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ADHD in Females Across the Lifespan and the Role of Estrogen

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ADHD IN FEMALES

Prevalence and Identification

Since its inception, ADHD has been a diagnosis predominantly identified with prepubescent boys. To date, the majority of studies have reported that boys' diagnoses exceed those of girls by a ratio of 2:1 to 3:1 (e.g., Willcutt, 2012). However, this discrepancy does not bear out into adulthood, with ADHD in adults now diagnosed at rates close to 1:1 (e.g., deZwaan et al., 2012). This discrepancy between girls and women suggests that ADHD may affect a larger proportion of girls than is indicated by the prevalence data during childhood (Rucklidge, 2010). It further invites questions regarding the nature of ADHD in females across the lifespan. In particular, what is the role of estrogen in the presentation, diagnosis, and treatment of ADHD in females?

We can best answer this question by examining the history of the disorder. Early clinic referrals sought treatment for young hyperactive boys. Data describing these clinic populations formed the basis of diagnostic criteria, which identified hyperactivity as the hallmark of ADHD. Only a minority of girls exhibiting behaviors most similar to hyperactive boys were diagnosed (Barkley, 2002; Hinshaw, 2002). However, the number of young girls who exhibited such hyperactive behaviors were vastly outnumbered by the boys. In addition, hyperactive behavior in boys waned as they matured, suggesting that ADHD resolved itself at puberty. DSM criteria from 1980 allowed for the possibility of inattention without hyperactivity (American Psychiatric Association, 1980), thereby facilitating diagnosis of predominantly inattentive type children, while our knowledge of ADHD in girls remained weighted toward the combined type.

Taken together, the literature told the story of ADHD as a childhood disorder predominantly affecting males (Lahey et al., 1994), and was classified with the Disruptive Behavior Disorders of Childhood in the DSM-IV (1994). This classification persisted

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until 2013, when additional research gave way to its reclassification as a neurodevelopmental disorder in the DSM-5, which increased the age cut-off to 12 years and provided criteria for adults (2013). Even today, adolescent girls exhibiting subtle hyperactive behaviors with mood-based symptoms present a diagnostic challenge; they may still be unable to meet DSM-5 criteria and are likely to be misdiagnosed and treated based on observable symptoms like anxiety and depression (Robison et al., 2008; Nussbaum, 2012). Further accounting for this diagnostic discrepancy, Nadeau et al. (2015) posited that girls are more likely to mask symptoms, which contributes to the underestimation of their struggles. The complexity of identification is highlighted by findings showing that girls with ADHD were more easily distinguished from control girls by their comorbidities than by ADHD symptomatology itself (Skogli et al., 2013). Thus, females in childhood may fly "under the radar" of ADHD diagnosis because of differences in the expression of the disorder.

This brings us back to the problem of the discrepancy. Parents and teachers are more likely to refer boys for evaluation than girls (Mowlem et al., 2019; Sciutto et al., 2004). The likelihood of an evaluation increases when girls exhibit visibly hyperactive and impulsive symptoms and other externalizing behaviors, but these may be gender-atypical. As such, the presentation of ADHD in young females is less familiar, which contributes to the trend of under-identification. This bias towards hyperactivity affects referral rates, assessment scales and the awareness of collateral sources, which all impede identification and diagnosis.

Girls are diagnosed an average of five years later than boys (Gershon, 2002), which offers one explanation for why the discrepancy gap closes to produce a 1:1 ratio by adulthood. This gender bias has clinical implications, as early diagnosis comes with the benefit of potential early intervention. In addition, pubescent females are likely to develop comorbidities common to ADHD, such as anxiety and depression, and are more likely to be misdiagnosed as *only* suffering from these disorders (Katzman et al., 2017). This gives way to theories such as the "female protective theory," which suggests that higher thresholds of exposure (both genetic and environmental) are required for females to meet diagnostic criteria (Taylor et al., 2016). Given the substantial rate of under-identification, it is possible that females with ADHD are at similar risk, but their numbers are not recognized.

In addition, most early studies of ADHD in childhood used clinic-based samples, which skew towards a more severely impaired subset of mostly male subjects. Data describing these children, who often had more severe behavioral profiles, shaped the metrics against which most girls have been measured (Tung et al., 2016). Studies reliant on clinic-based samples typically did not focus on gender differences (Biederman et al., 2004; Rucklidge, 2010). Rather, these studies found that overall impairment levels were similar (Bauermeister et al., 2007), including number and severity of symptoms, subtype distribution (O'Brien et al., 2010), academic underachievement (Frazier et al., 2007), executive dysfunction, number of comorbid disorders, tendencies toward risky behavior (Cortese et al., 2016), and the tolerance, efficacy, and side effects of stimulants (Rucklidge, 2008; Spencer et al., 2001). However, differences do exist.

