2024

Hormonal Effects on ADHD Symptoms in Adolescents Across the Menstrual Cycle

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Digital Object Identifier: https://doi.org/10.13023/etd.2024.286

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HORMONAL EFFECTS ON ADHD SYMPTOMS IN ADOLESCENTS ACROSS THE MENSTRUAL CYCLE

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

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2024

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ABSTRACT OF DISSERTATION

HORMONAL EFFECTS ON ADHD SYMPTOMS IN ADOLESCENTS ACROSS THE MENSTRUAL CYCLE

Background: Females with attention-deficit/hyperactivity disorder (ADHD) become particularly impaired during adolescence, experiencing increased rates of depression and anxiety, as well as important public and personal health outcomes like increased suicide attempts, risky sexual behavior, and substance use. However, female-specific risk factors for ADHD have been vastly understudied despite this increased impairment and comorbidity. One particularly understudied risk factor is the dramatically rising and fluctuating levels of ovarian hormones during late puberty that begin cycling monthly. In adult women, rapid decreases in estrogen levels increase risk for ADHD symptoms across the menstrual cycle, particularly for those with high trait impulsivity. Preliminary pilot work suggests increased ADHD-related comorbidity and impairment by later pubertal stages. The current project aims to (1) evaluate the effects of day-to-day changes in estrogen on ADHD symptoms across the menstrual cycle in adolescents and (2) determine if specific traits such as impulsivity and environmental stressors are associated with increased sensitivity to hormonal effects.

Methods: Participants were 19 adolescents aged 11 to 17 years who had begun menstruating, and over-recruited for ADHD. Participants collected saliva samples as a measure of estradiol and progesterone and completed measures of ADHD symptoms daily. At a laboratory visit, participants completed measures of pubertal development, trait impulsivity, family functioning, peer rumination, and perceived stress. Multilevel models with planned contrasts were used to detect differences in symptoms among menstrual cycle phases and test moderators.

Results: Analyses indicated inattention was positively associated with progesterone. Hyperactivity was negatively associated with estradiol, and these symptoms were more severe in the periovulatory phase. Impulsivity was highest in the midluteal phase, but analyses did not reveal any hormonal associations. Although pubertal stage was not found to moderate ADHD symptoms, results did indicate trait impulsivity, peer rumination, and perceived stress as moderators.

Discussion: Results demonstrating changes in ADHD symptoms across the menstrual cycle and several moderators of such effects highlight key factors in the symptom exacerbation and increased impairment seen during adolescence in females.

These findings suggest that menstrual cycle timing, as well as trait and social factors are important details that should be integrated with traditional tools during the assessment of ADHD symptoms. This study replicates findings that ADHD symptoms change across the menstrual cycle and adds to the overall work in this field by providing direct links between several environmental factors, ADHD symptoms, and the menstrual cycle.

KEYWORDS: Attention-Deficit/Hyperactivity Disorder, Menstrual Cycle, Ovarian Hormones, Adolescence, Peer Rumination, Perceived Stress

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06/12/2024

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ACKNOWLEDGMENTS

First and foremost, I wish to thank my dissertation chair and mentor, Dr. Michelle Martel, for her guidance, patience, and time over these past five years. I am extraordinarily thankful that she and I happened to find each other (despite the exacerbation I always felt when she sent back edits within an hour). I am also grateful to my dissertation committee and outside reader, respectively: Dr. Mark Fillmore, Dr. Greg Smith, Dr. Tom Curry, and Dr. Sarah Vos. Your input and feedback were critical for strengthening the quality of this project and challenging me to grow as a clinical scientist. Additionally, this dissertation would not have been possible without the help, expertise, and encouragement of Dr. Tory Eisenlohr-Moul and the CLEAR Lab. Similarly, this study was made possible through the generous funding provided by a fellowship from the American Psychological Foundation.

Furthermore, I received equally important support from my colleagues and friends: Patrick Goh, Pevitr Bansal, Urveesha Nirjar, Yancey Sizemore, Ashe Miller, Nina Monticello, William Bowling, Stephen Semcho, Colton Rippey, and Jordan Tipsword. You all were there for the ups and downs of graduate school (and data collection), for which I will forever be grateful. I would also like to extend my gratitude to the participants of the study included in this dissertation, as well as Jenny Casey, Tamra Nowitzki, and Kim Reeder for their assistance throughout my graduate training. Lastly, I would not be where I am or who I am without the loving support of my family.

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CHAPTER 1. INTRODUCTION

1.1 ADHD Overview

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that exhibits striking developmental differences, as well as sex differences, in symptoms, prevalence, and correlates. Yet, sex differences in ADHD across development are perhaps the most understudied aspect of this common and costly disorder. ADHD has a global prevalence rate of roughly 5% in children between the ages of 6 to 18 years (Polanczyk et al., 2015), and frequently persists through adolescence and into adulthood (American Psychiatric Association, 2022; Faraone & Biederman, 2005). Although in childhood, there is a significant gender-biased prevalence rate in ADHD of at least 3 to 1 favoring males, by adulthood, that ratio is closer to 1 to 1 (American Psychiatric Association, 2022; Das et al., 2012; Skogli et al., 2013).

ADHD is heterogeneous in nature and symptoms are classified in two domains. The inattentive domain consists of nine symptoms such as *is often forgetful in daily activities*, *often fails to give close attention to details or makes careless mistakes*, and *often has difficulty organizing tasks and activities*. The hyperactive/impulsive domain consists of six hyperactive and three impulsive symptoms such as *often fidgets with or taps hands or feet*, *often talks excessively*, and *often interrupts or intrudes on others*. Each domain requires at least six symptoms to be present for an ADHD diagnosis in children or at least five symptoms to be present in adults. At least some symptoms are also required to be present before the age of 12 in order to be diagnosed with ADHD. Individuals can be diagnosed with predominantly inattentive presentation, predominantly hyperactive/impulsive presentation, or combined presentation. However, research

suggests that these presentations are not necessarily stable (Lahey et al., 2005; Todd et al., 2008; Willcutt et al., 2012), and that symptom trajectories differ, as well as the factors that influence these trajectories, between males and females (Eng et al., 2023).

1.2 Sex Differences in ADHD

Before delving into the differences in ADHD between males and females, it is important to note that sex assigned at birth and gender are not necessarily synonymous for individuals. Until recently, researchers have also not always distinguished between biological sex and gender identity, and have reported all participants as women/men, girls/boys, or males/females, leaving it unclear how individual participants self-identify (Heidari et al., 2016). Even worse, many studies did not report sex or gender at all. In this paper, the term female is used to refer to sex assigned at birth as menstrual cycle research is uniquely female (Ota Wang, 2024). However, it is important to be clear that this term does not reflect, and is unable to capture, the complexities of gender identity. With this caveat, discussions of prior research will utilize the terms from those studies, although it is not always clear if the terms from those studies accurately represent sex or gender identity.

1.2.1 Childhood

In childhood, ADHD is more prevalent in males, and this has been attributed to several factors. First, during childhood, males tend to display more symptoms of hyperactivity and impulsivity than females (Eng et al., 2023). These symptoms are typically noticed by teachers and parents when children begin to attend school and their behaviors are noticeably different from those of same-aged peers. Secondly, boys are more likely to experience comorbid disruptive behavior disorders during childhood

(Mohammadi et al., 2021). Girls with ADHD are less likely to be identified by teachers, have less overt symptoms (such as forgetfulness and disorganization as opposed to disruptive behaviors), and are therefore less likely to be treated (Quinn, 2005).

1.2.2 Adolescence

Adolescence is a time where individuals transition from childhood to adulthood, including both gendered social transitions and a physical sexual maturation process known as puberty. In contrast to childhood, ADHD symptoms and impairment become more prominent in girls starting during adolescence, which is also when comorbidity, depression, and suicide risk increase (Biederman et al., 2008; Chronis-Tuscano et al., 2010; Eng et al., 2023). Beginning in early adolescence, females begin to exhibit low self-esteem, social pressures, sexuality, and increased expectations of maturity including a focus on body image (Deković et al., 1997; Forney et al., 2019; Galambos & Tilton-Weaver, 2000; Helfert & Warschburger, 2013; Rosenthal et al., 1991). Girls with ADHD are also at increased risk of experiencing important health outcomes like risky sexual behavior, unplanned pregnancies, substance use, pathological eating behaviors, and binge-drinking (Chronis-Tuscano et al., 2010; Flory et al., 2006; Mikami et al., 2008; Molina et al., 2007; Molina & Pelham, 2003). Puberty also seems to exacerbate these effects on depression (Costello et al., 2011; Eng et al., 2023; McGuire et al., 2019; Reardon et al., 2009). Yet, as in the ADHD literature generally, female adolescents with ADHD are particularly understudied.

1.2.3 Puberty and the Importance of Hormones

Adolescence and puberty may be particularly risky because that is when females experience dramatic rises in reproductive hormones, along with the onset of cyclical

hormonal shifts (and menstruation) that continue into adulthood. Estradiol and progesterone begin to fluctuate during late puberty as youth experience their first ovulation, leading also to their first menstruation. Yet only one prior study has directly examined pubertal effects on ADHD and associated problems. This study by Eng and colleagues (2023) examined the trajectories of ADHD symptoms, impairment, and comorbid depression in youth with ADHD across adolescence and puberty. Results indicated that although overall males had higher levels of hyperactivity, impulsivity, and inattention than females, females had higher levels of impairment than males. Additionally, inattentive symptoms in females did not show marked maturation changes across adolescence but appeared to decrease in males. Further, while age alone predicted declines in hyperactivity for males, for females it appeared that both age and pubertal development predicted declines in hyperactivity. Impulsivity appeared to decline for males, similar to inattention, but did not show marked changes in females. Lastly, depression increased as females advanced through pubertal stages, which may have contributed to the increases in impairment found in females at the same time. However, that study failed to capture the complexities of circulating hormone levels that begin to cycle monthly in females during late puberty as that study assessed participants yearly.

1.3 Hormones

1.3.1 Organizational-Activational Model

Organizational and activational effects of the reproductive neuroendocrine system may provide insight into how this system interplays with ADHD and depressive symptoms across development. There is some important extant theory that could guide such study. Organizational and activational hormonal effects and theory on more general

phenomena is well known and articulated. Organizational effects refer to the ability of steroids to dictate long-lasting structural and functional changes that persist past exposure to that steroid. The prenatal effects of testosterone on ADHD (Martel et al., 2008; Martel & Roberts, 2014), touted to be important for males, are organizational (Phoenix et al., 1959). Activational effects, in contrast, are more transient (e.g., during puberty), and serve to impact previously organized neural circuitry, behavior, and the body. The differential impact of hormones across multiple reproductive periods for females with ADHD suggest that activational effects may be particularly important for conceptualizing these developmental changes.

Early organization of sex development in utero through the first years of life sets the stage for secondary sex development during puberty (Schulz et al., 2009). During puberty, hormones activate growth of secondary sex characteristics (e.g., gonads, genitalia), sexually dimorphic systems (e.g., brain), and behaviors/symptoms (e.g., ADHD, depression). Puberty thus represents a sensitive developmental period when youth become increasingly vulnerable to emotional and behavioral dysregulation and psychiatric conditions (Cole et al., 2021). Youth with ADHD may be especially vulnerable to depression as they undergo physical and neurobiological changes related to activational effects of puberty and pubertal hormones that modulate neural networks implicating cognitive functioning (Roy et al., 2017), and reward neurocircuitry (Martel, 2009). Onset of mood symptoms in adolescence is also impacted by neurobiological sensitivity to cyclical ovarian hormone fluctuations in many individuals (Dubol et al., 2021). Cyclical changes in estradiol and testosterone predict daily severity of ADHD symptoms among females with high trait impulsivity (Roberts et al., 2018).

