Attention-Deficit/Hyperactivity Disorder and the Menstrual Cycle: Theory and Evidence

Ashley G. Eng[1], Urveesha Nirjar[1], Anjeli R. Elkins[1], Yancey J. Sizemore[1], Krystina N. Monticello[1], Madeline K. Petersen[1], Sarah A. Miller[1], Jordan Barone[2], Tory A. Eisenlohr-Moul[2], & Michelle M. Martel[1]

[1]University of Kentucky, Department of Psychology, 106-B Kastle Hall, Lexington KY 40506-0044

[2]University of Illinois Chicago at Chicago College of Medicine, Department of Psychiatry, 912 S. Wood St, Chicago IL 60612

Author Note

Correspondence concerning this article should be addressed to Ashley G. Eng, Department of Psychology, University of Kentucky, 171 Funkhouser Drive, Lexington, KY, 40506-0044. E-mail: Ashley.Eng@uky.edu. ORCID: 0000-0002-2396-7594

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that exhibits striking sex differences in symptoms, prevalence, and associated problems across development. Etiological factors and mechanisms underlying these sex differences remain one of the most understudied aspects of this disorder. The current paper seeks to provide a novel theoretical framework for understanding this phenomenon by reviewing evidence that females with ADHD may experience a "double whammy" of organizational and activational pubertal hormonal effects. We propose a novel theory of activational effects of cyclical circulating ovarian hormones on ADHD with increasing risk at times of rapid declines in estrogen. These declines may decrease executive function and trait control at two points of the cycle characterized by biphasic affective risk: (1) increases in approach/risk-taking behaviors at mid-cycle (periovulatory) and (2) increases in avoidance/negative affect perimenstrually. Low estrogen and control may then interact with increases in positive and negative affect, respectively, to increase hyperactivity-impulsivity symptoms post-ovulation and inattention symptoms perimenstrually. These interactions may be exacerbated by organizational pubertal effects on relatively overdeveloped limbic circuitry and adolescent-specific social pressures magnified in females with ADHD.

Keywords: ADHD, menstrual cycle, ovarian hormones, activational effects, affective risk

Attention-Deficit/Hyperactivity Disorder and the Menstrual Cycle: Theory and Evidence

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that exhibits striking developmental trajectories, 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 often persists into adolescence and adulthood (American Psychiatric Association, 2022; Faraone & Biederman, 2005). ADHD symptoms and impairment increase in girls starting during adolescence, which is also when comorbidity and suicide risk increase (Biederman et al., 2008; Chronis-Tuscano et al., 2010; Eng et al., 2023).

Gender and Sex Terminology

It is important to note that sex assigned at birth and gender are not necessarily synonymous for individuals. Within-person changes may be particularly relevant to individuals who were assigned female at birth (AFAB), as psychopathology does not just vary within-individuals between different stages of life but also within a single month. AFAB individuals experience cyclical changes in ovarian steroid hormones across the menstrual cycle (*See Figure 1*), which can represent a significant biological source of symptom variability. Historically, researchers have not always distinguished between biological sex and gender identity, and have reported all participants as women, girls, or female, leaving it unclear how individual participants self-identify (Heidari et al., 2016). In this paper, we attempt to be more conscientious in our use of the terms ‘girls’ and ‘women’ when discussing public health implications, especially in younger groups, and use the word ‘female’ when focusing on biological influences. However, we want to be clear that often we are generally focused on AFAB because our main focus is on

endogenous hormones and menstrual cycles (vs. how individuals identify their gender). Therefore, we may be both more and less inclusive than these limited terms can denote.

Gender & Sex Differences in ADHD

There is a significant gender-biased prevalence rate in ADHD of a ratio of at least 3:1 favoring boys in childhood (American Psychiatric Association, 2022; Skogli et al., 2013). However, these sex/gender differences in prevalence rates decrease during adolescence, and by adulthood, men and women experience ADHD at similar rates (Das et al., 2012).

Importantly, girls and women with ADHD become more impaired and exhibit higher rates of comorbidity than boys and men, beginning during adolescence and persisting into adulthood. Girls with ADHD are at increased risk of experiencing important health outcomes like increased suicide attempts, affective disorders, risky sexual behavior, substance use, and binge-drinking (Chronis-Tuscano et al., 2010; Flory et al., 2006; Molina et al., 2007; Molina & Pelham, 2003). Despite the prevalence of depressive symptoms in youth with ADHD, little work has examined why these symptoms increase as youth with ADHD age (Brunsvold et al., 2008). However, recent work suggests that these effects are exacerbated as youth advance through puberty, particularly in girls, suggesting possible hormonal influences (Eng et al., 2023).

Reproductive Periods as Risky for Girls & Women with ADHD

Unlike in males, in which the prenatal period seems to be the most critical period for development of ADHD risk (Shao et al., 2020; Zhu et al., 2015), females seem to experience multiple critical developmental periods corresponding with reproductive life events, including adolescence/puberty, pregnancy, and menopause (Kinsley et al., 2006; Martel et al., 2009; Rehbein et al., 2021; Schulz et al., 2009). Each of these periods seems characterized by particular profiles of risk and have distinct hormonal patterns.

Adolescence & Puberty

Adolescence is perhaps the most well-studied of these periods, particularly important because it is a time when individuals transition from childhood to adulthood, including both gendered social transitions and a physical sexual maturation process known as puberty. 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). Adolescence is also the period when depression, anxiety, conduct problems, and substance use increase (Lee & Hinshaw, 2006; Whitesell et al., 2013). Puberty also seems to exacerbate these effects on depression and anxiety in females (Costello et al., 2011; Eng et al., 2023; McGuire et al., 2019; Reardon et al., 2009). Although both males and females with ADHD experience increases in impairment as they age, females consistently show higher levels of impairment than males (Eng et al., 2023). Further, females with ADHD are also twice as likely to have an unplanned pregnancy and more likely to become pregnant earlier than their neurotypical peers (Hua et al., 2021; Meinzer et al., 2020).

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 changes (and menstruation) that continue into adulthood. Estradiol (E2) and progesterone begin to fluctuate during late puberty as youth experience their first ovulation, leading to their first menstruation. Yet, only one prior study has directly examined pubertal effects on ADHD and associated problems. That study indicated that pubertal development is associated with increased impairment and depressive symptoms and decreased hyperactive symptoms in females (Eng et al., 2023). However, studies that rely on pubertal stage do not capture the day to day changes in

hormones related to the menstrual cycle, and little is known about when hormonal effects on ADHD symptoms begin.

Pregnancy

Even less is known about other important reproductive periods in females compared to adolescence and puberty. Although higher absolute progesterone and estrogen levels, such as during estrus and pregnancy, are associated with improved memory and cognition in animal models (Paris & Frye, 2008), the literature in humans is inconsistent, perhaps due to differential hormone sensitivity. Pregnancy is also a time of elevated risk for affective disorders and both subjective and objective cognitive dysfunction (Carter & Kostaras, 2005; Davies et al., 2018; Marcus, 2009; Uguz et al., 2019). Cognitively, some females report experiences of "pregnancy brain," which refers to pregnancy-related deficits in cognitive functioning, memory, and executive functioning (Brown & Schaffir, 2019; Davies et al., 2018; Kumari, 2019). Neuroimaging research also shows reductions in gray matter that endure for years after pregnancy (Hoekzema et al., 2017). However, more research is needed to elucidate potential cognitive and emotional changes in patients with ADHD during pregnancy.

Menopause

The last reproductive life event females experience is the menopause transition. During this transition, there is evidence for elevated incidence of affective disorders (Freeman et al., 2006). Some females may experience both subjective symptoms and declines in cognitive performance similar to ADHD, such as difficulties in learning, verbal memory, attention, and forgetfulness during menopause which are linked to declines in estrogen as well as changes in brain structure and function, sleep, and mood (Greendale et al., 2020; Maki & Jaff, 2022).

Despite significant risks of affective, cognitive, and functional changes evident at reproductive life events characterized by large hormonal shifts, the exact mechanisms of such changes—and individual differences in susceptibility to such changes—remain largely understudied. This lack of understanding of cognitive hormone effects is particularly concerning in the case of ADHD, where patients are already experiencing cognitive difficulties.

Organizational and Activational Effects of Hormones

Most information about hormonal effects on cognition and mood across the lifespan, including the previously reviewed reproductive periods in girls and women, is based on research conducted in individuals without ADHD. Reproductive psychiatric disorders can be viewed as a continuum, where some individuals seem to be more or less sensitive to hormonal changes than others. However, in many cases, people with ADHD seem to be at elevated risk of these hormone-related symptoms. Yet, little work has evaluated the relevance of such effects to ADHD symptoms, or examined how such effects look in females with ADHD.

