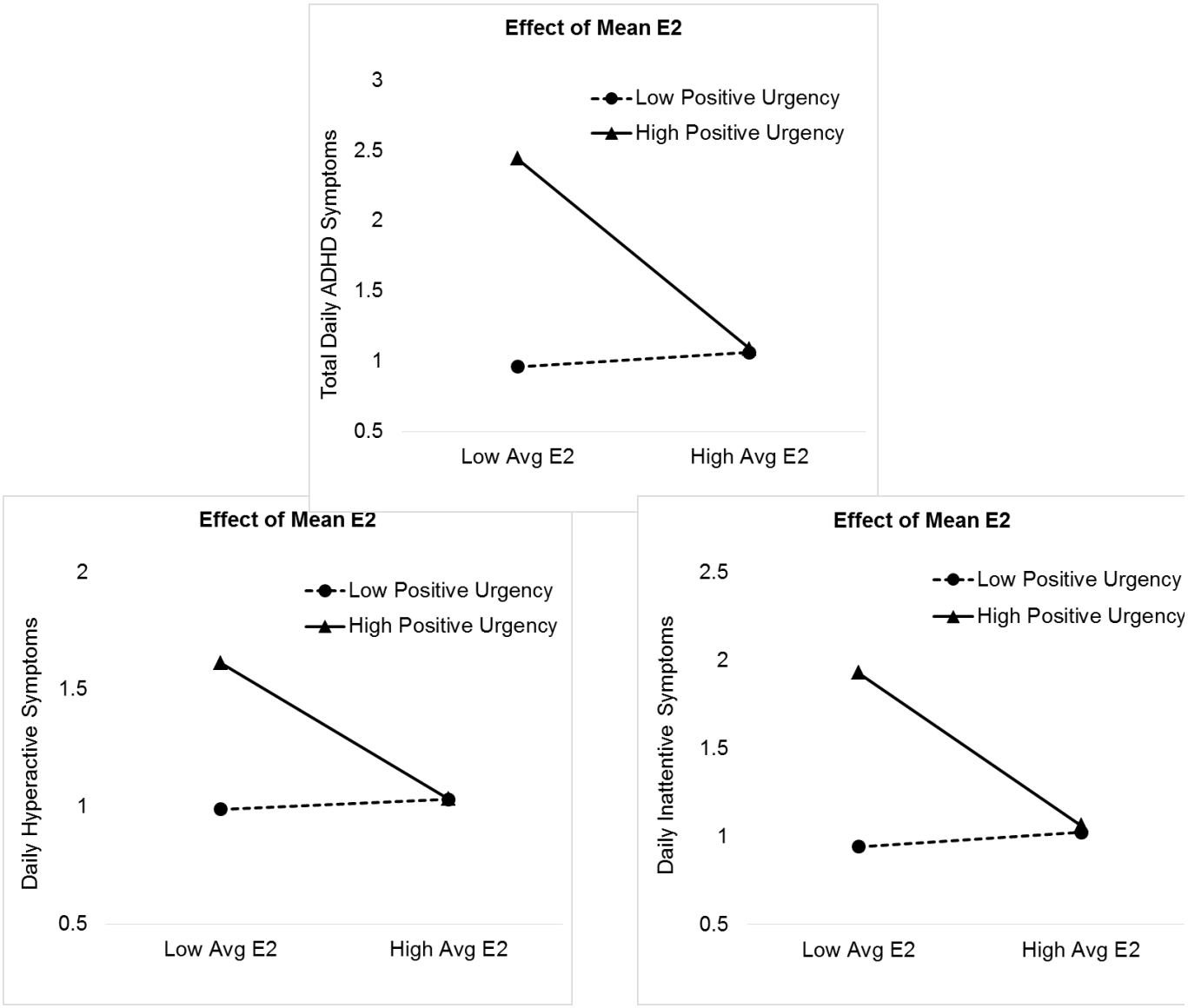


Figure 3.5. Interactive Effects of Trait Positive Urgency and Average E2 on Average Daily ADHD Symptoms in Women Across One Menstrual Cycle.

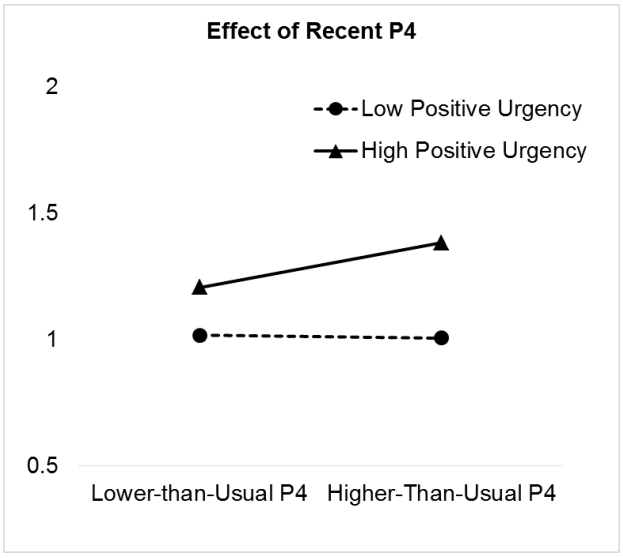


Figure 3.6. Interactive Effects of Trait Positive Urgency and Average P4 on Average Daily Hyperactive Symptoms in Women Across One Menstrual Cycle.