1.3.2 Hormones during Puberty

At its core, the organizational-activational hypothesis of hormonal influence posits that as youth traverse adolescence and undergo the process of pubertal maturation, hormonal changes affect risk in complex ways. At a cross-sectional level, age and pubertal stage are highly interrelated and statistical modeling of stage-for-age generates an index where youth are at a greater (or lower) stage compared to same-aged peers. It is impossible for cross-sectional studies to disentangle between-individual development, such as age and pubertal stage, from within-individual developmental processes, such as aging and pubertal maturation. Longitudinal investigation of symptomatology observed as youth mature from childhood to adolescence is required to advance understanding of how risk for psychopathology changes as youth mature. In addition to aging, pubertal development co-occurs at transitional ages marking the end of childhood and entry into adolescence, and pubertal stage-for-age varies across youth. Therefore, longitudinal models are needed that account for both within- and between-individual processes using statistical modeling approaches, such as multilevel models, that account for collinearity—high correlation between aging and pubertal development—while disentangling unique influence of these developmental variables on ADHD and depression symptomatology.

1.3.3 Pubertal Stage and Timing

Pubertal stage, also known as Tanner stage, is an indicator of sexual maturation and is based on physiological factors such as growth in height, changes in breast or testicular size and shape, skin changes, growth of pubertal and armpit hair, and the onset of menstruation. Menstruation begins in Tanner stage 4 and becomes more consistent in Tanner stage 5. By Tanner stage 5 sexual development is considered to be completed, and

the adolescent will often physically resemble an adult. The visible nature of Tanner stages may also impact their social environment, as their appearance may be more indicative of sexual development rather than age or cognitive development (Susman & Rogol, 2004).

The timing of puberty is also important and females may be preferentially vulnerable to the organizational effects of early puberty because it shifts the timing of the sensitive period of neurodevelopment in such a way as to predispose them to impulsivity and depression (Schulz et al., 2009; Sisk & Zehr, 2005). In addition to the compounding organizational effects of early puberty on the neurobiology implicated in impulsivity and depression, fluctuations in estrogen across the menstrual cycle appear to exacerbate risk. Estrogen surges and declines around ovulation appear to worsen impulsivity by interacting with dysregulated approach behaviors and reward sensitivity, in line with organizational effects on impulsivity at puberty (Eng et al., 2024). Further, activational declines in estrogen at the end of the menstrual cycle appear to worsen depression and inattention (Eng et al., 2024). This might allow known activational effects of hormones across the menstrual cycle to serve as a double whammy of risk.

1.3.4 Pilot Data on ADHD Symptoms Across the Menstrual Cycle

Our preliminary pilot work suggests that there are substantial but almost entirely ignored activational hormonal effects on ADHD across the menstrual cycle. Specifically, in nonclinical, community-recruited young adult females ages 18 to 25, declines in estrogen predicted clinically significant 2-fold increases in ADHD symptoms of inattention and hyperactivity-impulsivity (Roberts et al., 2018). These effects were particularly strong for the more impulsive females, and effects were moderated by

positive and negative urgency (or urgency due to positive and negative affect, respectively; Chester et al., 2016; Cyders & Smith, 2008).

These effects were somewhat different for hyperactivity-impulsivity and inattention respectively. Namely, effects for hyperactivity-impulsivity appeared mainly driven by declines in estrogen regardless of levels of progesterone, consistent with more of an ovulatory effect. In contrast, inattentive effects seemed more specific to point of cycle with declines in estrogen being more related to higher symptoms in context of higher than usual progesterone when an individual was higher in negative urgency consistent with perimenstrual effects at end of the cycle just before menstruation; higher than usual estrogen in context of lower than usual progesterone was related to more inattentive symptoms for those higher in positive urgency, consistent with a midcycle effect (Roberts et al., 2018).

Such results are consistent with the idea that rapid changes in estrogen, particularly declines, increase risk for ADHD symptoms, perhaps especially among people at risk for ADHD. Our preliminary pilot work and theory suggests that declines in estrogen are correlated with increased symptoms throughout the cycle, both just post-ovulatory and at the end of the cycle. Although pronounced individual differences are observed, estrogen appears generally protective for cognition across the menstrual cycle and has been implicated in emotion regulation (Rehbein et al., 2021). Therefore, midcycle declines in estrogen may interact with or exacerbate prior increases in approach and reward behaviors, leading differentially to hyperactivity and impulsivity midcycle, around ovulation. In contrast, at the end of the cycle, declines in estrogen may be

interacting with or exacerbate tendencies toward social withdrawal and negative affect, leading to more inattentive symptoms.

1.4 Moderators of Hormonal Effects

The minimal research on hormonal effects on ADHD symptoms offers both a limited number of factors that can be *expected* to act as moderators, such as impulsivity (Roberts et al., 2018), as well as a vast number of factors that could be *predicted* to act as moderators. The current study aims to examine the potential moderating effects of trait impulsivity, pubertal stage, family functioning, peer rumination, and perceived stress. Although many factors could reasonably influence hormonal effects, these variables were selected due to their importance within adolescent development (Berenbaum et al., 2015; Galván & Rahdar, 2013; Hummel et al., 2013; Roberts et al., 2018; Stone et al., 2010).

1.4.1 Evolutionary Theory

Theory suggests environmental effects are important for timing of pubertal development. Our prior work suggests that more impulsive women are more susceptible to hormonal effects (Roberts et al., 2018). This is in line with developmental evolutionary theory of life history strategies which suggests that female reproductive strategies are impacted by traits and environmental factors, particularly environmental harshness and unpredictability. Those who are exposed to greater environmental harshness and higher unpredictability develop faster, or more impulsive, life history strategies than those with less of these environmental experiences (Belsky et al., 2012; Brumbach et al., 2009). Therefore, environmental moderators such as family functioning, peer rumination, and stress influence individual variation in life history strategies such that poorer family functioning, greater peer rumination, and higher stress levels may be associated with

increased impulsivity and ADHD and more impacted by hormonal effects. In fact, poorer family functioning and stress levels have been associated with ADHD (Combs et al., 2015; Cussen et al., 2012).

1.4.2 Family Functioning

Prior works suggest family functioning may be uniquely affected by ADHD and vice versa. Families that contain children with ADHD report experiencing greater psychological distress, less feelings of parenting self-efficacy, less parenting consistency, greater parenting hostility, lower parental warmth, and more stressful life events (Bhide et al., 2023; Breaux & Harvey, 2019; Cussen et al., 2012; Moen et al., 2016). Over time, these families also experience lessening parent-partner support and parenting warmth (Bhide et al., 2023). A systematic review of the literature indicates that ADHD not only affects family functioning, but that family functioning also influences ADHD symptoms, with familial factors such as intrusiveness, reactivity, negativity, and discipline being associated with ADHD outcomes (Claussen et al., 2022).

1.4.3 Peer Rumination

Additionally, rumination, and more specifically peer rumination, may also moderate hormonal effects on ADHD symptoms. Studies of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) indicate that premenstrual disorders are strongly related to rumination and may contribute to the onset and maintenance of such symptoms by increasing the onset and slowing remission (Craner et al., 2014; Dawson et al., 2018). Further, high emotion-related impulsivity, like that commonly associated with ADHD, is also strongly related to premenstrual symptoms (Dawson et al., 2018).

Peer rumination, or co-rumination, refers to the construct of extensively discussing problems and negative feelings between friends. Research around this construct suggests that self-disclosure is important for closer-friendships but that fixating on negative topics can lead to emotional problems, especially in girls (Rose, 2002; Stone et al., 2010). Prior research indicates the increases in depressive symptoms in girls with ADHD (Eng et al., 2023), and peer rumination may help explain this phenomenon. However, peer rumination has yet to be studied in relation to ADHD until this project.

1.4.4 Perceived Stress

The evidence for perceived stress as a moderator for hormonal effects on ADHD symptoms is two-fold. First, there is substantial evidence that greater perceived stress negatively impacts premenstrual symptoms. Experiencing high levels of stress can influence the body on a physical level, leading to the cessation of or missed periods (Allsworth et al., 2007). At the hormone level, administration of sepranolone, a GABAA receptor modulation steroid antagonist, leads to clinically significant reductions of stress premenstrually compared to a placebo (Bäckström et al., 2021). Additionally, administration of estradiol and progesterone reduce levels of perceived stress (Eisenlohr-Moul et al., 2022). These studies indicate that progesterone, and possibly estradiol, are directly related to perceived stress.

Secondly, there is a growing body of evidence that perceived stress influences ADHD symptoms. Greater ADHD symptoms, particularly inattention, has been found to be predictive of higher levels of perceived stress (Combs et al., 2015). Further, the association between ADHD symptoms and suicidal ideation has been accounted for by perceived stress (Yeguez et al., 2018).

1.5 Limitations of Past Work

Prior work was limited by complete reliance on parental reports of pubertal status and no attention to actual biological levels of circulating hormones. Therefore, a critical next step is empirical examination of when female adolescents begin experiencing hormonal effects on ADHD symptoms, particularly given the increases in comorbidity and increases and fluctuations in hormones during this developmental period. In addition, given the critical nature of the social environment during adolescence, the current study also attempts to examine adolescent-specific moderators of these effects including family functioning, stress, and peer rumination, as well as evaluate whether these effects are moderated by trait impulsivity as indicated by our prior work (Roberts et al., 2018). Identifying when adolescent females begin to experience increased risk for ADHD would allow for personalized timing of intervention in females. In addition, identifying environmental and trait moderators would suggest additional treatment targets.

1.6 The Current Study

Unlike prior studies that have inferred pubertal development based on parent reports of pubertal stage, the current study is the first to examine actual levels of circulating hormones in adolescence in order to examine their impacts on ADHD symptoms. The long-term goal of this project is to revolutionize the assessment of ADHD and personalize the treatment of adolescent ADHD based on cycle phase. If there are moderate to large effects on hormones on ADHD, then pubertal status and/or cycle phase would be important to consider in assessment and treatment decisions for young females

with ADHD, a decision that could mitigate risk not only for ADHD but also depression and suicide risk prominent in this age range.

It is hypothesized that females will experience clinically significant increases in ADHD symptoms post-ovulation, on days when estradiol is declining, and during cycle phases characterized by rapid decreases in estradiol compared to phases associated with relatively stable levels of estradiol. These effects will be moderated by Tanner stage such that the effects will be stronger later during puberty once hormones are more consistently cycling, consistent with later adolescent effects. Females who are higher on trait impulsivity will be more likely to experience clinically significant increases in ADHD symptoms during cycle phases characterized by rapid decreases in estradiol than those with less trait impulsivity. Females with poorer family functioning, greater peer rumination, or greater stress will be more likely to experience clinically significant increases in ADHD symptoms during cycle phases characterized by rapid decreases in estradiol.

CHAPTER 2. METHODS

2.1 Participants

Participants were 19 adolescents who had begun to menstruate between the ages of 11 and 17 years old (M = 15.08, SD = 2.01) and their parents (15 of 19 self-identified as *mother*). Participants were 89% White. One participant indicated non-binary as their gender while the rest identified as female. Retrospective report indicated menarche occurred on average at age 10.97 (SD = 0.68). Height and weight measurements taken at laboratory visits were used to calculate body mass index (BMI; M = 23.63, SD = 5.85, range = 17.90-42.10). Descriptive information of ADHD symptoms is provided in Table 2.1.