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.

Menstrual Cycle as a Key Activational Event

The menstrual cycle is a key activational hormonal event in females, beginning toward the end of puberty. Monthly ovulation and menses (i.e., the menstrual cycle) typically begin between the ages of twelve and thirteen, although this age has been trending downward (Martinez, 2020), and is associated with a number of factors including ethnicity, breast development, and body mass index (Biro et al., 2018; Cheng et al., 2022). The psychological effects of estrogen and progesterone on cognition and emotional functioning are complex, with mixed evidence that appears to point to prominent individual differences in neurobiological sensitivity to normal hormonal events (Garcia et al., 2018; Klump et al., 2013; Sandstrom & Williams, 2001; Schiller et al., 2016). Estradiol (E2) is the most common type of estrogen in females during their reproductive years and contributes to a range of functions including learning and memory, fine motor control, pain perception and mood (Boulware & Mermelstein, 2005; Luine, 2014). The effects of progesterone on cognition and mood remain unclear with some studies finding effects and others not finding an effect (Barros et al., 2015; Henderson, 2018; Sofuoglu et al., 2011; Standeven et al., 2020).

Activational Effects of Ovarian Hormones on General Psychopathology Across the Menstrual Cycle

There has been more work on hormonal and menstrual cycle effects on other forms of psychopathology (i.e., not ADHD), with key examples being depression and eating disorders (Endicott, 1993; Klump et al., 2013; Martel et al., 2009). Extensive work on depression suggests a greater risk of depressive symptoms and suicide attempts in the late luteal and menstrual weeks (Baca-Garcia et al., 2010; Jang & Elfenbein, 2019). The hormonal causes of this late luteal or menstrual worsening of depression appear to be heterogeneous; they can be triggered in some

cases by delayed deleterious effects of periovulatory hormone surges (Schmidt et al., 1991, 2017), and in other cases by the immediate deleterious effects of perimenstrual steroid withdrawal (Eisenlohr-Moul et al., 2022). There is also even more limited and conflictual information around increases in drinking and risk-taking mid-cycle with rises in estrogen (Barone et al., 2023; Martel et al., 2017), and rises in anxiety mid to late luteal phase (Golub, 1976; Reynolds et al., 2018).

Based on this extant literature, our group has developed a cutting-edge theory about hormonal effects on psychopathology beginning during puberty with the onset of the menstrual cycle (Peters et al., Under Review). In our innovative Multiple Hormone Sensitivity Theory, there are three proposed cyclical mechanisms that have the potential to trigger or exacerbate transdiagnostic psychiatric symptoms at different phases of the cycle due to neurobiological sensitivity to normal hormone changes. Currently, we postulate that these distinct sensitivities include: 1) luteally bound increases in hypersensitivity resulting in symptoms such as heightened irritability, interpersonal reactivity, higher-arousal negative affect (e.g., anger and anxiety), and sensory sensitivities (e.g., misophonia), driven primarily by fluctuations in P4 metabolites, 2) perimenstrual increases in cognitive functioning, depression, anhedonia, anxiety, or suicidality, driven by E2 withdrawal and/or depletion, and 3) periovulatory increases in reward-seeking behavior, such as maladaptive substance use and proactive aggression, driven by sudden increases in E2. In addition, these sensitivities can interact with each other, with baseline personality and physiology, and with environmental factors to produce specific symptom profiles.

Our Multiple Hormone Sensitivity Theory suggests *estrogen withdrawal sensitivity* leads to perimenstrual decreases in executive cognitive functioning, producing symptoms such as

difficulties with attention and poorer emotion regulation behaviors. More specifically, this theory postulates facilitative effects of E2 on dopaminergic responses throughout the brain, and we propose two specific mechanisms through which perimenstrual E2 withdrawal effects on dopamine (DA) may contribute to the observed symptoms: 1) altered DA functioning in the prefrontal cortex resulting in temporary impairments in executive cognitive functions and downstream impairments in effective regulation of emotion and behavior, and 2) reduced DA functioning in mesolimbic regions, resulting in altered reward responsivity and related increases in anhedonia (Peters et al., Under Review).

In addition, such estrogen withdrawal can interact with the other psychological changes across the menstrual cycle, namely reward sensitivity at the end of the first half of the menstrual cycle and negative affect at the end of the cycle. Thus, rapidly changing and/or declining levels of estrogen may be expressed behaviorally as a function of the underlying approach or avoidance attitudes and also interact with individual differences in traits such as positive and negative affect or impulsivity.

Activational Effects of Ovarian Hormones on ADHD Across the Menstrual Cycle

Our preliminary pilot work suggests that there are likewise substantial activational hormonal effects on ADHD across the menstrual cycle. Specifically, in nonclinical, community-recruited young adult females ages 18 to 25, declines in E2 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 were driven by declines in estrogen but were moderated by levels of progesterone. Specifically, the effect of declines in estrogen in the context of lower than usual progesterone was strongest for individuals who were higher in negative urgency. In the context of lower than usual progesterone, the effect of declines in estrogen was strongest for individuals higher in positive urgency.

Such results are consistent with the idea that rapid changes in estrogen, particularly declines, increase the risk for ADHD symptoms. Our preliminary pilot work and theory suggest that declines in estrogen are correlated with increased ADHD symptoms throughout the cycle, both 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 also been implicated in emotion regulation (Rehbein et al., 2021). Therefore, mid-cycle declines in estrogen may interact with or exacerbate prior increases in approach and reward behaviors, leading differentially to hyperactivity and impulsivity mid-cycle, 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.

Activational Menstrual Cycle Effects During Adolescence as a Particularly Risky Sensitive Period for Girls with ADHD

Adolescents may be particularly vulnerable to these end of cycle and mid-cycle activational effects given adolescence is also a time of organizational effects (Sisk & Zehr, 2005). In particular, the prefrontal cortex is still underdeveloped during adolescence, so the

ability to control emotional impulses is not as strong as it is in adults (Vink et al., 2014). Adolescents with ADHD in particular have highly active limbic systems and demonstrate an abnormally high preference for small, immediate rewards compared to larger delayed rewards (Demurie et al., 2012; Scheres & Solanto, 2021). These increases in the environmental stressors associated with this time period provide more opportunities for emotional dysregulation and engagement in risk-taking behaviors.

The Critical Timing of Activational Effects During Puberty and Adolescence

The timing of puberty appears to play a significant role in the impact of hormonal effects on psychopathology, as the brain may be more sensitive to gonadal hormones during adolescence. Animal models have been utilized to parse the entanglement of aging and pubertal effects via experimental manipulations that would otherwise be unable to be utilized in humans. For example, this process has been modeled in rodents with females experiencing greater neuron loss in the medial prefrontal cortex than males across adolescence and prepubertally ovariectomized females having more neurons and white matter than controls (Koss et al., 2015; Willing & Juraska, 2015). Similarly, female mice that undergo hormonal treatments to induce early puberty show increases in inhibitory neurotransmission in the frontal cortex, indicating organizational effects of ovarian hormones during puberty (Piekarski et al., 2017).

The brain gradually becomes less sensitive to the organizing effects of circulating hormones, therefore, earlier puberty may have greater effects on the brain than on-time or late puberty (Schulz et al., 2009). Puberty may close a sensitive period for enhanced plasticity in the associative cortex (Piekarski et al., 2017). We theorize that early puberty may predispose some individuals to be more impulsive or have more negative affect due to a premature decrease in plasticity and thus the early closure of sensitive periods for cognitive development.

Overall, females may be preferentially vulnerable to the organizational effects of early puberty because it closes off the sensitive period of neurodevelopment in such a way as to predispose them to impulsivity and depression. 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. Further, activational declines in estrogen at the end of the menstrual cycle appear to worsen depression and inattention. This might allow known activational effects of hormones across the menstrual cycle to serve as a double whammy of risk.

Neurobiological Mechanisms of Activational Menstrual Cycle and Organizational Puberty Effects

Increasing evidence supports the existence of important interactions between sex hormones and neural processes related to emotion and cognition. E2 and progesterone are lipophilic and able to cross the blood-brain barrier, which allows these hormones to confer direct effects on a range of brain regions associated with behavior regulation (Bernal & Paolieri, 2022). Resultantly, both structural and functional brain differences have been found across the menstrual cycle. Menstrual cycle-related neuroplastic changes appear primarily in the striatum, thalamus, hippocampus, insula, hypothalamus, amygdala, anterior cingulate cortex, frontal cortex, and parietal cortex (Sacher et al., 2013), areas involved in processing/regulation of emotional information.