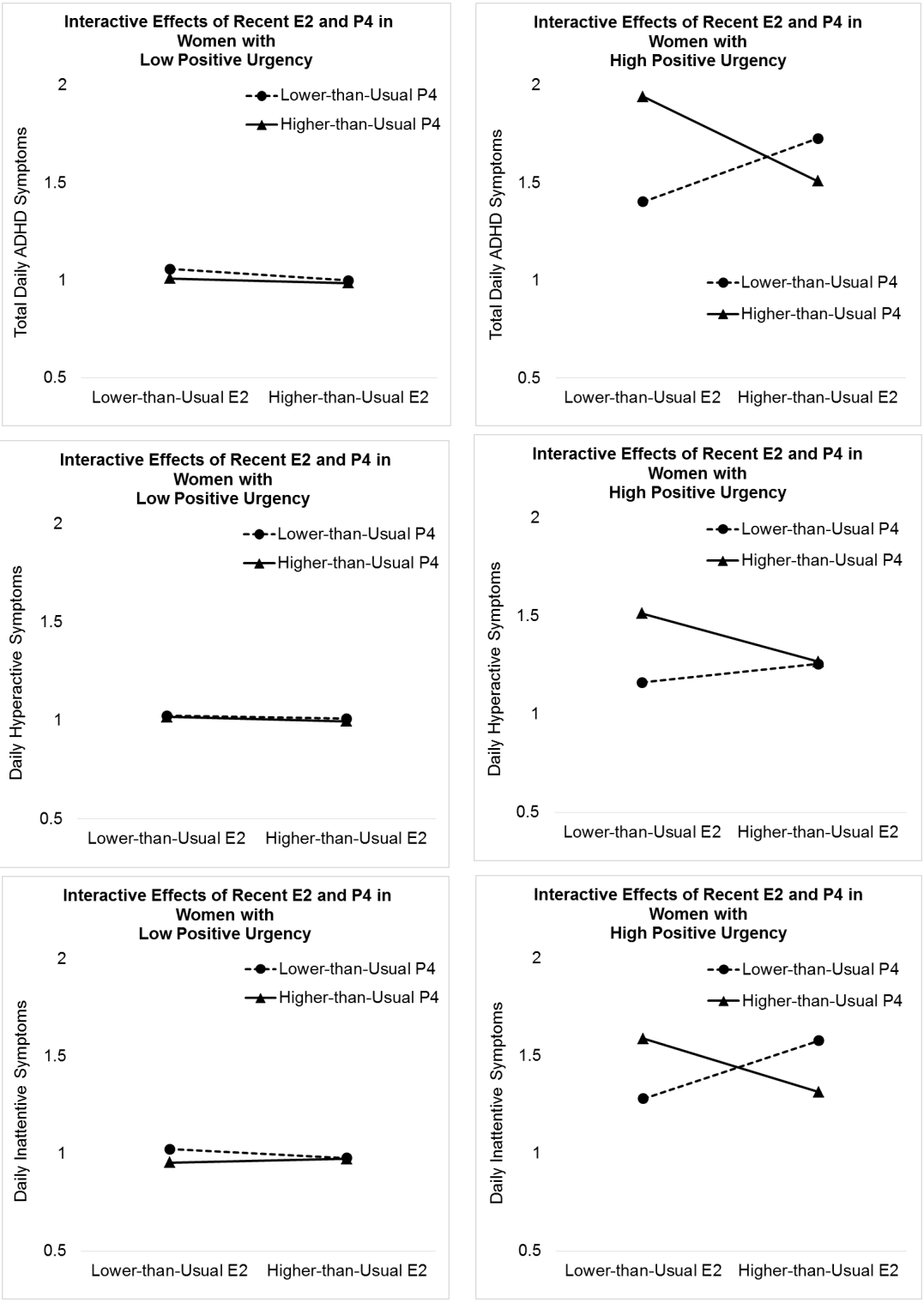


Figure 3.7. Interactive Effects of Trait Positive Urgency with Recent E2 and P4 (Person-Standardized) on Daily ADHD Symptoms in Women Across One Menstrual Cycle.

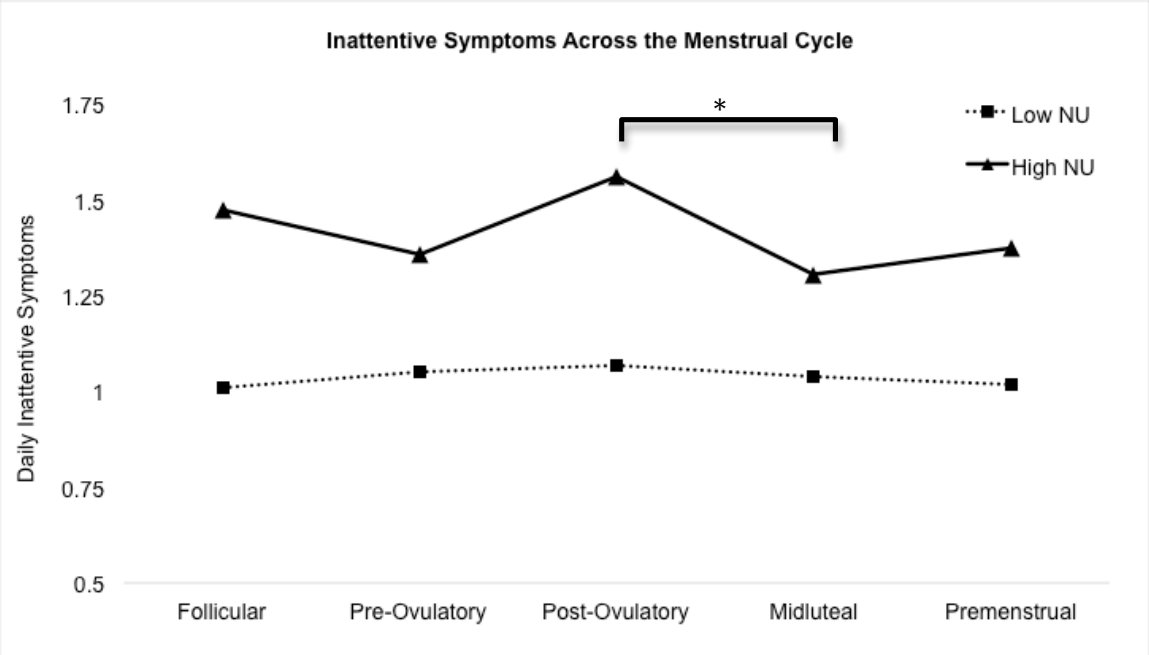


Figure 3.8. Phase analyses of Inattentive Symptoms for those high and low in trait Negative Urgency (there was no significant variability for Hyperactive-Impulsive Symptoms). *Indicates a significant difference ($p < .05$) between phases for the full sample.