2.1.1 Recruitment

Participants were recruited through a wide range of advertisements and other recruitment sources including through bulletin boards in the community and through social media. Advertisements targeted parents of adolescents ages 9 to 17 who were concerned they may have attention, overactivity, or impulsivity problems, who had begun menstruation (i.e., Tanner Stages 4 or 5), and who were not currently taking hormone-based medication.

2.1.2 Exclusions

Due to evidence that ADHD symptoms are best represented as dimensions (Haslam et al., 2006; Marcus & Barry, 2011), and based on particularly strong effects found in more impulsive females, advertisements targeted parents of adolescents who believed they have problems with inattention, hyperactivity, and impulsivity, although having or not having a diagnosis of ADHD was not exclusionary. However, in order to

rule out hormonal or biological confounds that might interfere with examination of hormonal associations with ADHD, study exclusionary criteria included: (a) have not begun menstruation; (b) use of hormone-based medication (e.g., hormone-based contraceptives or steroids); (c) known hormonal abnormalities (e.g., Polycystic Ovarian Syndrome, thyroid conditions) or self-report of pregnancy; (d) primary sensorimotor handicap; (f) frank neurological disorder (e.g., seizure disorders, brain tumor, cerebral palsy, hydrocephalus, head injury with loss of consciousness); (g) pervasive developmental disorder (i.e., autism, Asperger's, Rett's, childhood disintegrative disorder); (h) frank psychosis (i.e., schizophrenia, hallucinations, delusions); (i) diagnosed intellectual disability. Although participants in Tanner stage 4 have less regular menstrual cycles, both participants in stages 4 and 5 completed daily data collection.

2.2 Measures

2.2.1 Background Questionnaire

Participants completed a screening and medical history interview over the telephone which assessed relevant demographic information (i.e., sex assigned at birth, race/ethnicity, age), study exclusionary criteria, history of medical and psychiatric conditions, family history of medical and psychiatric conditions, history of medication use, and current medication use.

2.2.2 ADHD Symptoms

The Barkley Adult ADHD Rating Scale, Current Symptoms Scale (BAARS-IV CSS; Barkley & Murphy, 2006) is composed of 18 items which are rated on a scale from 0 (never or rarely) to 3 (very often) that assess current ADHD symptoms. The BAARS-

IV CSS was completed at the initial visit by both parents and adolescents and daily through the study just by adolescents. It has high reliability of .92 or above for scales and exhibits strong associations with functional outcomes such as occupational and social functioning (Barkley, 2011). Our pilot data indicated that this measure is sensitive to detection of associations between hormone and daily changes in ADHD symptoms (Roberts et al., 2018). Daily adolescent ratings were averaged according to symptom type (inattention: α = .93; hyperactivity: α = .77; impulsivity: α = .81).

2.2.3 Pubertal Development

The Pubertal Development Scale (PDS; Petersen et al., 1988) was used to collect information on pubertal development. The PDS is a five-item measure that asks about growth in height, body hair, skin changes, breast development, and menarche. Parents and participants were interviewed together and asked to rate each item on a 1 (barely started) to 4 (seems complete) scale. Prior research has indicated that adolescents are somewhat less reliable reporters of pubertal development (Eng et al., 2023), and the current project sought to improve the reliability of this measure by having adolescents and their parents discuss and come to an agreement on pubertal ratings. The PDS is reliable with alpha-coefficients ranging from .68 to .83 (Petersen et al., 1988) and has high correlations with physician ratings (.61-.67; Brooks-Gunn et al., 1987).

The PDS was converted into pubertal stages mapping onto adrenarcheal- and gonadarcheal-driven physical maturation and then a composite pubertal stage score was calculated using syntax from Shirtcliff and colleagues (Shirtcliff et al., 2009). In the current study, pubertal stage scores ranged from 4 to 5 by design. Based on the coding, stage 4 indicates that participants have peaked in maturation and likely reached menarche

(first menstrual cycle). Meanwhile, stage 5 indicates that the participant has reached full pubertal maturation when gonadarche is complete. Of the 19 participants, six participants received pubertal stage scores of 4.0 or 4.5 and 13 participants received a pubertal stage score of 5 ($M = 4.76$, $SD = 0.39$).

2.2.4 Estradiol and Progesterone

Participants were asked to collect a saliva sample 30 minutes after waking each morning. Saliva samples were used to collect hormone data across the menstrual cycle. The samples were collected in one 1.8 milliliter vial using passive drool procedures after refraining from eating, drinking, or smoking. Vials were pre-labeled with a random numerical identification number and date and were stored in a home freezer and then transported to the laboratory in a cooler at the end of daily data collection. Following sample return to the laboratory, the samples were transported from the laboratory by study staff to the Biochemical Analysis Laboratory in the CCTS on the University of Kentucky campus where hormone assays for estradiol (E2) and progesterone (P4) were conducted. P4 assays were conducted due to our pilot data suggesting interactions between E2 and P4. Salimetrics kits were used. For E2, the estradiol Salimetrics 17β-Estradiol immunoassay kit has a sensitivity of 0.1 pg/mL and high precision (% coefficient of variation ranging from 6.3 to 8.1). For P4, the progesterone enzyme immunoassay (EIA) kit has a sensitivity of 5 pg/mL (from 0) and precision of percent coefficient of variation between 4 and 8.4. These saliva-based assays also demonstrate high and significant correlations of .8 ($p < .01$) with serum levels of estradiol and progesterone. Such sensitivity and precision allow for accurate detection of changes in estradiol and progesterone levels across the cycle. Furthermore, the results of our pilot

data speak to these kits' ability to detect daily ovarian hormone changes using our current data collection procedures.

2.2.4.1 Current Status Update Form

Adolescents completed this brief questionnaire each morning as part of their daily data collection. This questionnaire assesses external factors that may affect levels of circulating hormones, including sleep schedule, exercise, medication use, drug/alcohol use, and stressful events (e.g., death in family). They were also asked to indicate if they started menstrual bleeding each day.

2.2.4.2 Height and Weight

Participants' height and weight were assessed using a medical balance beam scale with a height rod. This information is important as body mass index has been demonstrated to have an effect on circulating levels of hormones (Lukanova et al., 2004).

2.2.4.3 Menstrual Cycle Phase Coding

Menstrual cycle phases were determined by self-reported menses onset prior to and at the end of each adolescent's participation in the study. Per Schmalenberger et al., 2021, a cycle day variable was created such that the onset of menses was coded as +1 with the following days continuing a forward count (e.g., +2). The day prior to the onset of menses was coded as -1 with prior days following a backward count. Forward count codes ranged from +1 to +10 while backward count codes ranged from -1 to -15. Using this variable, four distinct cycle phases were coded: the *midfollicular phase*, days +4 to +7; the *periovulatory phase*, days -15 to -12; the *midluteal phase*, days -9 to -5; and the *perimenstrual phase*, days -3 to +2.

2.2.5 Trait Impulsivity

Adolescents completed the UPPS-P Impulsivity Scale, a 59-item questionnaire that assesses impulsivity-related traits (ie., urgency, perseverance, premeditation, sensation-seeking, and positive urgency) in adolescents with reliability and validity (Argyriou et al., 2020; Lynam et al., 2006). This study focused on the negative urgency score of the UPPS-P (α = .66) due to its moderation of hormonal effects on ADHD symptoms in prior work and its relevance to negative affect which increases across puberty in females (Brooks-Gunn et al., 1994; Eng et al., 2023; Roberts et al., 2018).

2.2.6 Family Functioning

Adolescents completed the McMaster Family Assessment Device (FAD; Epstein et al., 1983) which is a 60-item questionnaire that measures an individual's perceptions of their family. Each item is rated on a 4-point scale from strongly agree to strongly disagree. In addition to general functioning (α = .09), the FAD also contains subscales that assess problem solving (α = .55), communication (α = -.29), roles (α = .15), affective responsiveness (α = .30), affective involvement (α = .59), and behavior control (α = .17); this study focused on general functioning as that scale consists of items from all six scales and is intended to measure overall family functioning. Prior work found the reliability of the FAD to be higher than the present study, with internal consistency reliabilities for each scale ranging from .72-.83 and .92 for the general functioning scale (Sherman & Fredman, 2013). Due to the very low reliabilities found across the measure, in particular the general functioning scale, the FAD was ultimately excluded from analyses. This measure was completed last in the adolescent battery, so this low reliability may be due to participant fatigue.

2.2.7 Stress

Adolescents completed the Perceived Stress Scale (PSS; Cohen et al., 1983) which is a widely used psychological instrument for measuring the perception of stress. The PSS contains 10 items rated on a scale of 0 (never) to 4 (very often) and generates a total score of perceived stress (α = .83). Items were designed to assess individuals' perceptions of how unpredictable, uncontrollable, and overloaded they find their lives. It has high reliability of .89 and high correlation with similar measures (Roberti et al., 2006).

2.2.8 Peer Rumination

Co-rumination refers to extensively discussing and revisiting problems, speculating about problems, and focusing on negative feelings. Adolescents completed the Co-rumination Questionnaire (Co-RQ; Rose, 2002) which consists of 27-items rated on a scale of 1 (not at all true) to 5 (really true) and generates a total score (α = .98). Cronbach's alpha coefficients ranged from .86 to .95 and further psychometric properties are described elsewhere (Tanhaye Reshvanloo et al., 2022).

2.3 Procedures

Parents and/or adolescents completed a telephone screen assessing study eligibility criteria. When participants arrived at the laboratory for the full visit, parents completed the informed consent procedure, and adolescents completed an informed assent procedure, conducted in separate rooms. During the informed consent procedure, all participants were informed about study procedures, tasks, risks, and benefits. Participants were given an opportunity to ask questions and were informed that they

could withdraw from the research at any time. Procedures and consent forms complied with requirements of the University of Kentucky Institutional Review Board.

The laboratory visit lasted approximately two hours, during which time participants and their parents completed interviews and questionnaires about the adolescent's medical history and development, as well as current behaviors, cognition, traits, affect, and relationships with friends and family as described below. The adolescents had their height and weight recorded. At the end of this visit, participants were sent home with instructions, prelabeled saliva tubes and a cooler, and were instructed to begin up to 35 subsequent days of data collection the following morning. Procedures for collecting saliva samples were described and modeled.

Daily data collection at home consisted of collecting saliva and completing short questionnaires for up to 35 days (depending on cycle length). They received text reminders daily to complete these measures, which required access to a computer. If adolescents did not have a phone or email, these reminders were sent to a parent. A text was sent in the morning reminding them to collect their saliva sample when they woke up. When participants completed morning data collection, they also logged onto the data collection website to complete a short questionnaire, the Current Status Update Form, to assess environmental factors that may affect levels of circulating hormones. Every evening, they would again receive a text instructing them to follow a link to a secure Qualtrics site to complete additional questionnaires between 5 and 10 pm to assess for daily ADHD symptoms. This procedure continued daily throughout the remainder of their participation in order to ensure study compliance.

Following completion of data collection, they and their parents returned their materials to the laboratory and obtained payment for study completion. Participants received up to $200 for taking part in the study. This includes $100 for completion of the 2-hour laboratory visit and up to $100 for completion of at least 50% of data collection spread out across the month of data collection. Participants who completed any data collection but withdrew within the first week or two received $20.