Changes to the limbic system have been a particular focus of investigation into hormonal effects on brain structure and function in both human and animal models, as the limbic system is

essential for sexual behavior in rodents and for reproductive function, neuroendocrine homeostasis, memory, and emotional processing in humans (Barth et al., 2014; Catenaccio et al., 2016; Hara et al., 2015; Ter Horst, 2010). In humans, top-down modulation of the limbic system by the orbitofrontal cortex and other prefrontal regions is thought to be influenced by menstrual cycling; symptoms characteristic of menstrual cycle-related syndromes (premenstrual Syndrome; PMS), such as irritability, impulsivity, decreased concentration, anger, and anxiety may represent impairment to the prefrontal/limbic inhibitory circuit and the emotional learning and decision-making functions of these regions (Dubol et al., 2022). Mechanistically, menstrual cycle-related changes to limbic system function are thought to result from hormone-mediated effects on structural neuroplasticity (Catenaccio et al., 2016). Changes to the structural components underlying limbic and other brain networks – that is, network nodes (grey matter) and network connections (white matter) – in response to menstrual cycle hormonal fluctuations are increasingly well-supported (Arélin et al., 2015; Meeker et al., 2020; Syan et al., 2017).

Several neurosteroids such as dehydroepiandrosterone (DHEA) along with its sulfate metabolite dehydroepiandrosterone sulfate (DHEA-S), pregnenolone and allopregnanolone have also been implicated in the etiopathogensis of ADHD (Trent et al., 2013; Wang et al., 2019). These neurosteroids play a critical role from early brain development to adolescence, contributing to shaping behavioral function and modulating psychopathology risk factors (Goodyer et al., 2001). DHEA and pregnenolone have been linked to the pathophysiology of ADHD, with lower levels associated with higher ADHD symptoms and severity, particularly hyperactivity, suggesting a possible neuroprotective effect on the expression of ADHD symptomatology (Işık et al., 2018; Strous et al., 2001; Wang et al., 2011, 2017). Similarly, lower levels of serum allopregnanolone, a major neurosteroid that stimulates dopamine release have

been found to be significantly lower in children with ADHD compared to healthy controls (Rougé-Pont et al., 2002; Şahin et al., 2022). However, it is important to note that research on these neurosteroids and their connection to ADHD has predominantly focused on samples comprising either exclusively males, typically prepubertal boys, or included a low number of females. Consequently, failing to establish significant sex differences associated with these neurosteroids in relation to ADHD. Conversely, preclinical studies in rodents suggest sex differences in DA receptors that contribute to heightened susceptibility of males to develop ADHD. Female mice exhibited minimal changes during development, whereas, male mice exhibited an early increase in D1 and D2 receptors and a rapid decline in adulthood, indicating a potential link between increased D2 receptors and symptom development (Williams et al., 2021).

Menstrual cycle-related changes in DA represent another critical area of study in the comprehension of psychopathology/menstrual cycle interaction, as DA is an essential regulator of cognition-emotion integration and processing. One investigation discovered increased dopaminergic transmission rate in the late follicular phase, which elevated participants' performance on a working memory task. Decreased dopaminergic transmission rate was found in the early follicular phase and was associated with poorer performance on the working memory task (Jacobs & D'Esposito, 2011). Greater fMRI blood-oxygen-level-dependent response in brain regions associated with the dopamine-mediated reward system (i.e., amygdala, orbitofrontal cortex, midbrain, striatum) has been found during the mid-follicular phase, potentially suggesting increased reward system responsivity just before ovulation (Dreher et al., 2007). Differences in dopamine-related mesolimbic incentive processing between the late luteal versus late follicular phase have also been demonstrated. Using a reward incentive delay task,

one investigation found enhanced ventral striatal response during the late luteal phase, potentially underlying premenstrual increases in motivated behaviors (Ossewaarde et al., 2011).

Therefore, limbic and dopaminergic innervation appears to change with activational hormonal fluctuations across the menstrual cycle, likely interacting with the organizational neurostructural and functional changes at puberty to instantiate emotional dysregulation of positive and negative affect. Such organizational emotional proclivities likely interact with activational hormonal declines on cognition in such a way as to increase risk for approach dysregulation behaviors such as hyperactivity around ovulation and negative affect dysregulation and inattention at the end of the cycle.

Current Limitations of Extant Work Due to Lack of Theory

Menstrual cycle studies, with a few notable exceptions (e.g., Klump et al., 2013), have been hampered by a lack of general framework. Yet, theory could be particularly helpful in this area given that there are typically small sample sizes due to the intensive nature of data collection. This issue is exacerbated in samples with greater deficits in executive functioning (i.e., those with ADHD symptoms), given their difficulties engaging in consistent data collection across a month or longer. Using a well defined theory would allow for more specific hypotheses and tests, maximizing smaller samples. A number of studies have relied solely on case studies (e.g., Quinn, 2005), very small sample sizes, and retrospective report. Larger prospective studies with use of well defined and theoretically driven measures are critically needed (Schmalenberger et al., 2021). In addition, statistical methods, such as multilevel models, which allow for powerful use of longitudinal data and disentanglement of within versus between person effects are needed to accurately analyze effects of the menstrual cycle on ADHD.

In addition, theory would be particularly helpful for providing theoretical guidance about what moderators and applied outcomes would best be prioritized. Precise theories would allow for better selection of relevant measures thereby reducing potential impact of lengthy daily questionnaires and tasks on completion rates and respondent fatigue. Such theory has implications for better research for advancing our understanding of women's health risks and providing innovative new directions for assessment and treatment.

Theoretically-Guided Empirical Examination of Trait and Environmental Moderators

Related to this issue is the fact that trait and environmental moderators of hormonal effects are likely and yet, almost entirely unexamined. A few major potential moderators based on our theory come to mind. The first is trait impulsivity. As previously discussed, prior work suggests that more impulsive females are more susceptible to hormonal effects on ADHD symptoms (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). In addition, individual differences in propensity to experience impulsivity due to positive and negative affect may predispose individuals to swing in certain directions at particular points in their cycles. Therefore, high trait impulsivity may make women more vulnerable to hormonal effects on ADHD, including those generated by positive and negative affect, mid-cycle and at end of cycle respectively.

In line with this idea, general environmental stressors that predispose females toward positive and negative affect may be important potential moderators. Those most important to

pubertal and adolescent organizational and activational effects might be psychosocial stress and delinquent peers. Family functioning and attendant stressors influence individual variation in life history strategies, and poorer family functioning, and higher stress levels are associated with increased impulsivity and ADHD (Combs et al., 2015; Cussen et al., 2012). Individuals with a history of physical abuse have also shown greater sensitivity to hormonal effects on mood symptoms (Eisenlohr-Moul et al., 2016). Children with ADHD frequently have social deficits (Greene et al., 2001; Staikova et al., 2013), and such deficits may also create stress with peers and interact with emotion dysregulation, exacerbating frequent comorbid disorders such as depression and anxiety. Association with delinquent peers should also be evaluated due to its association with substance use and behavioral problems arising during adolescence (Monahan et al., 2014).

Treatment and Assessment Implications

This work is vitally important because knowledge of what ADHD looks like and the public health impacts of ADHD in females is limited, particularly in adolescents and young adults, which are understudied developmental periods in their own right in the ADHD field. Moreover, information about how ADHD looks over development, from puberty and beyond with consideration of state differences with hormones across the menstrual cycle would suggest important personalized assessment and intervention strategies. For example, if females present differently than males (e.g., with more inattention vs. hyperactivity), then assessment might need to be more sensitive or use a lower threshold, in females. In addition, pubertal and menstrual cycle phases might be important to consider during assessment of ADHD in females. That is, if risk for ADHD symptoms in females is highest at the midpoint of the cycle or impairment is higher beginning toward the end of puberty, then it might be important to time assessment to

those risky periods. Intervention might likewise need to be timed. For example, intervention on ADHD impairment in females might be best targeted to particular points of puberty (vs. in males when impairment seems to peak much earlier around school entry). Finally, knowledge of trait and environmental moderators might suggest additional treatment targets (e.g., trait impulsivity or association with delinquent peers).

There might also be sex differences in effectiveness of ADHD medications or even the need to tailor medication dosage or type to developmental or cycle phase hormonal profiles. For example, women are more sensitive to the effects of stimulants during the follicular phase when circulating estrogen levels are high and progesterone levels are low (Terner & de Wit, 2006). In addition, it is known that amphetamines interact with female sex hormones (Kok et al., 2020). Finally, if periods of hormone flux are particularly risky in females, this might suggest the treatment utility of hormone stabilization, for example, through use of hormonal contraceptives (Rapkin et al., 2019), GnRH analogs (Wyatt et al., 2004), or selective progesterone receptor modulators (Comasco et al., 2021).