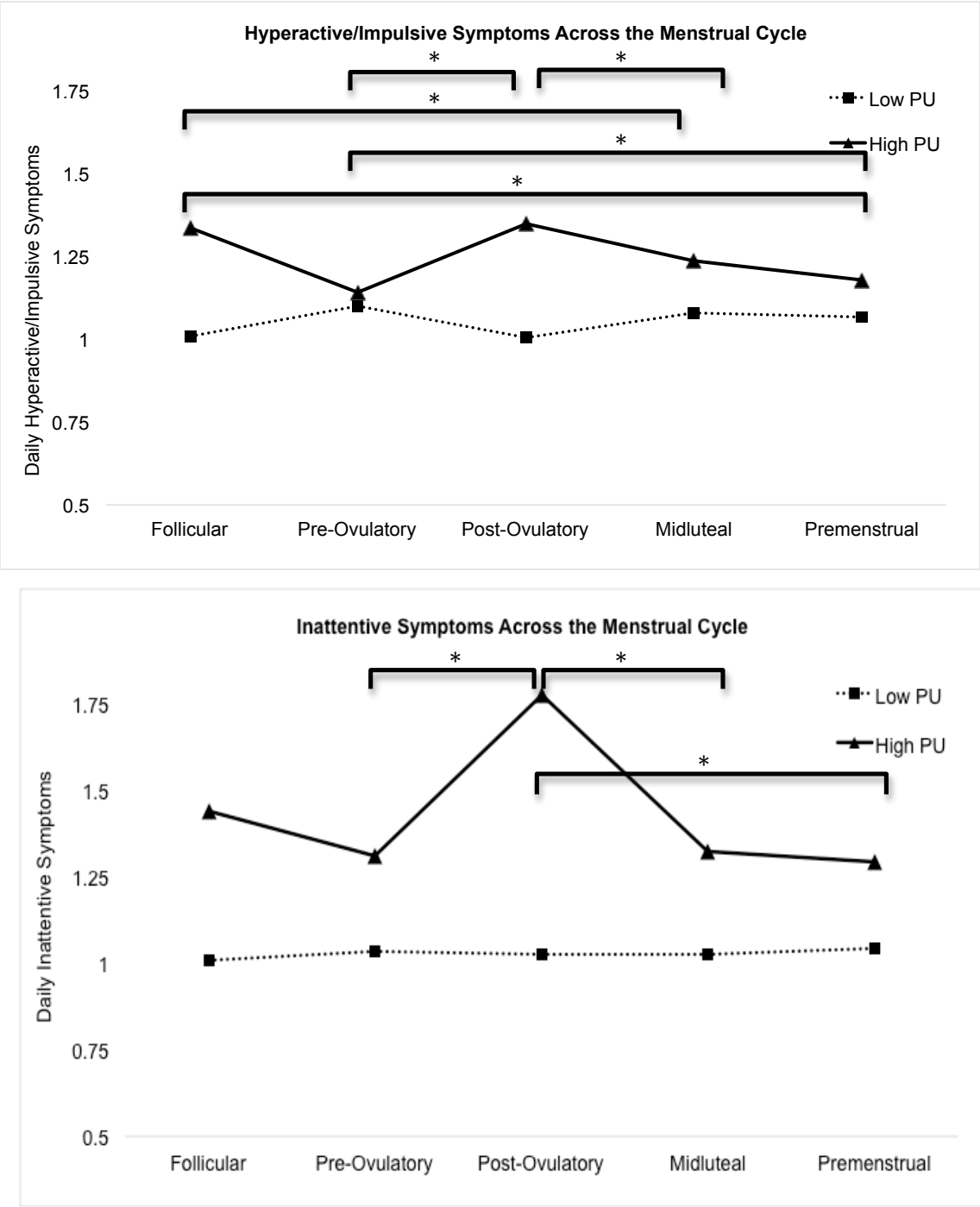


Figure 3.9. Phase analyses of Hyperactive-Impulsive Symptoms (TOP) and Inattentive Symptoms (BOTTOM) for those high and low in trait Positive Urgency. *Indicates a significant difference ($p < .05$) between phases for the full sample.