2.4 Analytic Plan

It was planned that youth who completed less than 50% of daily data collection would be listwise deleted, while youth who completed 50% or more of daily data collection would remain in analyses. However, all youth completed at least 50% of daily data collection.

Materials and analysis code for this study are available by emailing the corresponding author. Analyses were conducted as recommended by Schmalenberger and colleagues (2021), as described subsequently. Analyses were conducted in R version 4.2.1 using the package 'lme4' (Bates et al., 2014; R Core Team, 2020). Multilevel modeling (MLM) was used to test hypotheses using nested repeated measures data with a two-level structure (days or phases at level 1, nested within adolescents at level 2). Main outcomes were inattentive, hyperactive, and impulsive ADHD symptom severity, as measured by the daily BAARS-IV CSS completed by the adolescents. Inattention and hyperactivity were normally distributed while impulsivity was positively skewed. Residuals for all three outcomes were normally distributed. Because cycle phase is a categorical variable, modeling the effects of cycle phase on each outcome required four models per outcome in order to rotate the reference group for estimation of each pairwise

comparison. Pubertal stage, trait impulsivity, stress, and peer rumination were individually tested in models as moderators of hormonal effects on ADHD symptoms. Family functioning was not tested due to the measure's poor reliability. ICCs revealed that the majority of the variance in symptoms was at the between-person level for inattentive symptom severity (ICC = 0.73), hyperactive symptoms severity (ICC = .58), and impulsive symptom severity (ICC = .63). Power analyses suggested that the sample size of 19 provides sufficient power (.80) to detect small effects (.19).

Table 2.1 Descriptive Information of ADHD Symptoms

		Self-Report			Parent-Report		
		Mean	SD	Min.-Max.	Mean	SD	Min.-Max.
Symptom Count	Inattention	5.67	2.33	1-9	2.89	3.00	0-8
	Hyperactivity	3.00	1.33	1-5	1.26	1.19	0-3
	Impulsivity	0.72	0.96	0-3	0.26	0.56	0-2
Symptom Severity	Inattention	1.83	0.65	0.56-3.0	1.20	0.73	0.00-2.44
	Hyperactivity	1.49	0.46	0.50-2.33	0.75	0.53	0.00-1.67
	Impulsivity	1.06	0.74	0.00-3.00	0.35	0.61	0.00-1.67

Note. Scores are based on the current symptoms scale questionnaire from each participant's laboratory visit.

CHAPTER 3. RESULTS

3.1 Changes in ADHD Symptoms Across the Menstrual Cycle

3.1.1 Menstrual Cycle Phase Contrasts

In line with current etiological work on ADHD, primary analyses evaluated effects on inattentive, hyperactive, and impulsive symptoms as rated by adolescents daily (Sonuga-Barke, 2002; Willcutt et al., 2012). Symptom severity scores were calculated by averaging each symptom rating within a domain. Table 3.1 presents a summary of the results of hypothesis tests and Figure 3.1 provides a graphical representation. Fixed effects demonstrated that, on average, inattention showed no significant changes across the cycle. Hyperactivity was, on average, higher in the periovulatory phase than in the perimenstrual and midluteal phases. Impulsivity was, on average, higher in the midluteal phase than in the perimenstrual phase.

3.1.2 Association of Hormone Levels and ADHD Symptoms

Results of models predicting daily ADHD symptoms from recent steroids and their interactions revealed a significant effect of progesterone on inattention, such that higher levels of progesterone predicted more severe inattention (see Table 3.2, see Figure 3.2). Similarly, there was a significant effect of estradiol on hyperactivity, such that lower levels of estradiol predicted more severe hyperactivity (see Table 3.2, see Figure 3.3). No significant effects of estradiol or progesterone on impulsivity were found. No significant effect of BMI or interactions between estradiol or progesterone were found for any of the ADHD symptom domains.

3.1.3 Tanner Stage as a Moderator

Multilevel models with planned contrasts were used to examine Tanner stage as a potential moderator of cycle phase effects on ADHD symptoms. Results of these models indicated no significant effect of Tanner stage or interaction between Tanner stage and phase on inattention, hyperactivity, or impulsivity (see Table 3.3).

3.2 Moderators of Hormonal Effects on ADHD Symptoms

3.2.1 Trait Impulsivity as a Moderator

Multilevel models with planned contrasts were used to examine trait impulsivity as a potential moderator of cycle phase effects on ADHD symptoms (see Table 3.4 and Figure 3.4). The Negative Urgency (NU) scale from the UPPS was used. Results of these models indicated no significant effect of NU or interaction between NU and phase on inattention.

Results did, however, suggest NU significantly moderated differences in hyperactivity between the midfollicular phase and the periovulatory and midluteal phases. Follow-up analyses suggested that at high levels of NU, participants reported significantly less severe hyperactivity in the midluteal phase than the periovulatory (B = -0.24, p = .017) and midfollicular phases (B = -0.29, p = .003). Hyperactivity was no longer significantly different between the midfollicular and periovulatory phase at high levels of NU. However, at low levels of NU, analyses did not reveal any significant differences among phases.

Lastly, results suggested that NU significantly moderated differences in impulsivity between the periovulatory and midluteal phases. Follow-up analyses suggested that at low levels of NU, participants reported more severe impulsivity in the

midluteal phase versus the periovulatory phase (B = 0.22, p = .001). At high levels of NU, this effect diminished and reversed, although not to such an extent that the difference between phases was significant (B = -0.10, p = .156).

3.2.2 Peer Rumination as a Moderator

Multilevel models with planned contrasts were used to examine peer rumination as a potential moderator of cycle phase effects on ADHD symptoms (see Table 3.5 and Figure 3.5. The average score from the Co-Rumination Questionnaire was used. Analyses revealed a main effect of peer rumination (B = 0.46 to 0.57, $p \leq .001$), regardless of which phase was used as the reference group, indicating that higher levels of peer rumination were associated with more severe inattention. However, these analyses did not reveal any significant phase effects or interactions between peer rumination and cycle phase on inattention.

Similarly, analyses revealed a significant main effect of peer rumination on hyperactivity (B = 0.25 to 0.36, p = .003 to .025), regardless of which phase was used as the reference group, indicating that higher levels of peer rumination were associated with more severe hyperactivity. However, these analyses did not reveal any statistically significant interactions between peer rumination and cycle phase on hyperactivity.

Lastly, results suggested that peer rumination significantly moderated differences in impulsivity between the midfollicular phase and the midluteal and periovulatory phases. Follow-up analyses suggested that at high levels of peer rumination, participants reported more severe impulsivity in the midluteal phase versus the midfollicular phase (B = 0.24, p = .012). Similarly, although not statistically significant, at high levels of peer rumination, participants reported more severe impulsivity in the periovulatory phase than

the midfollicular phase (B = 0.17, p = .149). However, at low levels of peer rumination, these effects greatly diminished and differences between phases were no longer significant (midluteal vs. midfollicular: B = -0.02, p = .968; periovulatory vs. midfollicular: B = -0.10, p = .481).

3.2.3 Perceived Stress as a Moderator

Multilevel models with planned contrasts were used to examine perceived stress as a potential moderator of cycle phase effects on ADHD symptoms (see Table 3.6 and Figure 3.6). The Total Score from the Perceived Stress Scale was used. Results of these models are described below.

Results suggested that perceived stress moderated differences in inattention between the midfollicular phase and the perimenstrual, midluteal, and periovulatory phases. However, follow-up analyses using pairwise contrasts did not reveal statistically significant differences of inattention between phases at low or high levels of perceived stress. This may be due to a lack of power from small group size and should be interpreted cautiously.

Results also suggested that perceived stress moderated differences in hyperactivity between the periovulatory phase and all other phases. Follow-up analyses suggested that at low levels of perceived stress, participants reported more severe hyperactivity in the periovulatory phase than in the midfollicular (B = 0.22, p = .039), midluteal (B = 0.24, p = .012), or perimenstrual phases (B = 0.30, p = .001). At high levels of perceived stress, this effect greatly diminished and differences between phases were no longer significant. Lastly, analyses did not reveal any statistically significant

effects of perceived stress on impulsivity or interactions between perceived stress and menstrual cycle phase.

Table 3.1 Multilevel Model Results: Within-Person Menstrual Cycle Phase Contrasts for ADHD Symptoms

	Within-Person Phase Contrasts					
	PM			ML		PO
	v. ML	v. PO	v. MF	v. PO	v. MF	v. MF
Inattention Severity	0.03	0.10	0.03	0.07	0.00	-0.07
Hyperactivity Severity	0.05	**0.20****	0.09	**0.14***	0.04	-0.11
Impulsivity Severity	**0.14***	0.06	0.03	-0.08	-0.11	-0.03

Note. *$p \leq .05$, **$p \leq .01$. MF = Midfollicular, PO = Periovulatory, ML = Midluteal, PM = Perimenstrual.

Table 3.2 Models Predicting Daily ADHD Symptoms from Person-Standardized Hormone Levels

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	**1.64****	0.56	**1.68*****	0.39	**1.17***	0.47
BMI	-0.02	0.02	-0.02	0.02	-0.03	0.02
E2	0.00	0.08	**-0.18***	0.09	-0.04	0.09
P4	**0.001***	0.00	0.00	0.00	0.00	0.00
E2 x P4	0.00	0.00	0.00	0.00	0.00	0.00

Note. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$. E2=Estradiol, P4=Progesterone.

Table 3.3 Results of Mixed Model Analyses with Tanner Stage as a Moderator

Reference Group: Perimenstrual Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	**0.90****	0.28	**0.71****	0.21	0.44	0.25
TS	0.44	0.34	0.40	0.25	0.13	0.30
ML	0.01	0.12	0.04	0.11	0.15	0.12
PO	0.18	0.12	0.20	0.12	-0.01	0.12
MF	0.08	0.12	**0.23***	0.04	0.03	0.12
TS*ML	0.04	0.14	0.03	0.13	-0.01	0.14
TS*PO	-0.11	0.15	0.01	0.14	0.11	0.14
TS*MF	-0.07	0.14	-0.21	0.13	-0.01	0.14

Reference Group: Midluteal Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	**0.91****	0.27	**0.75****	0.20	**0.59***	0.24
TS	0.48	0.33	0.43	0.24	0.12	0.30
PO	0.17	0.11	0.16	0.10	-0.16	0.10
MF	0.08	0.11	0.19	0.10	-0.12	0.10
PM	-0.01	0.12	-0.04	0.11	-0.15	0.12
TS*PO	-0.15	0.13	-0.02	0.13	0.12	0.13
TS*MF	-0.11	0.13	-0.23	0.12	0.00	0.13
TS*PM	-0.04	0.14	-0.03	0.13	0.01	0.14

Reference Group: Periovulatory Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*

Table 3.3, Continued

Intercept	**1.08*** **	0.27	0.91***	0.20	0.43	0.24
TS	0.33	0.33	0.41	0.25	0.24	0.30
MF	-0.09	0.11	0.03	0.10	0.04	0.11
PM	-0.18	0.12	-0.20	0.12	0.01	0.12
ML	-0.17	0.11	-0.16	0.10	0.16	0.10
TS*MF	0.04	0.13	-0.21	0.13	-0.12	0.13
TS*PM	0.11	0.15	-0.01	0.14	-0.11	0.14
TS*ML	0.15	0.13	0.02	0.13	-0.12	0.13

Note. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$. TS = Tanner Stage, MF = Midfollicular, PO = Periovulatory, ML = Midluteal, PM = Perimenstrual. The Tanner Stage variable used in analyses is a categorical variable coded such that those in Tanner Stage 5 equaled 1 and those below Tanner Stage equaled 0.