Future Directions

Future studies should examine hormonal effects on ADHD both across reproductive life stages (e.g., over years and decades) and within different reproductive events (i.e., daily or monthly across puberty, pregnancy, menopause, and the menstrual cycle). Ovarian hormones vary greatly between and within these life stages so such effects should be examined separately. In addition, the influence of testosterone in females with ADHD remains vastly understudied and may play an important role in increases in approach behaviors seen mid-cycle. Puberty, its timing, and its neurobiological mechanisms is a particularly risky time in terms of its impact on health outcomes so it merits increased attention in research. Pubertal timing and environmental

influences should be further studied to examine if it may influence sensitivity to activational effects. Further, using the proposed theoretical framework, future research should empirically evaluate the possibility of activational and organizational pubertal effects in females with ADHD with attention to trait and environmental moderators of cyclical hormonal effects on ADHD symptoms, specifically during post-ovulatory and perimenstrual phases.

Another area of future work would be to utilize different hormonal and neuropharmacological interventions to modulate negative hormonal effects. Evaluation of the possibility of differential effects of menstrual cycle phase or reproductive period on psychostimulant efficacy is critical. Prior research suggests the use of selective serotonin reuptake inhibitors (SSRIs) is effective at reducing emotional, cognitive-behavioral, and physical symptoms for individuals with Premenstrual dysphoric disorder (PMDD) when used continuously or intermittently during the luteal phase (Bhatia & Bhatia, 2002; Jermain et al., 1999). Other studies suggest that oral contraceptives may be beneficial for treating PMDD but these results vary across studies (reviewed in (Maharaj & Trevino, 2015). Future studies should explore if hormonal birth control or SSRIs impact post-ovulatory or perimenstrually-impacted ADHD symptoms.

In summary, future work should take care when designing studies to test this theory. Specifically, the authors recommend that researchers use a prospective design, as retrospective reports may be less accurate particularly in a sample of individuals with ADHD. Further, due to the high variability between menstrual cycles, ovulation tests or actual circulating hormone levels should be assessed rather than simply tracking the onset of bleeding. It may also be important for future work to assess for pubertal timing, past and current medications, and perimenstrual exacerbation of symptoms. Lastly, useful information may be gathered from both

other-informants in the participants' lives and cognitive task data, in addition to the standard self-report of ADHD symptoms. Many practical recommendations for studying the menstrual cycle have been previously published (Schmalenberger et al., 2021).

Conclusion

Beginning in puberty, there is increased risk for numerous negative health outcomes, greater comorbidity, and increased impairment for girls with ADHD. ADHD symptoms vary cyclically with the menstrual cycle where changes in, and specifically declines in estrogen predict problems with control which interact with affective predispositions at particular points in the cycle, namely mid-cycle increases in approach behaviors including risk taking and increases in avoidance and negative affect at the end of the cycle. Such post-pubertal activational effects in approach and avoidance in females are likely exacerbated by pubertal organizational effects which result in increased affective dysregulation with rises in gonadal hormones due to prefrontal immaturity relative to the limbic system. Therefore, pubertal activational effects on ADHD symptoms may be experienced as "double whammy" of hormonal effects in females, effects that are mirrored in organizational prenatal and also pregnancy and menopausal periods. A better understanding of hormonal effects on neurobiological mechanisms and downstream behavioral symptoms across the lifespan is critical for advancing women's health through personalized assessment and intervention, taking these factors into consideration and even intervening on them or related phenotypes like affective dysregulation. Future research needs to focus on the hormonal impacts on females with ADHD, not just the impact of stimulant medications on fetuses.

Role of Funding Sources

This research was supported by the National Institute on Alcohol Abuse and Alcoholism training grant T32 AA027488, the National Institute of Mental Health (R01-MH119119; RF1-MH120843; T32MH067631), and by a fellowship from the American Psychological Foundation.

NIAAA, NIH, and APF had no role in the writing of the manuscript or the decision to submit the paper for publication.

Conflict of Interest

All authors declare that they have no conflicts of interest.

References

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (DSM-5-TR). American Psychiatric Association Publishing. https://doi.org/10.1176/appi.books.9780890425787

Arélin, K., Mueller, K., Barth, C., Rekkas, P. V., Kratzsch, J., Burmann, I., Villringer, A., & Sacher, J. (2015). Progesterone mediates brain functional connectivity changes during the menstrual cycle—A pilot resting state MRI study. *Frontiers in Neuroscience*, *9*. https://www.frontiersin.org/articles/10.3389/fnins.2015.00044

Baca-Garcia, E., Diaz-Sastre, C., Ceverino, A., Perez-Rodriguez, M. M., Navarro-Jimenez, R., Lopez-Castroman, J., Saiz-Ruiz, J., Leon, J. D., & Oquendo, M. A. (2010). Suicide attempts among women during low estradiol/low progesterone states. *Journal of Psychiatric Research*, *44*(4), 209–214. https://doi.org/10.1016/j.jpsychires.2009.08.004

Barone, J. C., Ross, J. M., Nagpal, A., Guzman, G., Berenz, E., Pang, R. D., & Eisenlohr-Moul, T. A. (2023). Alcohol use and motives for drinking across the menstrual cycle in a psychiatric outpatient sample. *Alcohol: Clinical and Experimental Research*, *47*(1), 127–142. https://doi.org/10.1111/acer.14971

Barros, L. A., Tufik, S., & Andersen, M. L. (2015). The role of progesterone in memory: An overview of three decades. *Neuroscience & Biobehavioral Reviews*, *49*, 193–204. https://doi.org/10.1016/j.neubiorev.2014.11.015

Barth, A. M. I., Ferando, I., & Mody, I. (2014). Ovarian cycle-linked plasticity of δ-GABAA receptor subunits in hippocampal interneurons affects γ oscillations in vivo. *Frontiers in Cellular Neuroscience*, *8*. https://www.frontiersin.org/articles/10.3389/fncel.2014.00222

Belsky, J., Schlomer, G. L., & Ellis, B. J. (2012). Beyond cumulative risk: Distinguishing

harshness and unpredictability as determinants of parenting and early life history strategy. *Developmental Psychology*, *48*(3), 662–673. https://doi.org/10.1037/a0024454

Bernal, A., & Paolieri, D. (2022). The influence of estradiol and progesterone on neurocognition during three phases of the menstrual cycle: Modulating factors. *Behavioural Brain Research*, *417*, 113593. https://doi.org/10.1016/j.bbr.2021.113593

Bhatia, S. C., & Bhatia, S. K. (2002). Diagnosis and treatment of premenstrual dysphoric disorder. *American Family Physician*, *66*(7), 1239–1249.

Biederman, J., Ball, S. W., Monuteaux, M. C., Mick, E., Spencer, T. J., McCREARY, M., Cote, M., & Faraone, S. V. (2008). New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(4), 426–434. https://doi.org/10.1097/CHI.0b013e31816429d3

Biro, F. M., Pajak, A., Wolff, M. S., Pinney, S. M., Windham, G. C., Galvez, M. P., Greenspan, L. C., Kushi, L. H., & Teitelbaum, S. L. (2018). Age of menarche in a longitudinal US cohort. *Journal of Pediatric and Adolescent Gynecology*, *31*(4), 339–345. https://doi.org/10.1016/j.jpag.2018.05.002

Boulware, M. I., & Mermelstein, P. G. (2005). The influence of estradiol on nervous system function. *Drug News & Perspectives*, *18*(10), 631–637. https://doi.org/10.1358/dnp.2005.18.10.959578

Brown, E., & Schaffir, J. (2019). “Pregnancy brain”: A review of cognitive changes in pregnancy and postpartum. *Obstetrical & Gynecological Survey*, *74*(3), 178. https://doi.org/10.1097/OGX.0000000000000655

Brumbach, B. H., Figueredo, A. J., & Ellis, B. J. (2009). Effects of harsh and unpredictable

environments in adolescence on development of life history strategies. *Human Nature*, *20*(1), 25–51. https://doi.org/10.1007/s12110-009-9059-3

Brunsvold, G. L., Oepen, G., Federman, E. J., & Akins, R. (2008). Comorbid depression and ADHD in children and adolescents: Consensus and controversy. *Psychiatric Times*, *25*(10), 13–17.

Carter, D., & Kostaras, X. (2005). Psychiatric disorders in pregnancy. *British Columbia Medical Journal*, *47*(2), 96–99.