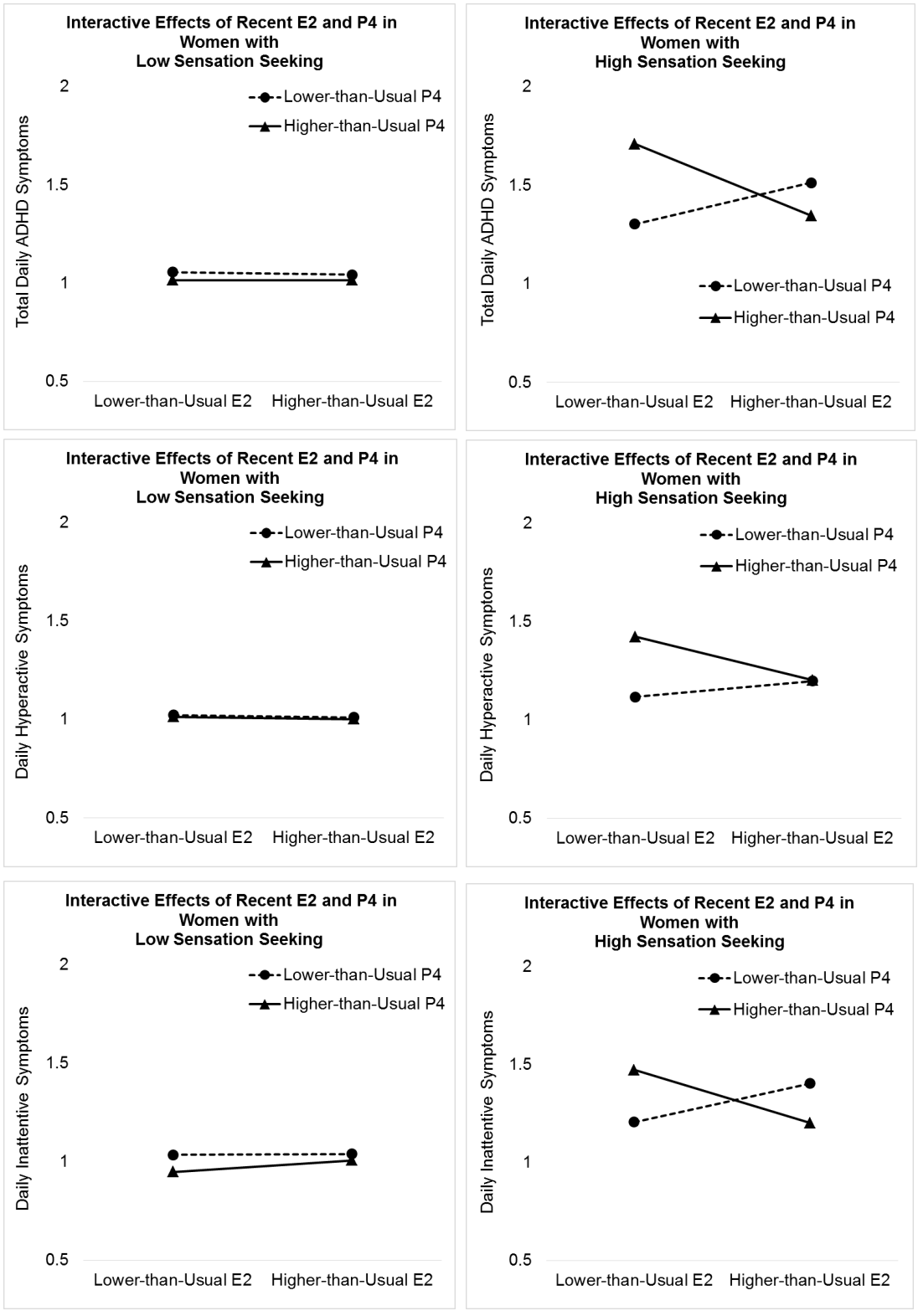


Figure 3.10. Interactive Effects of Trait Sensation Seeking with Recent E2 and P4 (Person-Standardized) on Daily ADHD Symptoms in Women Across One Menstrual Cycle.

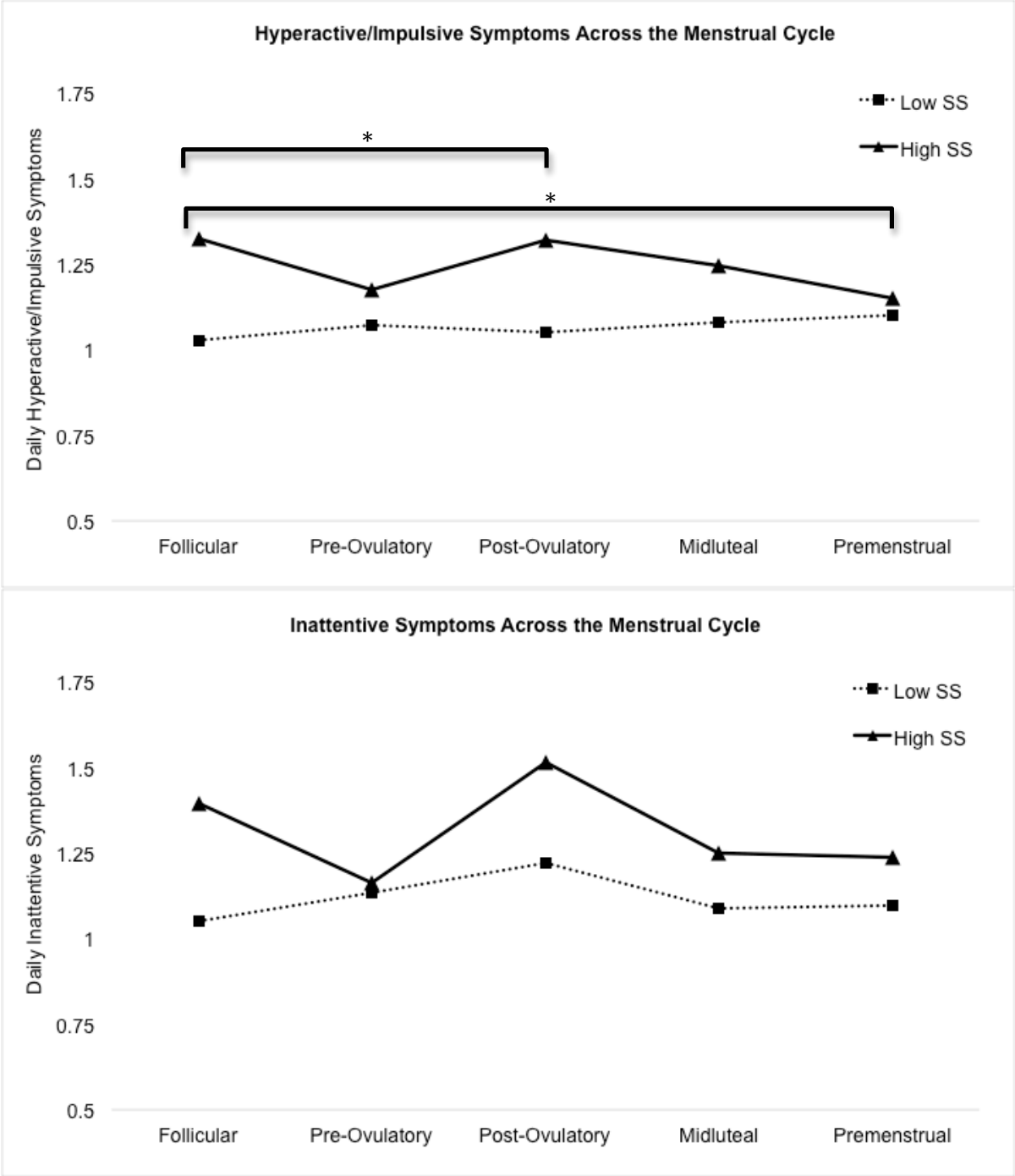


Figure 3.11. Phase analyses of Hyperactive-Impulsive (TOP) and Inattentive (BOTTOM) Symptoms for those high and low in trait Sensation Seeking. *Indicates a significant difference ($p < .05$) between phases for the full sample.

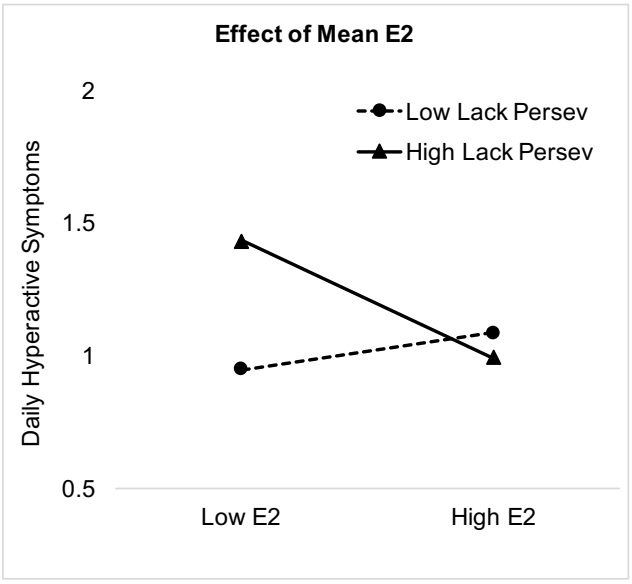


Figure 3.12. Interactive Effects of Trait Lack of Perseverance and Average E2 on Average Daily Hyperactive Symptoms in Women Across One Menstrual Cycle.