Table 3.4 Results of Mixed Model Analyses with Negative Urgency as a Moderator

Reference Group: Perimenstrual Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	1.29	1.20	1.28	0.86	0.77	0.96
NU	-0.06	0.43	-0.13	0.31	-0.11	0.35
ML	-0.08	0.48	0.69	0.43	0.52	0.37
PO	-0.63	0.49	0.39	0.44	-0.58	0.38
MF	-0.59	0.49	-0.46	0.44	0.00	0.38
NU*ML	0.05	0.17	-0.23	0.16	-0.15	0.13
NU*PO	0.28	0.18	-0.06	0.16	0.23	0.14
NU*MF	0.24	0.18	0.22	0.16	0.03	0.14

Reference Group: Midluteal Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	1.20	1.17	**1.97***	0.82	1.29	0.94
NU	0.00	0.42	-0.36	0.30	-0.26	0.34
PO	-0.54	0.42	-0.30	0.38	**-1.11*****	0.32
MF	-0.51	0.43	**-1.15****	0.39	-0.52	0.33
PM	0.08	0.48	-0.69	0.43	-0.52	0.37
NU*PO	0.22	0.15	0.17	0.14	**0.38****	0.12
NU*MF	0.19	0.16	**0.45***	0.14	0.18	0.12
NU*PM	-0.05	0.17	0.23	0.16	0.15	0.13

Reference Group: Periovulatory Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*

Table 3.4, Continued

Intercept	0.66	1.17	1.67	0.83	0.18	0.94
NU	0.22	0.42	-0.20	0.30	0.12	0.34
MF	0.04	0.44	**-0.85***	0.40	0.58	0.34
PM	0.63	0.49	-0.39	0.44	0.58	0.38
ML	0.54	0.42	0.30	0.38	**1.11*****	0.32
NU*MF	-0.04	0.16	**0.29***	0.14	-0.20	0.12
NU*PM	-0.28	0.18	0.06	0.16	-0.23	0.14
NU*ML	-0.22	0.15	-0.17	0.14	**-0.38****	0.12

Note. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$. NU = Negative Urgency, MF = Midfollicular, PO = Periovulatory, ML = Midluteal, PM = Perimenstrual.

Table 3.5 Results of Mixed Model Analyses with Peer Rumination as a Moderator

Reference Group: Perimenstrual Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	-0.38	0.36	-0.04	0.31	-0.43	0.38
PR	**0.57*** **	0.12	**0.36** **	0.11	**0.35***	0.13
ML	0.09	0.19	0.10	0.18	-0.01	0.18
PO	0.29	0.20	**0.39***	0.19	-0.10	0.19
MF	0.33	0.20	**0.40***	0.19	0.25	0.19
PR*ML	-0.02	0.06	-0.02	0.06	0.05	0.06
PR*PO	-0.07	0.07	-0.07	0.06	0.06	0.07
PR*MF	-0.11	0.07	-0.11	0.06	-0.08	0.06

Reference Group: Midluteal Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	-0.29	0.36	0.06	0.31	-0.44	0.37
PR	**0.55*** **	0.12	**0.35** **	0.11	**0.40** **	0.13
PO	0.20	0.19	0.28	0.18	-0.10	0.18
MF	0.24	0.19	0.30	0.18	0.26	0.18
PM	-0.09	0.19	-0.10	0.18	0.01	0.18
PR*PO	-0.05	0.07	-0.05	0.06	0.01	0.07
PR*MF	-0.09	0.06	-0.09	0.06	**-0.13***	0.06
PR*PM	0.02	0.06	0.02	0.06	-0.05	0.06

Reference Group: Periovulatory Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*

Table 3.5, Continued

Intercept	-0.09	0.36	0.34	0.31	-0.54	0.38
PR	**0.50*** **	0.13	**0.29***	0.11	**0.41****	0.13
MF	0.04	0.20	0.01	0.19	0.36	0.19
PM	-0.29	0.20	**-0.39***	0.19	0.10	0.19
ML	-0.20	0.19	-0.28	0.18	0.10	0.18
PR*MF	-0.04	0.07	-0.04	0.07	**-0.14***	0.07
PR*PM	0.07	0.07	0.07	0.06	-0.06	0.07
PR*ML	0.05	0.07	0.05	0.06	-0.01	0.07

Note. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$. PR = Peer Rumination, MF = Midfollicular, PO = Periovulatory, ML = Midluteal, PM = Perimenstrual.

Table 3.6 Results of Mixed Model Analyses with Perceived Stress as a Moderator

Reference Group: Perimenstrual Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	-0.50	0.77	0.36	0.62	-0.02	0.73
PSS	**0.07***	0.03	0.03	0.03	0.02	0.03
ML	0.05	0.30	0.10	0.29	0.22	0.30
PO	0.12	0.33	**0.80***	0.31	-0.09	0.33
MF	**0.66***	0.31	0.09	0.29	0.15	0.31
PSS*ML	0.00	0.01	0.00	0.01	0.00	0.01
PSS*PO	0.00	0.01	-0.03	0.01	0.01	0.01
PSS*MF	**-0.03***	0.01	0.00	0.01	-0.01	0.01

Reference Group: Midluteal Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	-0.46	0.76	0.46	0.61	0.21	0.72
PSS	**0.07***	0.03	0.02	0.02	0.02	0.03
PO	0.07	0.30	**0.70***	0.29	-0.31	0.30
MF	**0.61***	0.28	0.00	0.27	-0.07	0.28
PM	-0.05	0.30	-0.10	0.29	-0.22	0.30
PSS*PO	0.00	0.01	**-0.02***	0.01	0.01	0.01
PSS*MF	**-0.03***	0.01	0.00	0.01	0.00	0.01
PSS*PM	0.00	0.01	0.00	0.01	0.00	0.01

Reference Group: Periovulatory Phase

	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	-0.39	0.77	1.16	0.62	-0.10	0.73

Table 3.6, Continued

PSS	**0.07***	0.03	0.00	0.03	0.03	0.03
MF	0.54	0.31	**-0.70***	0.30	0.24	0.31
PM	-0.12	0.33	**-0.80***	0.31	0.09	0.33
ML	-0.07	0.30	**-0.70***	0.29	0.31	0.30
PSS*MF	**-0.03***	0.01	**0.03***	0.01	-0.01	0.01
PSS*PM	0.00	0.01	0.03	0.01	-0.01	0.01
PSS*ML	0.00	0.01	**0.02***	0.01	-0.01	0.01

Note. *$p \leq .05$. PSS = Perceived Stress Score, MF = Midfollicular, PO = Periovulatory, ML = Midluteal, PM = Perimenstrual.