Catenaccio, E., Mu, W., & Lipton, M. L. (2016). Estrogen- and progesterone-mediated structural neuroplasticity in women: Evidence from neuroimaging. *Brain Structure and Function*, *221*(8), 3845–3867. https://doi.org/10.1007/s00429-016-1197-x

Cheng, T. S., Ong, K. K., & Biro, F. M. (2022). Trends toward earlier puberty timing in girls and its likely mechanisms. *Journal of Pediatric and Adolescent Gynecology*, *35*(5), 527–531. https://doi.org/10.1016/j.jpag.2022.04.009

Chester, D. S., Lynam, D. R., Milich, R., Powell, D. K., Andersen, A. H., & DeWall, C. N. (2016). How do negative emotions impair self-control? A neural model of negative urgency. *NeuroImage*, *132*, 43–50. https://doi.org/10.1016/j.neuroimage.2016.02.024

Chronis-Tuscano, A., Molina, B. S. G., Pelham, W. E., Applegate, B., Dahlke, A., Overmyer, M., & Lahey, B. B. (2010). Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *67*(10), 1044–1051. https://doi.org/10.1001/archgenpsychiatry.2010.127

Comasco, E., Kopp Kallner, H., Bixo, M., Hirschberg, A. L., Nyback, S., de Grauw, H., Epperson, C. N., & Sundström-Poromaa, I. (2021). Ulipristal acetate for treatment of premenstrual dysphoric disorder: A proof-of-concept randomized controlled trial. *The*

American Journal of Psychiatry, *178*(3), 256–265. https://doi.org/10.1176/appi.ajp.2020.20030286

Combs, M. A., Canu, W. H., Broman-Fulks, J. J., Rocheleau, C. A., & Nieman, D. C. (2015). Perceived stress and ADHD symptoms in adults. *Journal of Attention Disorders*, *19*(5), 425–434. https://doi.org/10.1177/1087054712459558

Costello, E. J., Copeland, W., & Angold, A. (2011). Trends in psychopathology across the adolescent years: What changes when children become adolescents, and when adolescents become adults? *Journal of Child Psychology and Psychiatry*, *52*(10), 1015–1025. https://doi.org/10.1111/j.1469-7610.2011.02446.x

Cussen, A., Sciberras, E., Ukoumunne, O. C., & Efron, D. (2012). Relationship between symptoms of attention-deficit/hyperactivity disorder and family functioning: A community-based study. *European Journal of Pediatrics*, *171*(2), 271–280. https://doi.org/10.1007/s00431-011-1524-4

Cyders, M. A., & Smith, G. T. (2008). Emotion-based dispositions to rash action: Positive and negative urgency. *Psychological Bulletin*, *134*(6), 807–828. https://doi.org/10.1037/a0013341

Das, D., Cherbuin, N., Butterworth, P., Anstey, K. J., & Easteal, S. (2012). A population-based study of attention deficit/hyperactivity disorder symptoms and associated impairment in middle-aged adults. *PLOS ONE*, *7*(2), e31500. https://doi.org/10.1371/journal.pone.0031500

Davies, S. J., Lum, J. A., Skouteris, H., Byrne, L. K., & Hayden, M. J. (2018). Cognitive impairment during pregnancy: A meta-analysis. *Medical Journal of Australia*, *208*(1), 35–40. https://doi.org/10.5694/mja17.00131

Deković, M., Noom, M. J., & Meeus, W. (1997). Expectations regarding development during adolescence: Parental and adolescent perceptions. *Journal of Youth and Adolescence*, *26*(3), 253–272. https://doi.org/10.1007/s10964-005-0001-7

Demurie, E., Roeyers, H., Baeyens, D., & Sonuga-Barke, E. (2012). Temporal discounting of monetary rewards in children and adolescents with ADHD and autism spectrum disorders. *Developmental Science*, *15*(6), 791–800. https://doi.org/10.1111/j.1467-7687.2012.01178.x

Dreher, J.-C., Schmidt, P. J., Kohn, P., Furman, D., Rubinow, D., & Berman, K. F. (2007). Menstrual cycle phase modulates reward-related neural function in women. *Proceedings of the National Academy of Sciences*, *104*(7), 2465–2470. https://doi.org/10.1073/pnas.0605569104

Dubol, M., Stiernman, L., Wikström, J., Lanzenberger, R., Neill Epperson, C., Sundström-Poromaa, I., Bixo, M., & Comasco, E. (2022). Differential grey matter structure in women with premenstrual dysphoric disorder: Evidence from brain morphometry and data-driven classification. *Translational Psychiatry*, *12*(1), Article 1. https://doi.org/10.1038/s41398-022-02017-6

Eisenlohr-Moul, T. A., Bowers, S. M., Prinstein, M. J., Schmalenberger, K. M., Walsh, E. C., Young, S. L., Rubinow, D. R., & Girdler, S. S. (2022). Effects of acute estradiol and progesterone on perimenstrual exacerbation of suicidal ideation and related symptoms: A crossover randomized controlled trial. *Translational Psychiatry*, *12*(1), 528. https://doi.org/10.1038/s41398-022-02294-1

Eisenlohr-Moul, T. A., Rubinow, D. R., Schiller, C. E., Johnson, J. L., Leserman, J., & Girdler, S. S. (2016). Histories of abuse predict stronger within-person covariation of ovarian

steroids and mood symptoms in women with menstrually related mood disorder. *Psychoneuroendocrinology*, *67*, 142–152. https://doi.org/10.1016/j.psyneuen.2016.01.026

Endicott, J. (1993). The menstrual cycle and mood disorders. *Journal of Affective Disorders*, *29*(2), 193–200. https://doi.org/10.1016/0165-0327(93)90033-G

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

Faraone, S. V., & Biederman, J. (2005). What is the prevalence of adult adhd? Results of a population screen of 966 adults. *Journal of Attention Disorders*, *9*(2), 384–391. https://doi.org/10.1177/1087054705281478

Flory, K., Molina, B. S. G., Pelham, Jr., William E., Gnagy, E., & Smith, B. (2006). Childhood ADHD predicts risky sexual behavior in young adulthood. *Journal of Clinical Child & Adolescent Psychology*, *35*(4), 571–577. https://doi.org/10.1207/s15374424jccp3504_8

Forney, K. J., Keel, P. K., O'Connor, S., Sisk, C., Burt, S. A., & Klump, K. L. (2019). Interaction of hormonal and social environments in understanding body image concerns in adolescent girls. *Journal of Psychiatric Research*, *109*, 178–184. https://doi.org/10.1016/j.jpsychires.2018.12.008

Freeman, E. W., Sammel, M. D., Lin, H., & Nelson, D. B. (2006). Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Archives of General Psychiatry*, *63*(4), 375–382. https://doi.org/10.1001/archpsyc.63.4.375

Galambos, N. L., & Tilton-Weaver, L. C. (2000). Adolescents' psychosocial maturity, problem behavior, and subjective age: In search of the adultoid. *Applied Developmental Science*, *4*(4), 178–192. https://doi.org/10.1207/S1532480XADS0404_1

Garcia, N. M., Walker, R. S., & Zoellner, L. A. (2018). Estrogen, progesterone, and the menstrual cycle: A systematic review of fear learning, intrusive memories, and PTSD. *Clinical Psychology Review*, *66*, 80–96. https://doi.org/10.1016/j.cpr.2018.06.005

Golub, S. (1976). The effect of premenstrual anxiety and depression on cognitive function. *Journal of Personality and Social Psychology*, *34*(1), 99–104. https://doi.org/10.1037/0022-3514.34.1.99

Goodyer, I. M., Park, R. J., Netherton, C. M., & Herbert, J. (2001). Possible role of cortisol and dehydroepiandrosterone in human development and psychopathology. *The British Journal of Psychiatry*, *179*(3), 243–249. https://doi.org/10.1192/bjp.179.3.243

Greendale, G. A., Karlamangla, A. S., & Maki, P. M. (2020). The menopause transition and cognition. *JAMA*, *323*(15), 1495–1496. https://doi.org/10.1001/jama.2020.1757

Greene, R. W., Biederman, J., Faraone, S. V., Monuteaux, M. C., Mick, E., DuPRE, E. P., Fine, C. S., & Goring, J. C. (2001). Social impairment in girls with ADHD: Patterns, gender comparisons, and correlates. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(6), 704–710. https://doi.org/10.1097/00004583-200106000-00016

Hara, Y., Waters, E. M., McEwen, B. S., & Morrison, J. H. (2015). Estrogen effects on cognitive and synaptic health over the lifecourse. *Physiological Reviews*, *95*(3), 785–807. https://doi.org/10.1152/physrev.00036.2014