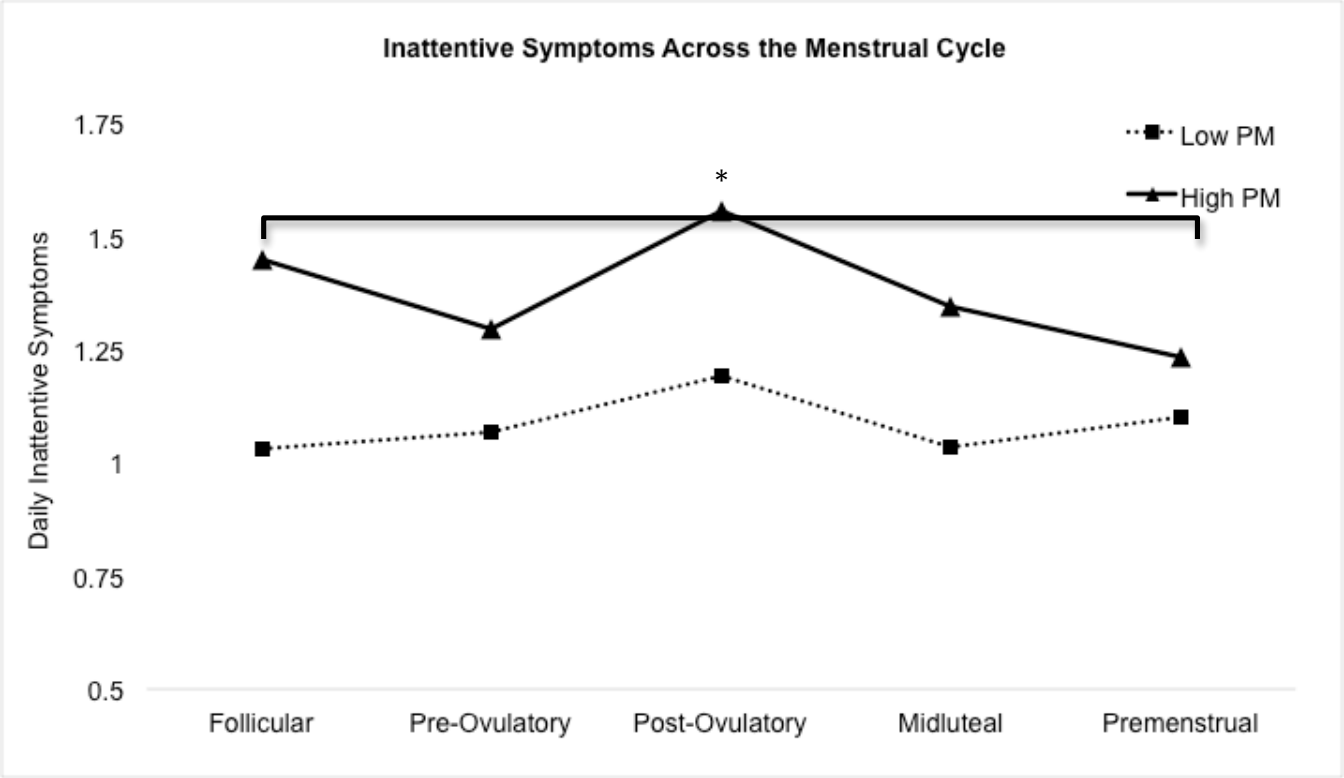


Figure 3.13. Phase analyses of Inattentive Symptoms for those high and low in trait Lack of Premeditation (there was no significant variability in Hyperactive-Impulsive symptoms). *Indicates a significant difference ($p < .05$) between phases for the full sample.

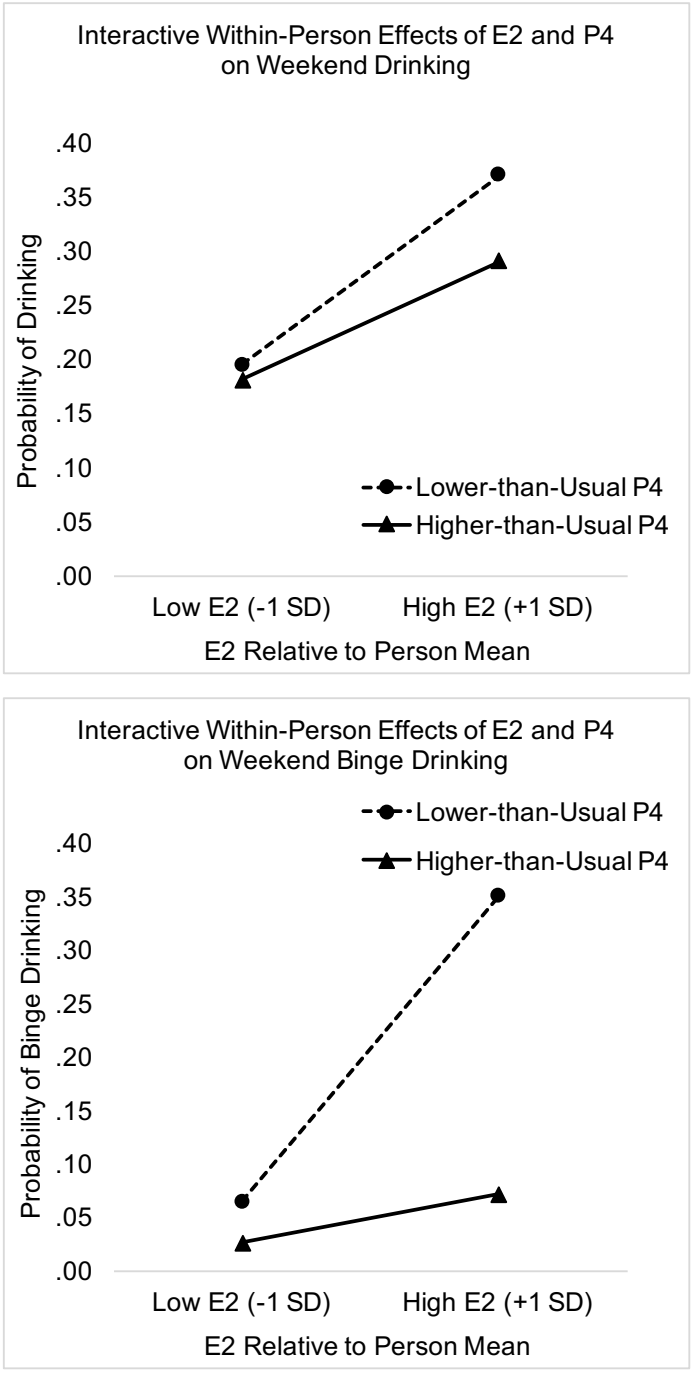
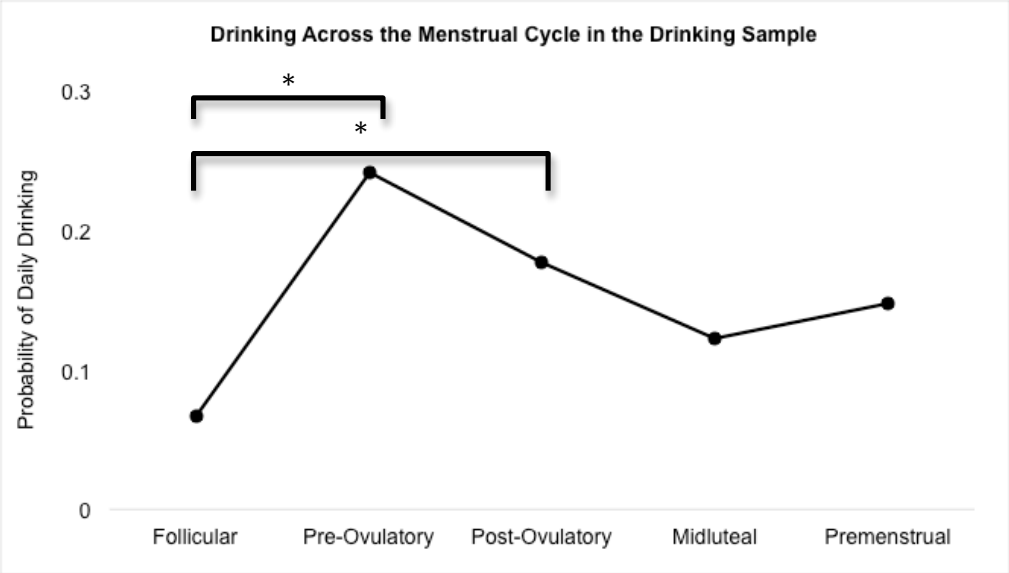