Figure 3.1 Average Fluctuations in ADHD Symptoms Across the Menstrual Cycle

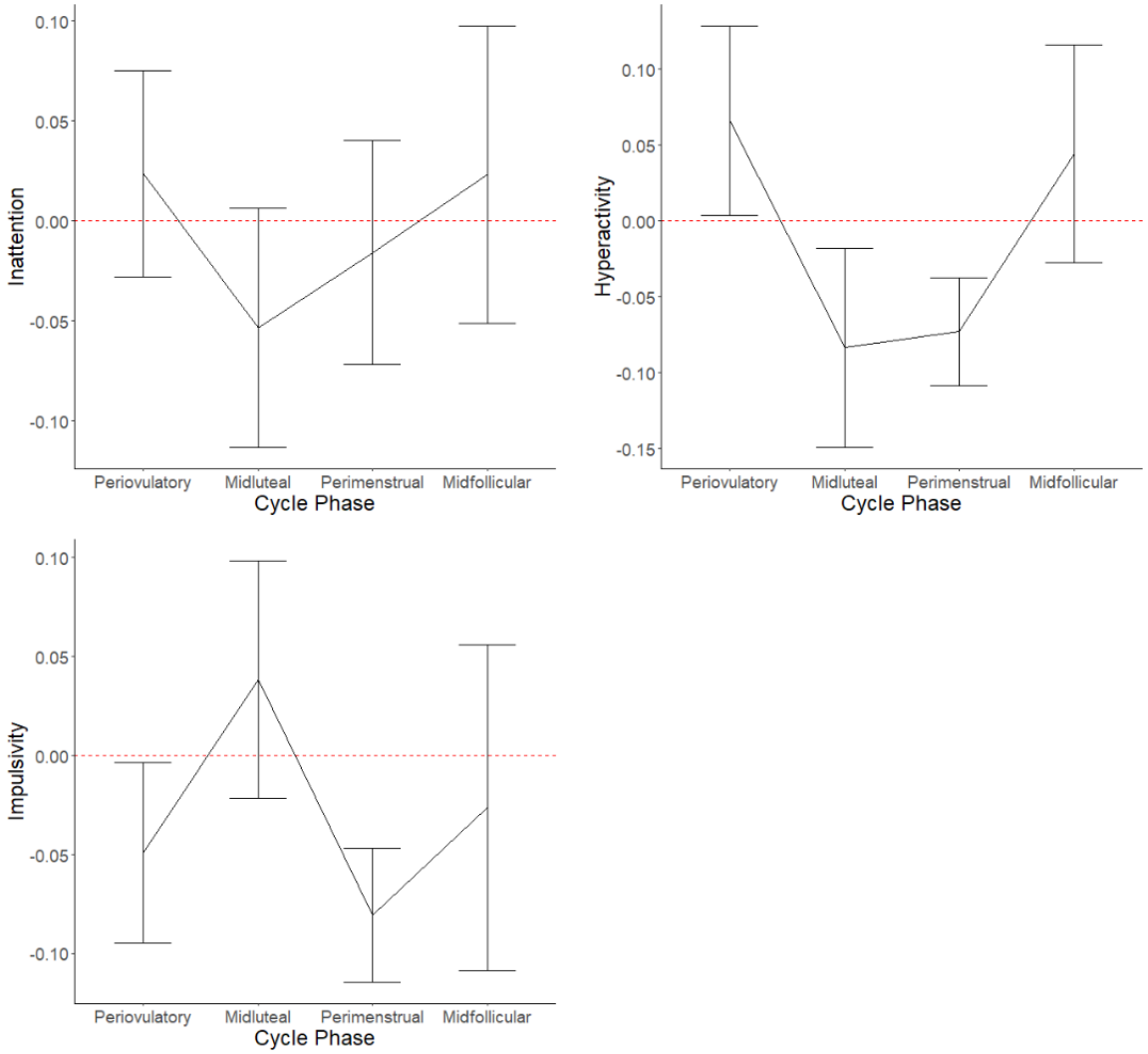


Figure 3.2 Progesterone Predicts Inattention

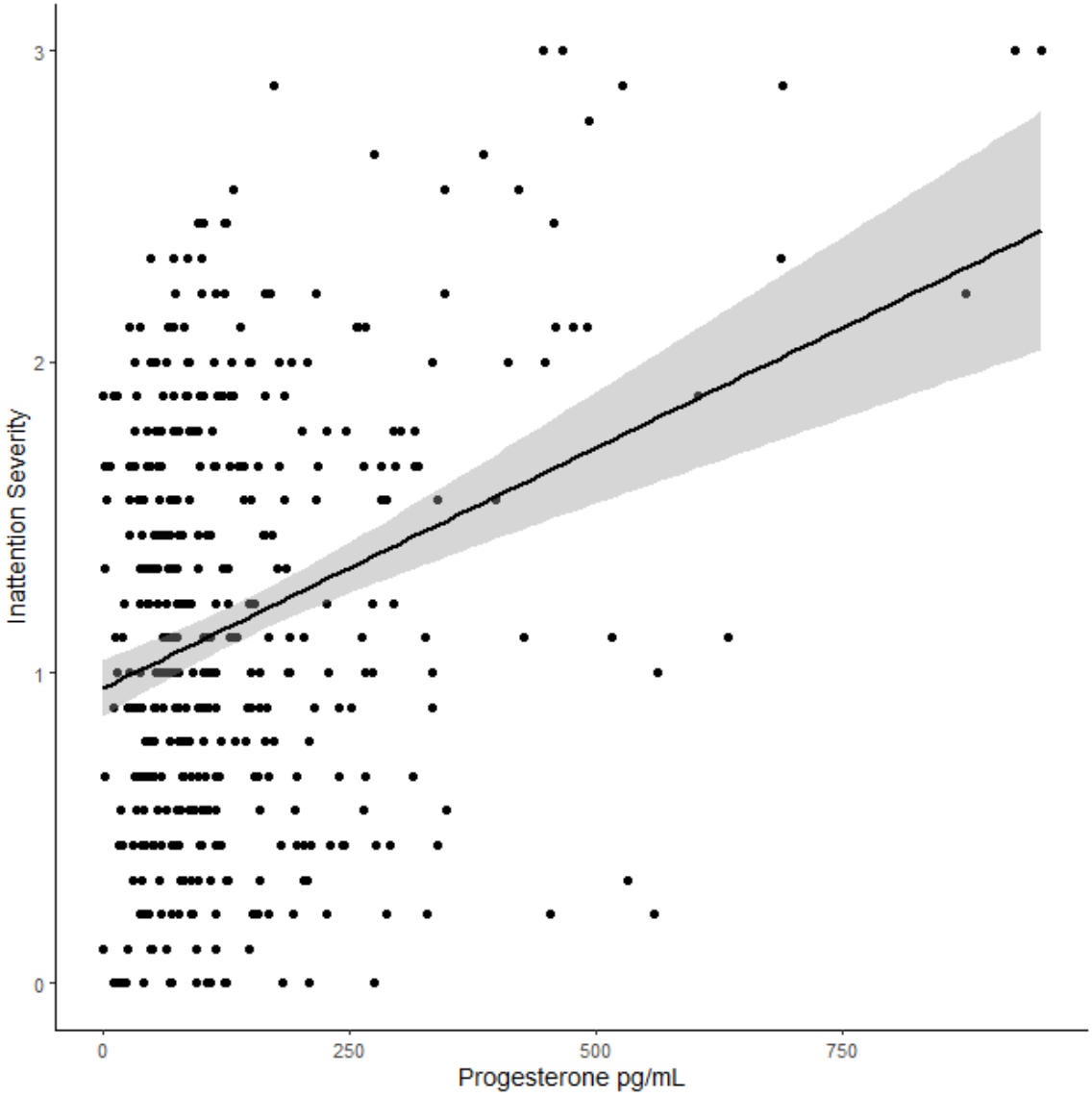


Figure 3.3 Estradiol Predicts Hyperactivity

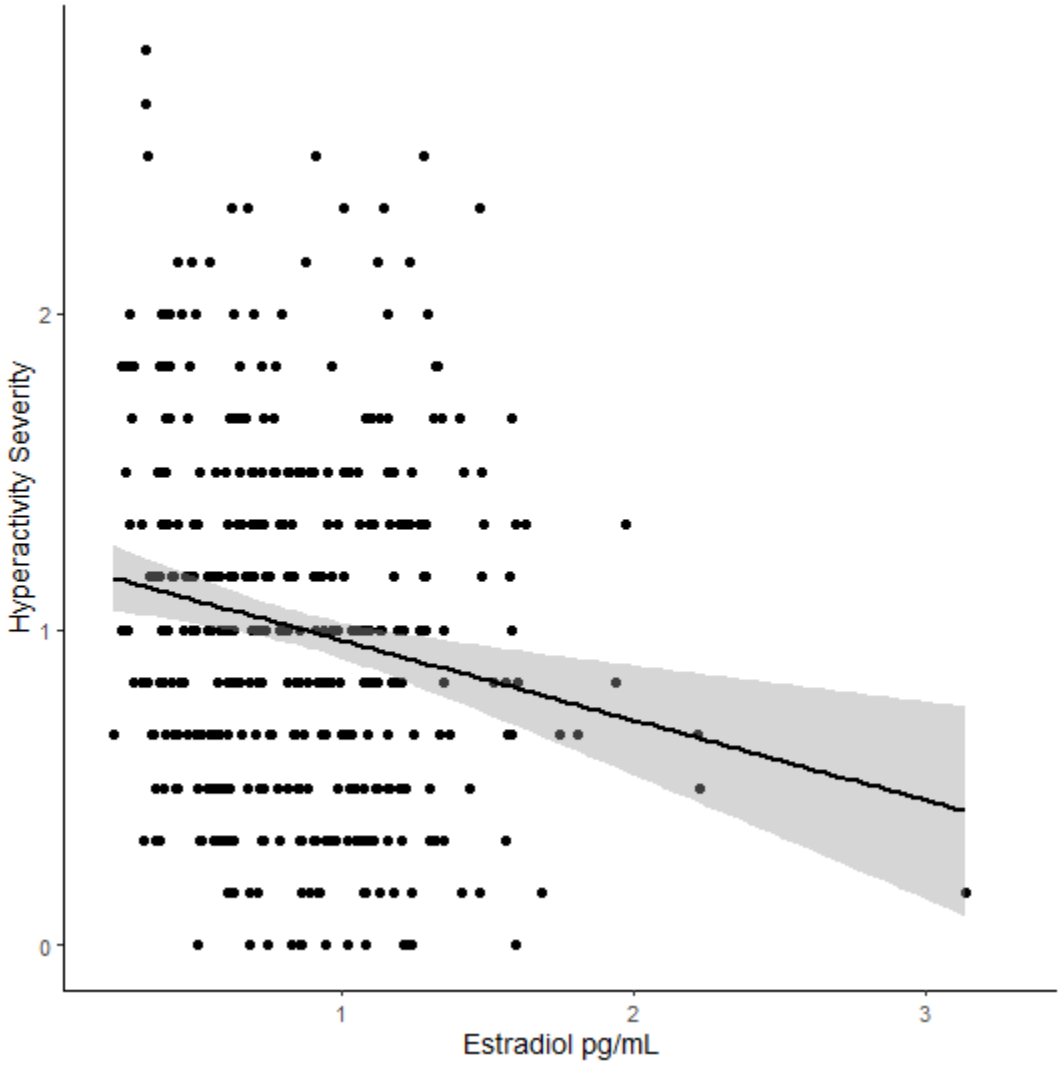


Figure 3.4 Negative Urgency Moderates Hyperactivity and Impulsivity

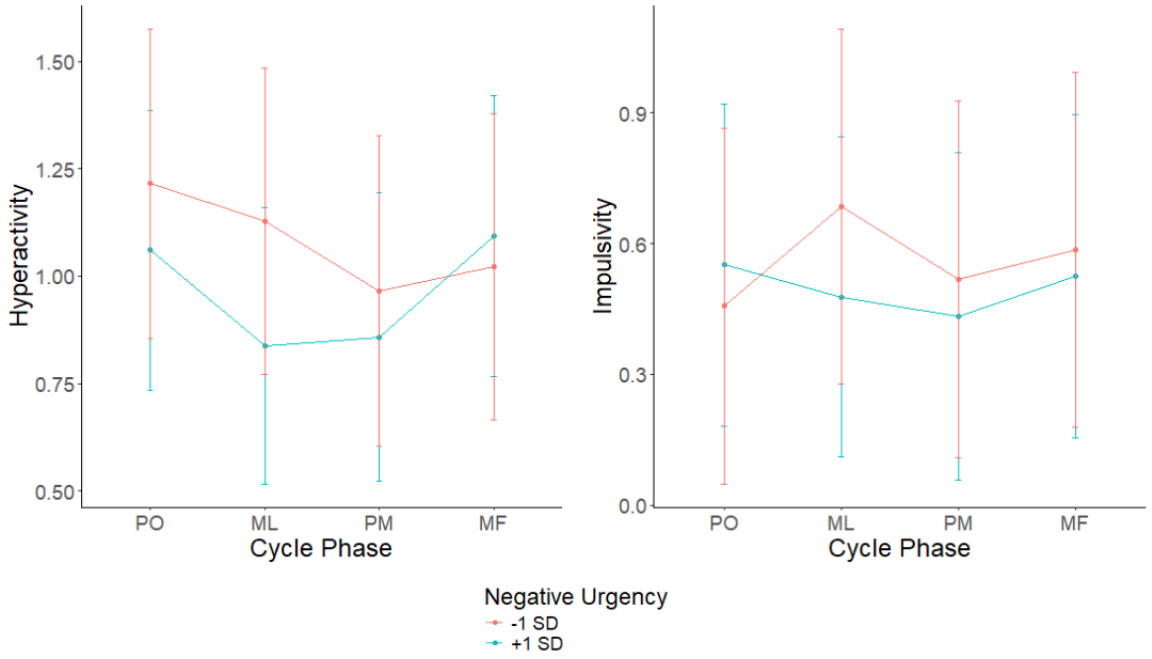


Figure 3.5 Peer Rumination Moderates Impulsivity

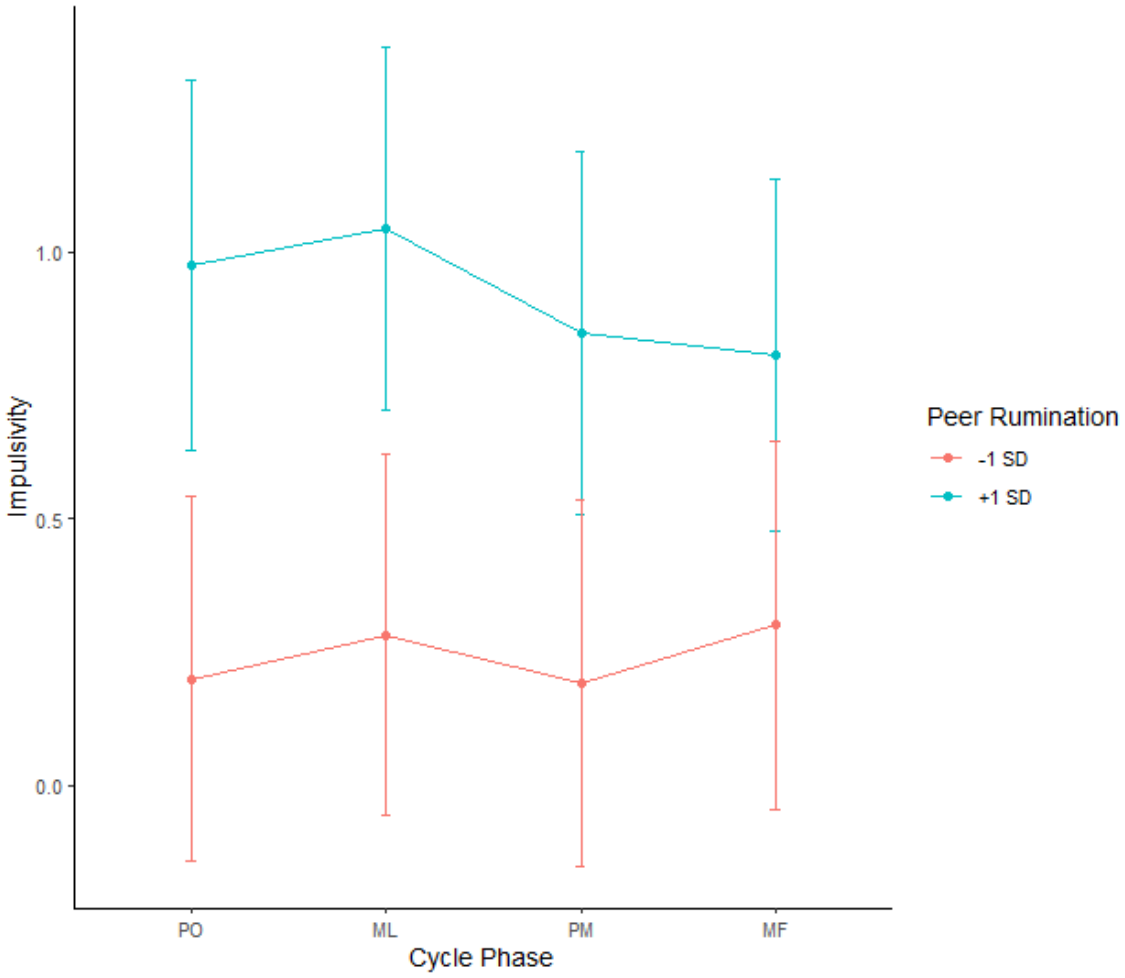
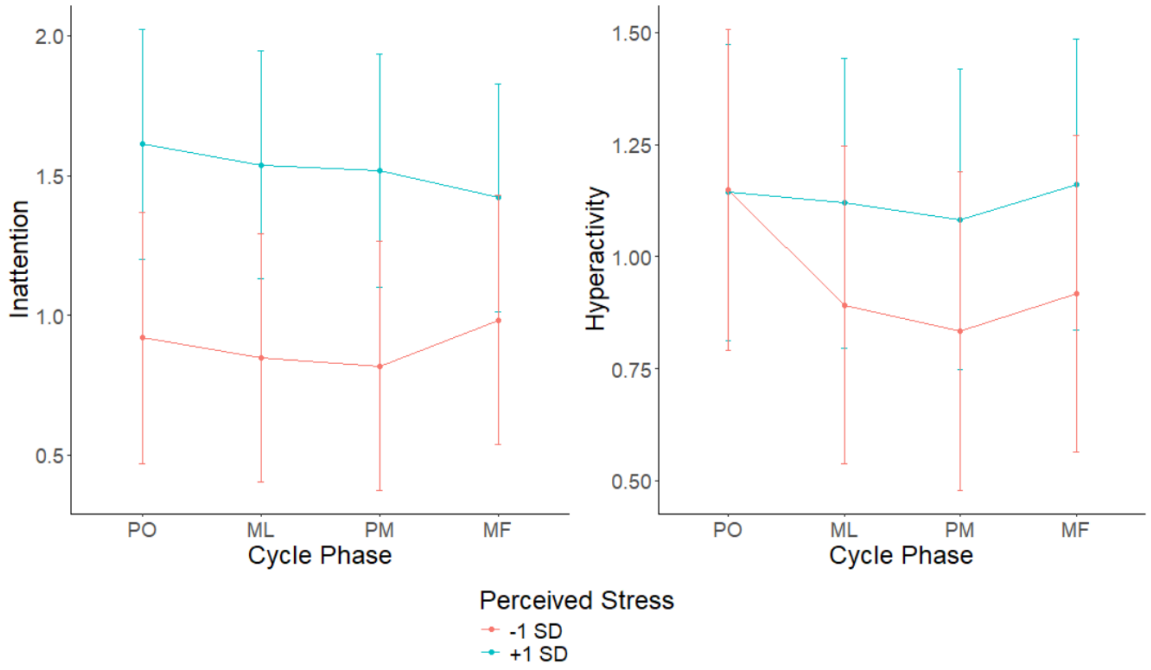


Figure 3.6 Perceived Stress Moderates Inattention and Hyperactivity



CHAPTER 4. DISCUSSION

The primary aim of this study was to gain a better understanding of changes in ADHD symptoms across the menstrual cycle in adolescents with attention to hormones and moderators. While inattention did not show menstrual cycle phase effects, hyperactivity was higher in the periovulatory phase and impulsivity was higher in the midluteal phase. Further, high P4 was associated with worse inattention, low E2 was associated with high hyperactivity, and there were no effects of hormones on impulsivity. Trait and environmental factors significantly moderated menstrual cycle phase results, and although higher levels of each moderator generally predicted more ADHD symptoms, higher levels of moderators did not necessarily account for more symptoms change across the menstrual cycle.

While inattention did not significantly differ among phases, hyperactivity was more severe in the periovulatory phase than the midluteal and perimenstrual phases, and impulsivity was more severe in the midluteal phase than in the periovulatory phase. Higher levels of P4 were associated with greater inattention. Hyperactivity was also higher in the context of lower E2. Lastly, results did not indicate significant hormone associations with impulsivity. These findings are somewhat in alignment with our prior work that theorized declines in estrogen may interact with changes in positive and negative affect to increase hyperactive and impulsive symptoms post-ovulation and inattention symptoms perimenstrually (Eng et al., 2024), and the pattern of results is consistent with the previous literature that found lower levels of E2 predicted higher levels of hyperactivity (Roberts et al., 2018). Midluteal phase effects may be due to the higher levels of arousal experienced during the midluteal phase (Peters et al., under

review) or may be explained by the fact that individuals with less regular menstrual cycles, like adolescents, experience exacerbations in affect in different menstrual cycle phases than their more regularly cycling counterparts (Klusmann et al., 2023).

Trait impulsivity was important for both hyperactivity and impulsivity, but in different ways. Individuals with higher levels of trait impulsivity reported greater changes in hyperactivity across the menstrual cycle than those with lower levels of trait impulsivity. However, for impulsivity, it was individuals with lower levels of trait impulsivity that reported greater changes in impulsivity across the menstrual cycle. It is possible that for individuals high in trait impulsivity, there is a ceiling effect such that it is difficult to detect menstrual cycle changes in impulsivity at levels so high there is nowhere to go. Hyperactivity may not demonstrate this same ceiling effect as hyperactivity often declines with age and is therefore, not as high as impulsivity (Eng et al., 2023). Associations between negative urgency and ADHD symptoms are in line with evidence that trait impulsivity moderates menstrual cycle phase effects (Roberts et al., 2018).

The present study indicated that perceived stress moderates the relationship between menstrual cycle phase and ADHD symptoms. Individuals with high perceived stress reported more severe inattention across almost all phases than those with low perceived stress; however, follow-up analyses did not reveal statistically significant differences in inattention between phases at low or high perceived stress. In contrast, the effect of perceived stress was clearer for hyperactivity. Individuals with high perceived stress reported more severe hyperactivity across almost all phases; however, it was the individuals with low perceived stress that reported the most differences in hyperactivity

between cycle phases. Individuals with low perceived stress reported hyperactivity to be most severe during the periovulatory phase (at a similar level as those with high perceived stress), compared to all other phases (which were lower than those with high perceived stress). In other words, low perceived stress interacted with menstrual cycle phase effects to raise hyperactivity during the periovulatory phase to be on par with those with high perceived stress. It is possible that those with low perceived stress may be more sensitive to the effect of estradiol, while those with more perceived stress experience more consistently high levels of hyperactivity. These results are consistent with past work that found ADHD symptoms to be positively associated with perceived stress (Combs et al., 2015), and for ADHD symptoms to be highest as estradiol decreases (Roberts et al., 2018).