Heidari, S., Babor, T. F., De Castro, P., Tort, S., & Curno, M. (2016). Sex and gender equity in research: Rationale for the sager guidelines and recommended use. *Research Integrity*

and Peer Review, *1*(1), 2. https://doi.org/10.1186/s41073-016-0007-6

Helfert, S., & Warschburger, P. (2013). The face of appearance-related social pressure: Gender, age and body mass variations in peer and parental pressure during adolescence. *Child and Adolescent Psychiatry and Mental Health*, *7*(1), 16. https://doi.org/10.1186/1753-2000-7-16

Henderson, V. W. (2018). Progesterone and human cognition. *Climacteric*, *21*(4), 333–340. https://doi.org/10.1080/13697137.2018.1476484

Hoekzema, E., Barba-Müller, E., Pozzobon, C., Picado, M., Lucco, F., García-García, D., Soliva, J. C., Tobeña, A., Desco, M., Crone, E. A., Ballesteros, A., Carmona, S., & Vilarroya, O. (2017). Pregnancy leads to long-lasting changes in human brain structure. *Nature Neuroscience*, *20*(2), Article 2. https://doi.org/10.1038/nn.4458

Hua, M.-H., Huang, K.-L., Hsu, J.-W., Bai, Y.-M., Su, T.-P., Tsai, S.-J., Li, C.-T., Lin, W.-C., Chen, T.-J., & Chen, M.-H. (2021). Early pregnancy risk among adolescents with ADHD: A nationwide longitudinal study. *Journal of Attention Disorders*, *25*(9), 1199–1206. https://doi.org/10.1177/1087054719900232

Işık, Ü., Bilgiç, A., Toker, A., & Kılınç, I. (2018). Serum levels of cortisol, dehydroepiandrosterone, and oxytocin in children with attention-deficit/hyperactivity disorder combined presentation with and without comorbid conduct disorder. *Psychiatry Research*, *261*, 212–219. https://doi.org/10.1016/j.psychres.2017.12.076

Jacobs, E., & D'Esposito, M. (2011). Estrogen shapes dopamine-dependent cognitive processes: Implications for women's health. *The Journal of Neuroscience*, *31*(14), 5286–5293. https://doi.org/10.1523/JNEUROSCI.6394-10.2011

Jang, D., & Elfenbein, H. A. (2019). Menstrual cycle effects on mental health outcomes: A meta-

analysis. *Archives of Suicide Research*, *23*(2), 312–332. https://doi.org/10.1080/13811118.2018.1430638

Jermain, D. M., Preece, C. K., Sykes, R. L., Kuehl, T. J., & Sulak, P. J. (1999). Luteal phase sertraline treatment for premenstrual dysphoric disorder: Results of a double-blind, placebo-controlled, crossover study. *Archives of Family Medicine*, *8*(4), 328. https://doi.org/10.1001/archfami.8.4.328

Kinsley, C. H., Trainer, R., Stafisso-Sandoz, G., Quadros, P., Marcus, L. K., Hearon, C., Meyer, E. A. A., Hester, N., Morgan, M., Kozub, F. J., & Lambert, K. G. (2006). Motherhood and the hormones of pregnancy modify concentrations of hippocampal neuronal dendritic spines. *Hormones and Behavior*, *49*(2), 131–142. https://doi.org/10.1016/j.yhbeh.2005.05.017

Klump, K. L., Keel, P. K., Racine, S. E., Burt, S. A., Neale, M., Sisk, C. L., Boker, S., & Hu, J. Y. (2013). The interactive effects of estrogen and progesterone on changes in emotional eating across the menstrual cycle. *Journal of Abnormal Psychology*, *122*(1), 131–137. https://doi.org/10.1037/a0029524

Kok, F. M., Groen, Y., Fuermaier, A. B. M., & Tucha, O. (2020). The female side of pharmacotherapy for ADHD—A systematic literature review. *PLOS ONE*, *15*(9), e0239257. https://doi.org/10.1371/journal.pone.0239257

Koss, W. A., Lloyd, M. M., Sadowski, R. N., Wise, L. M., & Juraska, J. M. (2015). Gonadectomy before puberty increases the number of neurons and glia in the medial prefrontal cortex of female, but not male, rats. *Developmental Psychobiology*, *57*(3), 305–312. https://doi.org/10.1002/dev.21290

Kumari, R. (2019). Baby brain or pregnancy brain or momnesia. *International Journal of*

Nursing Education and Research, *7*(1), 115. https://doi.org/10.5958/2454-2660.2019.00023.1

Lee, S. S., & Hinshaw, S. P. (2006). Predictors of adolescent functioning in girls with attention deficit hyperactivity disorder (ADHD): The role of childhood ADHD, conduct problems, and peer status. *Journal of Clinical Child & Adolescent Psychology*, *35*(3), 356–368. https://doi.org/10.1207/s15374424jccp3503_2

Luine, V. N. (2014). Estradiol and cognitive function: Past, present and future. *Hormones and Behavior*, *66*(4), 602–618. https://doi.org/10.1016/j.yhbeh.2014.08.011

Maharaj, S., & Trevino, K. (2015). A comprehensive review of treatment options for premenstrual syndrome and premenstrual dysphoric disorder. *Journal of Psychiatric Practice*, *21*(5), 334. https://doi.org/10.1097/PRA.0000000000000099

Maki, P. M., & Jaff, N. G. (2022). Brain fog in menopause: A health-care professional's guide for decision-making and counseling on cognition. *Climacteric*, *25*(6), 570–578. https://doi.org/10.1080/13697137.2022.2122792

Marcus, S. M. (2009). Depression during pregnancy: Rates, risks and consequences. *Journal of Population Therapeutics and Clinical Pharmacology*, *16*(1).

Martel, M. M., Eisenlohr-Moul, T., & Roberts, B. (2017). Interactive effects of ovarian steroid hormones on alcohol use and binge drinking across the menstrual cycle. *Journal of Abnormal Psychology*, *126*(8), 1104–1113. https://doi.org/10.1037/abn0000304

Martel, M. M., Gobrogge, K. L., Breedlove, S. M., & Nigg, J. T. (2008). Masculinized finger-length ratios of boys, but not girls, are associated with attention-deficit/hyperactivity disorder. *Behavioral Neuroscience*, *122*(2), 273–281. https://doi.org/10.1037/0735-7044.122.2.273

Martel, M. M., Nigg, J. T., & Von Eye, A. (2009). How do trait dimensions map onto ADHD symptom domains? *Journal of Abnormal Child Psychology*, *37*(3), 337–348. https://doi.org/10.1007/s10802-008-9255-3

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. https://doi.org/10.1016/j.ntt.2014.05.001

Martinez, G. (2020). *Trends and patterns in menarche in the United States: 1995 through 2013–2017* (146; National Health Statistics Reports, pp. 1–11). Centers for Disease Control and Prevention. https://stacks.cdc.gov/view/cdc/93643

McGuire, T. C., McCormick, K. C., Koch, M. K., & Mendle, J. (2019). Pubertal maturation and trajectories of depression during early adolescence. *Frontiers in Psychology*, *10*. https://www.frontiersin.org/articles/10.3389/fpsyg.2019.01362

Meeker, T. J., Veldhuijzen, D. S., Keaser, M. L., Gullapalli, R. P., & Greenspan, J. D. (2020). Menstrual cycle variations in gray matter volume, white matter volume and functional connectivity: Critical impact on parietal lobe. *Frontiers in Neuroscience*, *14*. https://www.frontiersin.org/articles/10.3389/fnins.2020.594588

Meinzer, M. C., LeMoine, K. A., Howard, A. L., Stehli, A., Arnold, L. E., Hechtman, L., Hinshaw, S. P., Molina, B. S. G., Murray, D. W., Sibley, M. H., Swanson, J. M., Tamm, L., & Chronis-Tuscano, A. (2020). Childhood ADHD and involvement in early pregnancy: Mechanisms of risk. *Journal of Attention Disorders*, *24*(14), 1955–1965. https://doi.org/10.1177/1087054717730610

Molina, B. S. G., & Pelham, W. E. (2003). Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *Journal of Abnormal Psychology*, *112*(3),

497–507. https://doi.org/10.1037/0021-843X.112.3.497

Molina, B. S. G., Pelham, W. E., Gnagy, E. M., Thompson, A. L., & Marshal, M. P. (2007). Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcoholism, Clinical and Experimental Research*, *31*(4), 643–654. https://doi.org/10.1111/j.1530-0277.2007.00349.x

Monahan, K. C., Rhew, I. C., Hawkins, J. D., & Brown, E. C. (2014). Adolescent pathways to co-occurring problem behavior: The effects of peer delinquency and peer substance use. *Journal of Research on Adolescence*, *24*(4), 630–645. https://doi.org/10.1111/jora.12053

Ossewaarde, L., van Wingen, G. A., Kooijman, S. C., Bäckström, T., Fernández, G., & Hermans, E. J. (2011). Changes in functioning of mesolimbic incentive processing circuits during the premenstrual phase. *Social Cognitive and Affective Neuroscience*, *6*(5), 612–620. https://doi.org/10.1093/scan/nsq071

Paris, J. J., & Frye, C. A. (2008). Estrous cycle, pregnancy, and parity enhance performance of rats in object recognition or object placement tasks. *Reproduction*, *136*(1), 105–115. https://doi.org/10.1530/REP-07-0512

Peters, J. R., Martel, M. M., Eng, A. G., Schmalenberger, K. M., Stumper, A., & Eisenlohr-Moul, T. A. (Under Review). *Multiple hormone sensitivity theory: A transdiagnostic framework for menstrual cycle influences on psychopathology*.