Figure 3.14. Interactive Within-Person Effects of Recent E2 Levels and Recent P4 Levels on Drinking (TOP) and Binge Drinking (BOTTOM) on Weekend Days



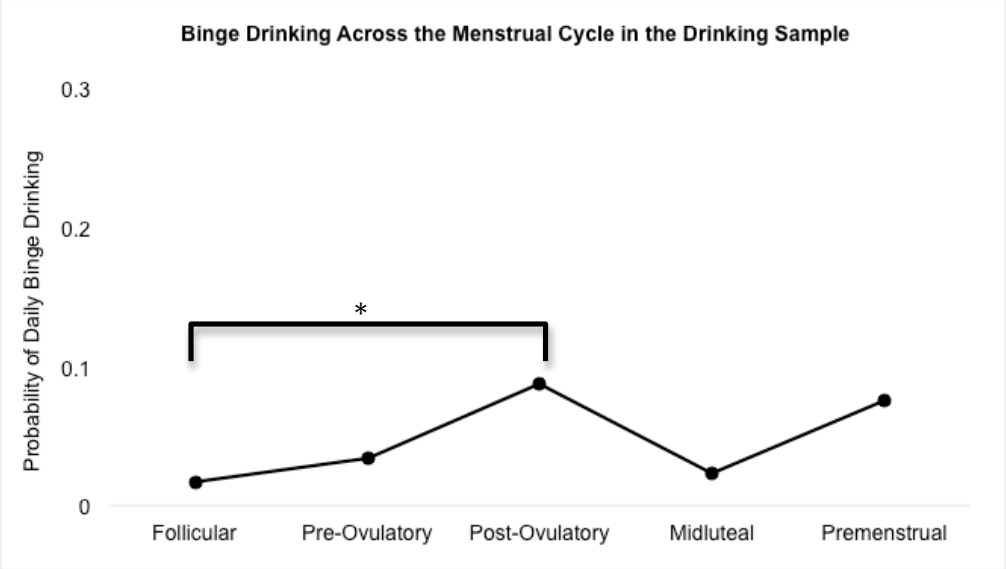


Figure 3.15. Phase analyses for probability of drinking (TOP) and binge drinking (BOTTOM) across the cycle. *Indicates a significant difference ($p < .05$) between phases.

CHAPTER FOUR: DISCUSSION

Although research suggests that women with ADHD may exhibit greater impairment at puberty, no prior study has directly examined circulating hormone levels in relation to ADHD symptoms and other risk-taking behaviors in young adulthood, the goals of the present study. In line with prior work on hormones and EF and in line with study hypotheses, lower average between-person levels of E2, and periods of lower-than-average E2 across the cycle, increased risk for ADHD symptoms. However, results demonstrated the importance of interactions between E2 and P4. Within-person effects of low E2 were only significant when recent P4 was also higher-than-average (i.e. in the luteal phase). Specifically, women with lower-than-average levels of E2 reported higher hyperactive-impulsive symptoms during periods of higher concurrent levels of P4. Further, somewhat in line with study hypotheses, only women who were high on the traits of negative urgency, positive urgency, or sensation seeking (but not high in lack of perseverance or premeditation) exhibited an association between lower-than-average E2 levels and high ADHD symptoms. In contrast to study hypotheses, high within-person E2 was associated with increased drinking particularly in the context of low P4. Overall, study results suggest multiple pathways to ADHD symptoms contingent on the interactive effects for hormones, at least for women at-risk based on affective personality factors, and these effects differ from what is seen in relation to risk-taking behavior such as binge drinking.

Hormonal Effects on ADHD Symptoms

Results demonstrated that lower-than-average E2 in the context of higher-than-average P4 is associated with increased symptoms, in line with case studies suggesting

symptoms of ADHD worsen the week before menstruation, when E2 falls from its mid-luteal peak and P4 is still higher-than-average (Quinn, 2005). In fact, our phase analyses suggested an early luteal, or post-ovulatory, increase in ADHD symptoms (seemingly driven by post-ovulatory and peri-menstrual reductions in E2). These findings are in line with research demonstrating that high E2 facilitates cognitive functioning in women with decreases in E2 being risky for cognitive functioning, EF, and attention (Jacobs et al., 1998; Schmidt et al., 1996; Sherwin, 1997). These effects may be mediated through E2 effects on the dopamine system, since lower synaptic dopamine and dopamine receptors are correlated with lower E2 levels (Archer, 1999; Gibbs, 2010). ADHD is also associated with lower extracellular dopamine and medications used to treat ADHD increase dopamine levels (Volkow et. al., 2001), but high E2 appears to enhance dopamine; thus, it appears to be protective against ADHD symptoms. In any case, low or declining levels of E2 seem to be risky for ADHD symptoms.