There was a direct relationship of peer rumination on both inattention and hyperactive symptom severity, such that individuals with higher levels of peer rumination reported greater symptoms than those with lower levels. However, peer rumination only appeared to moderate the cycle phase effects for impulsivity, such that those with higher levels of peer rumination reported greater changes in impulsivity across the menstrual cycle that those with lower levels of peer rumination, with the most severe impulsivity in the midluteal phase. This suggests a pattern of peer rumination increasing risk for all ADHD symptoms and that peer rumination may also interact with ovarian hormones to increase risk for impulsivity in the midluteal phase. These results represent the first direct demonstration of the moderation of ADHD symptoms by peer rumination, although prior research had linked peer rumination with premenstrual disorders (Craner et al., 2014; Dawson et al., 2018).

There was no statistical support for the idea that Tanner stage would moderate menstrual cycle phase effects on ADHD symptoms, as hypothesized, but this may be due to a lack of power and having almost twice as many participants in Tanner stage 5 than Tanner stage 4. Pubertal development is highly correlated with age but in order to disentangle the effects of puberty with age, both must be included within the model. Failure to do so would render analyses unable to determine if changes in ADHD symptoms were due to Tanner stage or maturation with age. Prior research from Eng and colleagues (2023) found both age and pubertal development influenced ADHD symptoms, although differently for males and females. For example, hyperactivity declined in both males and females as they aged, yet for females only, hyperactivity also declined as they progressed in pubertal stage. Meanwhile, impulsivity decreased in males, but not females, as they aged and impairment showed larger increases in females than males (Eng et al., 2023). The present study may have lacked sufficient individuals in Tanner stages 4 and under to be powered to detect such effects.

Overall, these results suggest that ADHD symptoms are affected by menstrual cycle changes, and by the E2 and P4 levels and changes that underlie them. This suggests that contrary to popular conception, ADHD may not be best conceptualized as a trait but rather these behaviors exhibit state-like changes across the menstrual cycle with some differences based on domain. While inattention did not exhibit menstrual cycle phase differences, more severe inattention was associated with higher P4 and higher peer rumination. Additionally, menstrual cycle phase effects on inattention were moderated by perceived stress. Hyperactivity was highest during the periovulatory period and associated with lower E2, indicating that hyperactivity is most severe as estradiol is

falling after ovulation. Menstrual cycle phase effects on hyperactivity were moderated by trait impulsivity and perceived stress. Furthermore, impulsivity was most severe during the midluteal phase and menstrual cycle phase effects on impulsivity were moderated by trait impulsivity and peer rumination.

While many of these results were consistent with new theory suggesting high hyperactivity and impulsivity midcycle and increased inattention at the end of the cycle (Peters et al., Under Review), the present study provides a novel examination of adolescent ADHD. Although periovulatory and low E2 effects were consistent with adult work (Roberts et al., 2018), later cycle effects may be due to lower levels of regulatory control and adolescents' longer, less consistent cycles. In addition, unlike our prior work in young adulthood (Roberts et al., 2018), effects during adolescence were substantially moderated by the environment, particularly peer rumination and perceived stress, which is in line with evolutionary theory work suggesting the importance of ovarian hormone moderators of behavior during adolescence (Schulz & Sisk, 2016).

4.1 Implications and Applications of Findings

This work is vitally important as the knowledge of hormonal influences on ADHD symptoms in females is limited, particularly in adolescence. These results suggest that menstrual cycle phases may be important to consider during the assessment of ADHD, as the risk for different ADHD symptoms change across the cycle. Assessments should take note where in the menstrual cycle phase the individual is and consider if the timing of the assessment fell when a particular symptom may be at its lowest. This would be especially important for any symptoms that appeared to be just under the clinical threshold. For example, hyperactivity may be lowest during the midluteal and

perimenstrual phases. If the assessment falls at the end of this time period and the clients report that hyperactivity has been subclinical the last two weeks, it is possible that the assessment would not capture the clinical levels of hyperactivity that had occurred during the periovulatory phase. Further, results suggest that during adolescence, social factors should also be a target of the assessment process due to their significant moderating effects. Identifying the factors that contribute to more ADHD symptoms during the assessment helps identify individualized treatment plans.