Phoenix, C. H., Goy, R. W., Gerall, A. A., & Young, W. C. (1959). Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology*, *65*(3), 369–382. https://doi.org/10.1210/endo-65-3-369

Piekarski, D. J., Boivin, J. R., & Wilbrecht, L. (2017). Ovarian hormones organize the

maturation of inhibitory neurotransmission in the frontal cortex at puberty onset in female mice. *Current Biology*, *27*(12), 1735-1745.e3. https://doi.org/10.1016/j.cub.2017.05.027

Polanczyk, G. V., Salum, G. A., Sugaya, L. S., Caye, A., & Rohde, L. A. (2015). Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of Child Psychology and Psychiatry*, *56*(3), 345–365. https://doi.org/10.1111/jcpp.12381

Quinn, P. O. (2005). Treating adolescent girls and women with ADHD: Gender-specific issues. *Journal of Clinical Psychology*, *61*(5), 579–587. https://doi.org/10.1002/jclp.20121

Rapkin, A. J., Korotkaya, Y., & Taylor, K. C. (2019). Contraception counseling for women with premenstrual dysphoric disorder (PMDD): Current perspectives. *Journal of Contraception*, *10*, 27–39. https://doi.org/10.2147/OAJC.S183193

Reardon, L. E., Leen-Feldner, E. W., & Hayward, C. (2009). A critical review of the empirical literature on the relation between anxiety and puberty. *Clinical Psychology Review*, *29*(1), 1–23. https://doi.org/10.1016/j.cpr.2008.09.005

Rehbein, E., Kogler, L., Hornung, J., Morawetz, C., Bayer, J., Krylova, M., Sundström-Poromaa, I., & Derntl, B. (2021). Estradiol administration modulates neural emotion regulation. *Psychoneuroendocrinology*, *134*, 105425. https://doi.org/10.1016/j.psyneuen.2021.105425

Reynolds, T. A., Makhanova, A., Marcinkowska, U. M., Jasienska, G., McNulty, J. K., Eckel, L. A., Nikonova, L., & Maner, J. K. (2018). Progesterone and women's anxiety across the menstrual cycle. *Hormones and Behavior*, *102*, 34–40. https://doi.org/10.1016/j.yhbeh.2018.04.008

Roberts, B., Eisenlohr-Moul, T., & Martel, M. M. (2018). Reproductive steroids and ADHD

symptoms across the menstrual cycle. *Psychoneuroendocrinology*, *88*, 105–114. https://doi.org/10.1016/j.psyneuen.2017.11.015

Rosenthal, D., Moore, S., & Flynn, I. (1991). Adolescent self-efficacy, self-esteem and sexual risk-taking. *Journal of Community & Applied Social Psychology*, *1*(2), 77–88. https://doi.org/10.1002/casp.2450010203

Rougé-Pont, F., Mayo, W., Marinelli, M., Gingras, M., Le Moal, M., & Piazza, P. V. (2002). The neurosteroid allopregnanolone increases dopamine release and dopaminergic response to morphine in the rat nucleus accumbens. *European Journal of Neuroscience*, *16*(1), 169–173. https://doi.org/10.1046/j.1460-9568.2002.02084.x

Sacher, J., Okon-Singer, H., & Villringer, A. (2013). Evidence from neuroimaging for the role of the menstrual cycle in the interplay of emotion and cognition. *Frontiers in Human Neuroscience*, *7*. https://www.frontiersin.org/articles/10.3389/fnhum.2013.00374

Şahin, İ., Say, G. N., Avcı, B., & Kesim, N. (2022). Low serum allopregnanolone levels in children with attention deficit hyperactivity disorder. *Psychoneuroendocrinology*, *146*, 105923. https://doi.org/10.1016/j.psyneuen.2022.105923

Sandstrom, N. J., & Williams, C. L. (2001). Memory retention is modulated by acute estradiol and progesterone replacement. *Behavioral Neuroscience*, *115*(2), 384–393. https://doi.org/10.1037/0735-7044.115.2.384

Scheres, A., & Solanto, M. V. (2021). Do ADHD symptoms, executive function, and study strategies predict temporal reward discounting in college students with varying levels of ADHD symptoms? A pilot study. *Brain Sciences*, *11*(2), Article 2. https://doi.org/10.3390/brainsci11020181

Schiller, C. E., Johnson, S. L., Abate, A. C., Schmidt, P. J., & Rubinow, D. R. (2016).

Reproductive steroid regulation of mood and behavior. *Comprehensive Physiology*, *6*(3), 1135–1160. https://doi.org/10.1002/cphy.c150014

Schmalenberger, K. M., Tauseef, H. A., Barone, J. C., Owens, S. A., Lieberman, L., Jarczok, M. N., Girdler, S. S., Kiesner, J., Ditzen, B., & Eisenlohr-Moul, T. A. (2021). How to study the menstrual cycle: Practical tools and recommendations. *Psychoneuroendocrinology*, *123*, 104895. https://doi.org/10.1016/j.psyneuen.2020.104895

Schmidt, P. J., Martinez, P. E., Nieman, L. K., Koziol, D. E., Thompson, K. D., Schenkel, L., Wakim, P. G., & Rubinow, D. R. (2017). Premenstrual dysphoric disorder symptoms following ovarian suppression: Triggered by change in ovarian steroid levels but not continuous stable levels. *American Journal of Psychiatry*, *174*(10), 980–989. https://doi.org/10.1176/appi.ajp.2017.16101113

Schmidt, P. J., Nieman, L. K., Grover, G. N., Muller, K. L., Merriam, G. R., & Rubinow, D. R. (1991). Lack of effect of induced menses on symptoms in women with premenstrual syndrome. *New England Journal of Medicine*, *324*(17), 1174–1179. https://doi.org/10.1056/NEJM199104253241705

Schulz, K. M., Molenda-Figueira, H. A., & Sisk, C. L. (2009). Back to the future: The organizational–activational hypothesis adapted to puberty and adolescence. *Hormones and Behavior*, *55*(5), 597–604. https://doi.org/10.1016/j.yhbeh.2009.03.010

Shao, S., Wang, J., Huang, K., Wang, S., Liu, H., Wan, S., Yan, S., Hao, J., Zhu, P., & Tao, F. (2020). Prenatal pregnancy-related anxiety predicts boys' ADHD symptoms via placental C-reactive protein. *Psychoneuroendocrinology*, *120*, 104797. https://doi.org/10.1016/j.psyneuen.2020.104797

Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior.