However, these effects of hormones on ADHD symptoms may only be important for some women. Somewhat in line with study hypotheses, only women who were high on the traits of negative urgency, positive urgency or sensation seeking showed a negative association between lower-than-average E2 levels and high ADHD symptoms, and only women high on the trait of lack of perseverance showed a negative association between average levels of E2 and high hyperactive-impulsive symptoms. In contrast to study hypotheses, the other facet of impulsivity, lack of premeditation, did not moderate any hormone effects on ADHD symptoms. These urgency-related effects during the luteal phase of the menstrual cycle replicate findings from a study of a personality phenotype characterized by negative urgency (Borderline Personality Disorder). That

study showed an identical pattern of interactive within-person effects of E2 and P4 on impulsivity and related psychopathology among women high in trait borderline features (Eisenlohr-Moul et al., 2015), which are characterized by a behavioral phenotype highly similar to negative urgency (Settles et al., 2012).

Hormonal Effects on Risk-Taking

The results of hormonal effects on drinking were in contrast to study hypotheses and results of hormonal effects on ADHD symptoms. The effects of E2 and P4 on alcohol use (in the subsample of women who drank alcohol) suggested that higher-than-average recent levels of E2, in the co-occurring contexts of (1) lower-than-average P4 (i.e. the follicular phase) and (2) during the weekend, were associated with increased risk of drinking and binge drinking. Though this effect of E2 was significant at all levels of P4, the effect was stronger when P4 was low and weaker when P4 was high, likely reflecting the antagonistic influence of P4 on E2 (Singh, Su, & Ng, 2013) and further highlighting the importance of the interactions of P4 and E2 (Klump et al., 2008; 2013; Eisenlohr-Moul et al., 2015).

The effects of E2 and P4 on drinking may also be mediated through dopamine and GABA. For example, animal studies suggest that high E2 decreases GABA neurotransmission, which increases dopamine release in the striatum and nucleus accumbens (Becker & Hu, 2008; Lynch, Roth, & Carroll, 2002). Additionally, high E2 down-regulates dopamine receptor binding (Becker & Hu, 2008). Abnormalities in dopaminergic neurotransmission and elevated E2 can increase reward sensitivity, which is a key mechanism of substance craving, use, and other risk-taking behaviors (Dreher et

al., 2007; Hyman, Malenka, & Nestler, 2006; Koob & Le Moal, 2001; Lofgren et al., 2009; Robinson & Berridge, 1993; Volkow et al., 2010).

Results are consistent with increases in female risk-taking behaviors around ovulation, in line with evolutionary developmental theory suggesting that females may be more likely to engage in risk-taking behaviors such as alcohol use as they approach ovulation, potentiated by rising E2, which might operate to facilitate conception (Gangestad, Thornhill, & Garver-Apgar, 2002; Geary, 2010; Larson et al., 2013). This might also provide a partial explanation for increases in alcohol use and other risk-taking behaviors around puberty (Spear, 2010), again potentiated by rapidly rising levels of sex steroids, and at a time when fertility is increasing. Furthermore, such results suggest a large impact of environmental influences, such as opportunity for drinking and availability of alcohol on weekends on college campuses.

Clinical Implications

The present study challenges current research practices by suggesting that ADHD symptom presentation in post-pubertal females may fluctuate across the cycle. Perhaps, if the presentation of ADHD in post-pubertal women is not static, then it might not constitute a true trait, as currently conceptualized in DSM-5 (APA, 2013). Rather, ADHD in women might be better conceptualized as a series of states in which some symptoms may worsen due to biological changes. Further, it is possible that women may also fluctuate through their life -and even within a single month- to the degree that they would not always meet DSM-5 criteria for ADHD. Prior work has suggested that women go undiagnosed due to the higher incidence of inattentive versus hyperactive-impulsive symptoms among women (Gaub & Carlson, 1997; Gershon & Gershon, 2002). However,

the present study suggests another alternative. Perhaps some women do not reach diagnostic threshold or impairment until hormones rise and begin to cycle at puberty.

These findings suggest a number of potential implications for the diagnosis and treatment of women with ADHD. For example, results support that clinicians may need to know a woman's cycle phase and hormonal status, including medications that affect hormone levels like birth control, when assessing ADHD in young women (Quinn & Nadeau, 2002). Finally, trait levels of impulsivity may be important to consider in assessments, and inclusion of assessment of trait impulsivity may help to identify those women who are more at risk for hormonal influences on ADHD symptoms.

Limitations and Future Directions

This study has a number of notable strengths as it was the first, to my knowledge, to directly and empirically examine associations between E2 and ADHD symptoms, associated risk-taking behaviors, and a marker of the disorder, namely impulsivity. However, it is not without limitations. Importantly, the present study utilized a community (vs. clinical) sample, which may limit the generalizability of these findings, despite the fact that research suggests ADHD is best characterized by a continuous dimension (Barkley, 2006; Haslam et al., 2006; Larsson, Anckarsater, Råstam, Chang, and Lichtenstein, 2012; Marcus & Barry, 2011). The distribution of ADHD symptoms in the current sample was positively skewed, and risky behaviors were rare. Future studies should include larger samples and include more women meeting diagnostic criteria for ADHD and samples with higher rates of drinking, substance use and risky sexual behaviors. However, obtaining a sample of women willing and able to complete 35 days of data collection successfully was challenging; obtaining a sample of women with

ADHD who could also accomplish this task, requiring a high level of conscientiousness and organization, would be even more of a challenge. The present study also relied on women's self-report. Future studies could utilize other report measures of symptoms (which we had on only a very small subsample of the women) and/or other measures of impulsivity and/or impulse control, such as neuropsychological testing.