More speculatively, the work likely has implications for treatment. Results suggest that treatment might be usefully targeted to particular times in the menstrual cycle, and it may be important for interventions to focus on social factors by providing psychoeducation about the important aspects, stress management skills, cognitive therapy strategies to decrease rumination, and dialectical behavior therapy to decrease emotion-based impulsivity. Some potential future avenues of work might be to consider hormonal interventions like hormone stabilization via hormonal contraceptives. Hormonal contraceptives that provide continuous hormones (in contrast to those that stop hormone delivery for a week to induce a period), may mitigate the menstrual cycle phase effects by drastically reducing hormone fluctuations. However, some individuals may be more sensitive to the hormones delivered via hormonal contraceptives and may have adverse reactions. Furthermore, newly emerging research suggests that individuals with ADHD that use an oral hormonal contraceptive experience a sixfold increase in risk of developing depression than their non-ADHD counterparts (Lundin et al., 2023).

Alternatively, it might be useful to tailor stimulant medication dosage to cycle phase. Prior work has established that females may be more sensitive to the effects of

stimulants during certain cycle phases and that amphetamines interact with female sex hormones (Kok et al., 2020; Terner & de Wit, 2006) so further study would be needed to evaluate this line of treatment. Future research should also explore if stimulant medication use decreases the fluctuations in ADHD symptoms across the menstrual cycle. Some individuals, especially those who are more sensitive to stimulant medication, may also find it helpful to increase the dosage of their stimulant medication at the points in their cycle where their ADHD symptoms are greatest and reduce the dosage when their ADHD symptoms are mildest. This would require careful examination of their typical menstrual cycle and symptoms in order to appropriately titrate stimulant dosage to phase.

4.2 Limitations and Future Directions

Certain limitations of this study could be addressed in future research. For example, future studies could benefit from larger sample sizes, in particular, more participants in earlier Tanner stages. Including individuals in Tanner stages 1 to 3 would provide a methodological challenge as they would not have begun to menstruate; however, these individuals are still experiencing hormonal changes and different social environments. In addition, future studies may want to include either ovulation testing or examine luteinizing hormone. The inclusion of this data would allow for more detailed exploration of menstrual cycle regularity and more precisely measure menstrual cycle phase.

In addition, objective measures of ADHD symptoms across the menstrual cycle may be useful to provide further evidence of within-person changes without relying on self-report of symptoms. These objective measures might consist of completing tests of executive or cognitive functioning. Further, the complex nature and limited sample size

of the present study required extensive exclusionary criteria in order to avoid potential confounds. To this point, it would vastly improve the generalizability of the research to study ADHD across the menstrual cycle in individuals with commonly co-occurring disorders such as autism. Finally, this study recruited from the local area and was predominantly White which limits generalizability. This may have been due to the recruitment methods used. It is extremely important that future studies include more diverse samples as these effects may be different in different populations.

4.3 Conclusion

Results demonstrating changes in ADHD symptoms across the menstrual cycle and several moderators of such effects highlight key factors in the symptom exacerbation and increased impairment seen during adolescence in females. Results demonstrated that while inattention did not show menstrual cycle phase effects, hyperactivity was higher in the periovulatory phase and impulsivity was higher in the midluteal phase. Additionally, high P4 was associated with worse inattention, low E2 was associated with high hyperactivity, and there were no effects of hormones on impulsivity. Adolescents, like adults, experience fluctuations in ADHD symptoms across the menstrual cycle; however, trait and environmental factors interact with these hormonal changes to formulate a uniquely adolescent profile of risk. These findings suggest that menstrual cycle timing, trait impulsivity, peer relationships, and perceived stress are important factors which may have assessment and treatment implications.

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VITA

ASHLEY G. ENG, M.A.

EDUCATIONAL INSTITUTIONS ATTENDED AND DEGREES AWARDED

Anticipated 2025	**Ph.D. in Clinical Psychology** University of Kentucky; Lexington, KY Mentor: Michelle M. Martel, Ph.D. Dissertation: *Hormonal effects on ADHD symptoms in adolescents across the menstrual cycle*
2024-2025	**Clinical Psychology Internship Placement** Cincinnati Children's Hospital Medical Center; Cincinnati, OH Clinical Intern: Child Clinical Track
2019	**M.A. in Psychological Science: Focus in Children, Families, and Cultures** The Catholic University of America; Washington, DC Mentor: Brendan A. Rich, Ph.D. Master's Thesis: *Youth behavior problems: Correlations with family functioning and effect on group therapy outcomes among two distinct populations*
2017	**B.A. in Psychology and Minor in Biology** Stonehill College; Easton, MA

PROFESSIONAL POSITIONS HELD

2019-2024	**Doctoral Research Assistant** RISK Laboratory, University of Kentucky; Lexington, KY *PI: Dr. Michelle M. Martel*
2019-2024	**Clinical Therapist/Assessment Trainee** Jesse G. Harris Psychological Services Center; Lexington, KY
2023	**Program Leader** The Resilience Builder Program, The Lexington School; Lexington, KY
2022-2023	**Clinician**

	Center on Trauma and Children, Child and Adolescent Trauma Treatment and Training Institute; Lexington, KY
2019-2023	**Graduate Teaching Assistant & Guest Lecturer** Department of Psychology, University of Kentucky; Lexington, KY
2021-2022	**Individual Therapist** MindPsi Psychological Services; Lexington, KY
2021-2022	**Graduate Associate Clinician** The Amend Group; Lexington, KY
2020-2021	**Instructor of Record: PSY 534 Child Psychopathology** University of Kentucky; Lexington, KY
2020-2021	**Practicum Student Therapist** University of Kentucky Counseling Center; Lexington, KY
2017-2019	**Intake Coordinator & Graduate Therapist** Alvord, Baker, & Associates, LLC; Chevy Chase, MD
2017-2019	**Graduate Research Assistant** Child Cognition, Affect, and Behavior Laboratory; Washington, DC *PI: Dr. Brendan A. Rich*
2017	**Milieu Therapist** Adolescent Partial Hospital Program, Bradley Hospital; Providence, RI
2016-2017	**Undergraduate Research Assistant** Brown University and Rhode Island Hospital; Providence, RI *PI: Dr. Lindsay Orchowski*
2016	**Practicum Student** Arnone School; Brockton, MA
2014-2015	**Undergraduate Research Assistant** Stonehill College; Easton, MA *PI: Dr. Bonnel Klentz*

SCHOLASTIC AND PROFESSIONAL HONORS

University of Kentucky

2023-2024 Elizabeth Munsterberg Koppitz Child Psychology Graduate Student Fellowship, American Psychological Foundation
2022-2024 National Institute on Alcohol Abuse and Alcoholism Training Fellowship (T32 AA027488)
2023 Ashley and Ruth Mixson Psychology Award

Stonehill College
2018 Psi Chi International Honor Society for Psychology
2015-2017 Dean's List
2016 Research Excellence Award, Stonehill Psychology Department

PROFESSIONAL PUBLICATIONS

Peters, J. R., Schmalenberger, K., **Eng, A. G.**, Stumper, A., Martel, M. M., & Eisenlohr-Moul, T. A. (in prep). Dimensional affective sensitivity to hormones across the menstrual cycle (DASH-MC): A transdiagnostic framework for ovarian steroid influences on psychopathology.

Eng, A. G., Miller, S. A., Monticello, K., Sizemore, Y. J., Nirjar, U., & Martel, M. M. (Under Review). ADHD and pregnancy: A call for action.

Eng, A. G., Barone, J., Monticello, K., Petersen, M. K., Sizemore, Y., Nirjar, U., Nagpal, A., Schmalenberger, K. M., Eisenlohr-Moul, T. A., & Martel, M. M. (Under Review). Menstrual cycle-related affective changes in attention-deficit/hyperactivity disorder.

Martel, M.M., Goh, P.K., **Eng, A.G.,** Monticello, N., Litteral, C.A., & Eisenlohr-Moul, T.A. (Under Review). Impulsivity moderates end but not mid cycle effects on affect, cognition, and ADHD symptoms.

Goh, P. K., **Eng, A. G.,** Bansal, P. S., Kim, Y. T., Miller, S. A., Martel, M. M., & Barkley, R. A. (In Press). Application and expansion of an algorithm predicting ADHD and impairment to a nationally representative sample.

Eng, A. G., Nirjar, U., Elkins, A. R., Sizemore, Y., Monticello, K., Petersen, M., Miller, S. A., Barone, J., Eisenlohr-Moul, T. A., & Martel, M. M. (2024). Attention-deficit/hyperactivity disorder and the menstrual cycle: Theory and evidence. *Hormones and Behavior*. https://doi.org/10.1016/j.yhbeh.2023.105466

Eng, A. G., Phan, J. M., Shirtcliff, E. A., Eisenlohr-Moul, T. A., Goh, P. K., & Martel, M. M. (2023). Aging and pubertal development differentially predict symptoms of ADHD, depression, and impairment in children and adolescents: An eight-year longitudinal study. *Research on Child and Adolescent Psychopathology*. https://doi.org/10.1007/s10802-023-01030-7

Goh, P. K., Elkins, A. R., Bansal, P. S., **Eng, A. G.**, & Martel, M. M. (2023). Data-driven methods for predicting ADHD diagnosis and related impairment: The potential of a machine learning approach. *Research on Child and Adolescent Psychopathology*. https://doi.org/10.1007/s10802-023-01022-7

Eng, A. G., Bansal, P. S., Goh, P. K., Nirjar, U., Petersen, M. K., & Martel, M. M. (2023). Evidence-based assessment for attention-deficit/hyperactivity disorder. *Assessment*. https://doi.org/10.1177/10731911221149957

Martel, M. M., Elkins, A. R., **Eng, A. G.**, Goh, P. K., Bansal, P. S., Thomas-Smith, T. E., Thaxton, M. H., Ryabinin, P., Mooney, M. A., Gustafsson, H. C., Karalunas, S. L., & Nigg, J. T. (2022). Longitudinal temperament pathways to ADHD between childhood and adolescence. *Research on Child and Adolescent Psychopathology*, 1-12.

Bansal, P. S., Goh, P. K., **Eng, A. G.**, Elkins, A. R., Thaxton, M. H., & Martel, M. M. (2021). Utility of the limited prosocial emotions specifier in preschoolers with conduct problems. *Assessment*. *Advanced Online Publication*. https://doi.org/10.1177/10731911211051070

Bansal, P. S., Goh, P. K., **Eng, A. G.**, Elkins, A. R., Thaxton, M., Smith, T. E., & Martel, M. M. (2021). Identifying the inter-domain relations among ODD, CD, and CU traits in preschool children using network analysis. *Research on Child and Adolescent Psychopathology*.

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Goh, P. K., Martel, M. M., Jones, P. J., Bansal, P. S., **Eng, A. G.**, Elkins, A. R., Thaxton, M. H., & Barkley, R. A. (2021). Clarifying relations between ADHD and functional impairment in adulthood: Utilization of network and machine learning approaches. *Assessment. Advanced online publication. https://doi.org/10.1177/10731911211050921*

Goh, P. K., Smith T. E., Lee, C. A., Bansal, P. S., **Eng, A. G.**, & Martel, M. M. (2021). Etiological networks of attention-deficit/hyperactivity disorder during childhood and adolescence. *Journal of Clinical Child and Adolescent Psychology*. DOI: 10.1080/15374416.2021.1946820

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