Frontiers in Neuroendocrinology, *26*(3), 163–174. https://doi.org/10.1016/j.yfrne.2005.10.003

Skogli, E. W., Teicher, M. H., Andersen, P. N., Hovik, K. T., & Øie, M. (2013). ADHD in girls and boys – Gender differences in co-existing symptoms and executive function measures. *BMC Psychiatry*, *13*(1), 298. https://doi.org/10.1186/1471-244X-13-298

Sofuoglu, M., Mouratidis, M., & Mooney, M. (2011). Progesterone improves cognitive performance and attenuates smoking urges in abstinent smokers. *Psychoneuroendocrinology*, *36*(1), 123–132. https://doi.org/10.1016/j.psyneuen.2010.07.005

Staikova, E., Gomes, H., Tartter, V., McCabe, A., & Halperin, J. M. (2013). Pragmatic deficits and social impairment in children with ADHD. *Journal of Child Psychology and Psychiatry*, *54*(12), 1275–1283. https://doi.org/10.1111/jcpp.12082

Standeven, L. R., McEvoy, K. O., & Osborne, L. M. (2020). Progesterone, reproduction, and psychiatric illness. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *69*, 108–126. https://doi.org/10.1016/j.bpobgyn.2020.06.001

Strous, R. D., Spivak, B., Yoran-Hegesh, R., Maayan, R., Averbuch, E., Kotler, M., Mester, R., & Weizman, A. (2001). Analysis of neurosteroid levels in attention deficit hyperactivity disorder. *The International Journal of Neuropsychopharmacology*, *4*(3), 259–264. https://doi.org/10.1017/S1461145701002462

Syan, S. K., Minuzzi, L., Costescu, D., Smith, M., Allega, O. R., Coote, M., Hall, G. B. C., & Frey, B. N. (2017). Influence of endogenous estradiol, progesterone, allopregnanolone, and dehydroepiandrosterone sulfate on brain resting state functional connectivity across the menstrual cycle. *Fertility and Sterility*, *107*(5), 1246-1255.e4.

https://doi.org/10.1016/j.fertnstert.2017.03.021

Ter Horst, G. J. (2010). Estrogen in the limbic system. In G. Litwack (Ed.), *Vitamins & hormones* (Vol. 82, pp. 319–338). Academic Press. https://doi.org/10.1016/S0083-6729(10)82017-5

Terner, J. M., & de Wit, H. (2006). Menstrual cycle phase and responses to drugs of abuse in humans. *Drug and Alcohol Dependence*, *84*(1), 1–13. https://doi.org/10.1016/j.drugalcdep.2005.12.007

Trent, S., Dean, R., Veit, B., Cassano, T., Bedse, G., Ojarikre, O. A., Humby, T., & Davies, W. (2013). Biological mechanisms associated with increased perseveration and hyperactivity in a genetic mouse model of neurodevelopmental disorder. *Psychoneuroendocrinology*, *38*(8), 1370–1380. https://doi.org/10.1016/j.psyneuen.2012.12.002

Uguz, F., Yakut, E., Aydogan, S., Bayman, M. G., & Gezginc, K. (2019). Prevalence of mood and anxiety disorders during pregnancy: A case-control study with a large sample size. *Psychiatry Research*, *272*, 316–318. https://doi.org/10.1016/j.psychres.2018.12.129

Vink, M., Derks, J. M., Hoogendam, J. M., Hillegers, M., & Kahn, R. S. (2014). Functional differences in emotion processing during adolescence and early adulthood. *NeuroImage*, *91*, 70–76. https://doi.org/10.1016/j.neuroimage.2014.01.035

Wang, L.-J., Chan, W.-C., Chou, M.-C., Chou, W.-J., Lee, M.-J., Lee, S.-Y., Lin, P.-Y., Yang, Y.-H., & Yen, C.-F. (2017). Polymorphisms of STS gene and SULT2A1 gene and neurosteroid levels in Han Chinese boys with attention-deficit/hyperactivity disorder: An exploratory investigation. *Scientific Reports*, *7*, 45595. https://doi.org/10.1038/srep45595

Wang, L.-J., Huang, Y.-S., Hsiao, C.-C., Chiang, Y.-L., Wu, C.-C., Shang, Z.-Y., & Chen, C.-K. (2011). Salivary dehydroepiandrosterone, but not cortisol, is associated with attention

deficit hyperactivity disorder. *The World Journal of Biological Psychiatry*, *12*(2), 99–109. https://doi.org/10.3109/15622975.2010.512090

Wang, L.-J., Lee, S.-Y., Chou, M.-C., Lee, M.-J., & Chou, W.-J. (2019). Dehydroepiandrosterone sulfate, free testosterone, and sex hormone-binding globulin on susceptibility to attention-deficit/hyperactivity disorder. *Psychoneuroendocrinology*, *103*, 212–218. https://doi.org/10.1016/j.psyneuen.2019.01.025

Whitesell, M., Bachand, A., Peel, J., & Brown, M. (2013). Familial, social, and individual factors contributing to risk for adolescent substance use. *Journal of Addiction*, *2013*, e579310. https://doi.org/10.1155/2013/579310

Williams, O. O. F., Coppolino, M., George, S. R., & Perreault, M. L. (2021). Sex differences in dopamine receptors and relevance to neuropsychiatric disorders. *Brain Sciences*, *11*(9), 1199. https://doi.org/10.3390/brainsci11091199

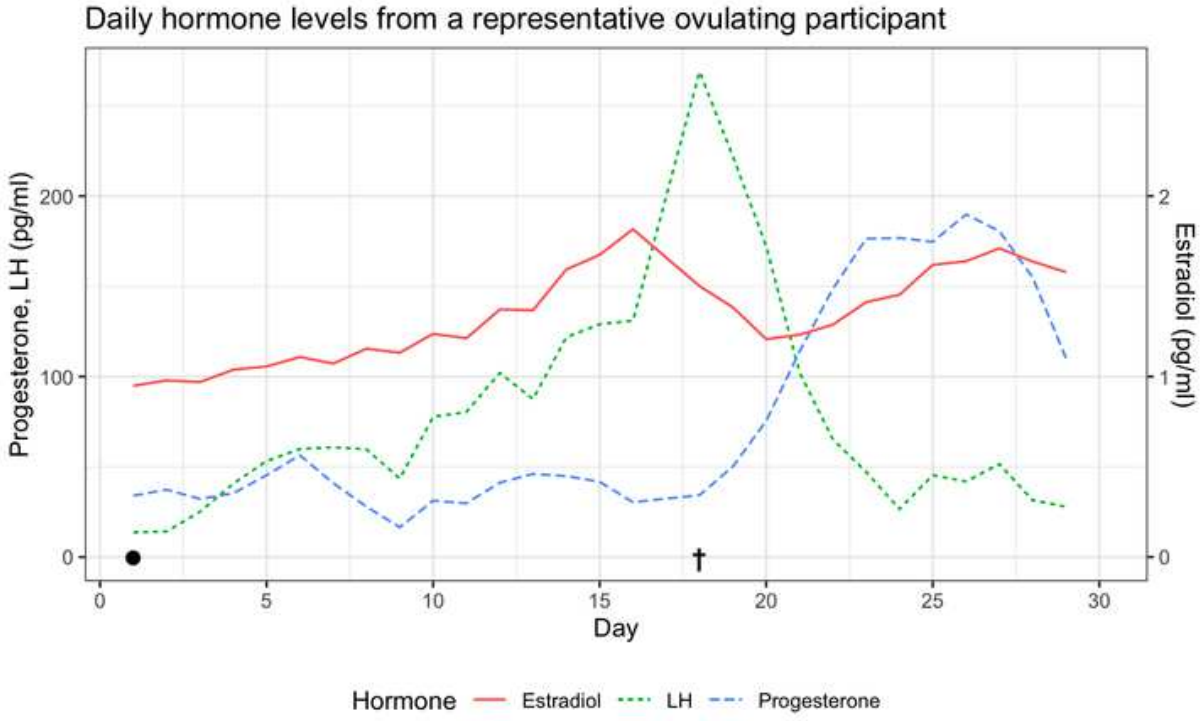
Willing, J., & Juraska, J. M. (2015). The timing of neuronal loss across adolescence in the medial prefrontal cortex of male and female rats. *Neuroscience*, *301*, 268–275. https://doi.org/10.1016/j.neuroscience.2015.05.073

Wyatt, K. M., Dimmock, P. W., Ismail, K. M. K., Jones, P. W., & O'Brien, P. M. S. (2004). The effectiveness of GnRHa with and without "add-back" therapy in treating premenstrual syndrome: A meta analysis. *Bjog: An International Journal of Obstetrics and Gynaecology*, *111*(6), 585–593. https://doi.org/10.1111/j.1471-0528.2004.00135.x

Zhu, P., Hao, J.-H., Tao, R.-X., Huang, K., Jiang, X.-M., Zhu, Y.-D., & Tao, F.-B. (2015). Sex-specific and time-dependent effects of prenatal stress on the early behavioral symptoms of ADHD: A longitudinal study in China. *European Child & Adolescent Psychiatry*, *24*(9), 1139–1147. https://doi.org/10.1007/s00787-015-0701-9

Figure 1.

Example of Typical Shifts in Estradiol, Progesterone, and Luteinizing-Hormone in a Regularly-Cycling Adult Female



Note. Progesterone, luteinizing hormone (LH), and estradiol levels measured by daily saliva sample in a representative ovulating female (three-day rolling average calculated per hormone). • Repre□ent□fir□t day of men□e□; † Repre□ent□po□itive ovulation te□t.