Recent experimental work suggests that it may be *acute change* in E2 or P4 (rather than higher or lower than average levels) that can have a dysregulating effect on brain function and behavior in susceptible women (reviewed in Schiller et al., 2016 and Gordon et al., 2015). Therefore, it is possible that the effects of lower-than-average E2 in the present study are attributable in part to the acute, day-to-day effects of withdrawal from E2 in the luteal phases of vulnerable women. Although post-hoc analyses examining the effects of two-day changes in hormones did not reveal a consistent pattern of effects, it is possible that the effects of hormone change operate on a shorter lag (e.g., 24-hour change) than was possible here with every-other-day hormone sampling (i.e., 48-hour change). Future work with daily samples of E2 and P4 could assess the degree of impact of a 24-hour change in hormones, in addition to relative recent hormone levels when assessing their relationship with ADHD symptoms.

There are numerous other important directions for future work. Due to E2's effects on cognitive functioning and symptoms, results of neuropsychological testing could be affected, and this should be examined. Further, the effect of E2 and P4 on psychostimulant medication response and efficacy is another important area for future research with large clinical implications. Additionally, the effects of birth control on ADHD symptoms and psychostimulants are important areas for future research. For

example, studies could compare the effects of 21/7 birth control to 24/4 or continuous birth control methods, as the latter may decrease fluctuations in P4 and E2 (Sullivan, 1999) and could be beneficial for women with ADHD. Future studies should also examine potentially developmental effects of hormones across different important developmental periods (e.g., puberty, menopause) and pregnancy. The present study stressed the importance of consideration of interactions between E2 and P4 in line with some previous studies (Klump et al., 2008; 2013; Eisenlohr-Moul et al., 2015). Further studies should also examine the interaction of other hormones that may affect psychopathology and cognition, such as testosterone and dehydroepiandrosterone. Incorporating associated genetic factors (e.g. DRD2, COMT etc.) is another promising avenue for future research.

State impulsivity was not assessed in the present study after data inspection revealed data as suspect. The response scale of the state measure of impulsivity, a shortened version of UPPS, was coded in such a way that the likert scale was in reverse of other measures. Given this finding, and the negative correlation of the state measure to the trait UPPS, the data seemed suspect and could not be utilized for analyses. Future studies should examine whether state impulsivity mediates the association of hormones and ADHD, perhaps due to their similar brain pathways involving the amygdala, orbitofrontal cortex, and ventromedial prefrontal cortex (Cyders & Smith, 2008).

Conclusion

The present study suggests a great deal of complexity in the presentation of ADHD in young adult women. Low levels and decreases in E2 appear to worsen ADHD symptoms, challenging the conceptualization of ADHD as a trait, at least in young adult

women high in trait impulsivity. These relationships are significant only in the context of high P4, and only among women who are high in certain types of trait impulsivity, further suggesting ADHD is a heterogeneous disorder characterized by equifinality. These results may have implications for assessment and treatment approaches for young women with ADHD.

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VITA
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EDUCATION

2017	Ph.D., Clinical Psychology University of Kentucky Lexington, KY
2017	Clinical Psychology Internship Placement Geropsychology Intern North Florida/South Georgia Veteran's Medical Center Gainesville, FL
2011	M.S., Applied Biopsychology University of New Orleans New Orleans, LA
2008	B.S., Psychology Michigan State University East Lansing, MI

HONORS AND AWARDS

2015	Recipient, University of Kentucky Graduate School Travel Award
2013, 2015	Recipient, Department of Psychology Travel Award
2012	Recipient, University of New Orleans Travel Award
2012	Andrew S. Wensel Distinguished Graduate Student Commendation
2010	Recipient, University of New Orleans Psychology Travel Award
2009-2012	Crescent City Doctoral Scholarship
2007- Present	Psi Chi National Psychology Honors Society
2006-2008	Dean's List, Michigan State University

PROFESSIONAL AFFILIATIONS

2014-present	Founding Member of the UK Graduate Student Advocacy Group
2014-present	Kentucky Psychological Association (KPA)
2012-present	American Psychological Association (APA)

PUBLICATIONS:

Martel, M.M., Eisenlohr-Moul, T. & **Roberts**, B. (Under Review). Ovarian steroid dynamics and alcohol use: Interactive levels, estradiol surges, and progesterone withdrawal. *Psychological Medicine.*

Martel, M. M., & **Roberts**, B. A. (2014). Prenatal Testosterone Increases Sensitivity to Prenatal Stressors in Males with Disruptive Behavior Disorders. *Neurotoxicology and Teratology*, *44*, 11-17.

Martel, M.M., Gremillion, M.L., **Roberts**, B.A., Zastrow, B., L. & Tackett, J.L. (2014). Longitudinal Prediction of the One-year Course of Preschool ADHD Symptoms: Implications for Models of Personality – ADHD Associations. *Personality and Individual Differences, 64*, 58-61.

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Martel, M.M., Eisenhour-Moul, T., Roberts, B. (In press).

CONFERENCE PRESENTATIONS

Roberts, B.A., Gremillion, M.L., Martel, M., & Nigg, J. (2015, July). Gene-Environment-Hormone Interactions and ADHD Symptoms In Children: Differential Risk Based on Hormones & Genotype In Martel, M (chair), *Hormones as epigenetic mechanisms of environmental influences on developmental psychopathology*. Symposium conducted at the International Society for Research on Child and Adolescent Psychology, Portland, Oregon.

Eisenhower-Moul, T., **Roberts**, B, Martel, M., & Dewall, N. (2014, March). Pubertal Hormone Associations with Psychopathology: Dynamic Cyclic and Moderated Effects In Nikolas, M (chair), *Illuminating Sex Differences in Adolescent Psychopathology: The Role of Pubertal Development and Gonadal Hormones*. Symposium conducted at the Society for Research in Adolescence, Austin, Texas.

Barr, A.H., **Roberts**, B.A., Gremillion, M.L., & Martel, M.M. (2014). The correlation between young adults with Attention-Deficit/Hyperactivity Disorder symptoms and their associations with delinquent peers. (National Conference of Undergraduate Research). Lexington, Kentucky.

Matveeva, E., **Roberts**, B.A., & Martel, M.M. (2014). Gender Differences in College Students with Attention-Deficit/Hyperactivity Disorder. (National Conference of Undergraduate Research). Lexington, Kentucky.

Roberts, B.A., & Gremillion, M.L (2013, April). Prenatal Testosterone and Substance Exposure Interacts Differentially Based on Child Sex to Predict Externalizing Psychopathology. In Nikolas, M. (Chair), *Development of sex differences in externalizing psychopathology: Familial risk, prenatal exposures, and temperamental trait mechanisms.* Symposium conducted at the meeting of the Society for Research in Child Development, Seattle, Washington.

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