Core Differences

While sex differences in childhood presentation of ADHD have historically fallen through the cracks, some later studies have made comparisons. Girls with ADHD are more likely to exhibit internalizing disorders compared to boys with ADHD, or control girls, while boys with ADHD are more likely to exhibit externalizing disorders—than either girls with ADHD or control boys (Hinshaw, 2002; Staller & Faraone 2006) in comparison to girls with ADHD and typical children. Compared to men with ADHD, women with ADHD have higher lifetime incidences of internalizing symptoms, such as somatization,

anxiety, and depression (Williamson et al., 2015).

Women with ADHD tend to experience more functional impairment and face different long-term outcomes than both control women and men with ADHD (Hinshaw et al., 2012). They experience greater sensory dysregulation, including both hyper- and hyposensitivities, compared to ADHD men and control women (Bijlenga et al., 2020). Also, compared to men with ADHD and control women, women with ADHD have an increased risk of developing eating disorders, with bulimia nervosa and binge eating disorder being the most common (Biederman et al., 2007, Mikami et al., 2010, Ptacek et al., 2016). In addition, they are more likely to have childhood histories of physical and/or sexual abuse and neglect (Rucklidge et al., 2006). Compared to control women, women with ADHD are at increased risk for physically violent victimization in intimate relationships (Guendelman et al., 2016).

One of the most concerning outcomes for women with ADHD is their significantly high risk for self-harm, including non-suicidal self-injury and suicide attempts, with impulsive women at highest risk (O'Grady & Hinshaw, 2021; Swanson et al., 2014). In addition to lifetime histories of depression, educational underachievement, substance abuse, and childhood exposure to domestic violence and social rejection further increase the risks for self-harm and suicidality (Fuller-Thomson et al., 2020; Meza et al., 2016). Although ADHD is associated with significantly higher rates of early mortality in both genders (Barkley, 2020), it is found to disproportionately impact females (Dalsgaard et al., 2015). Moreover, this increased risk for self-harm and suicidality is associated with symptom persistence and the diagnosis of combined type ADHD (Swanson et al., 2014). Women with childhood histories of social rejection have similar profiles (Meza et al., 2016).

COMPLEXITIES OF ESTROGEN

In an effort to understand the differences in prevalence, impairment, and outcome severity, we consider the role of hormonal mediation. Fluctuations in the presence of sex hormones may have a prominent role in expression and diagnosis of ADHD in females. Extant case studies have already noted that hormonal fluctuations throughout the menstrual cycle may be associated with changes in ADHD symptomatology (Nadeau et al., 2015).

Basic Science

Estrogen refers to a category of hormones that exist in multiple forms throughout the body. In humans, the four related estrogens are estrone (E1), estradiol (E2), estriol (E3) and estetrol (E4). Estradiol is the most common type during childbearing years, estriol is the main type of estrogen during pregnancy, estrone is produced after menopause, and estetrol is produced by a fetus during pregnancy (Fuentes & Silvreyra, 2019). Estrogens are produced primarily by the ovaries, but are also produced in the cortex by neurons and astrocytes, as well as the hippocampus, amygdala, hypothalamus and cerebellum (Barth et al., 2015). Of significance to our question, much of the early research assessing the impact of estrogen on cognition used estrogen collected from horses (i.e., Conjugated Equine Estrogen, CEE). As estrogens differ between the species, this may account for the inconsistent findings between studies using CEE versus those using estradiol (Sherwin, 2003; Morgan et al., 2018).

Across species, all estrogens exert their effects by binding with three different types of estrogen receptors (ER) throughout the entire body, including the central nervous system. Two of those ERs act via transcription of genes in the cell nucleus (i.e., ER alpha and ER beta) and have their impact over hours or days. The other receptor, G protein-coupled estrogen receptors (sometimes known as GPR30), instead binds estrogen to G proteins in the cell membrane and rapidly affects coordination between cells. Thus, ER actions range from immediate (GPR30) to long-term (both nuclear receptors). ERs are distributed differentially in various brain regions, and the various forms of estrogen (E1, E2, E3, etc.) bind to receptors with different affinity and strength of response. This can lead to different or even opposite actions, depending on which receptor is activated and where (Almay et al., 2015; Fuentes et al., 2019; Hwang et al., 2021).

Further complicating the significance of this hormone's potential neurological significance, estrogen levels fluctuate over the stages of reproductive life, as well as over the course of each menstrual cycle. That is, estrogen levels gradually increase in puberty, rapidly increase during pregnancy, fall off steeply after delivery, fluctuate during perimenopause, and diminish profoundly after menopause. Similarly, but on a more microscopic scale, estrogen levels fluctuate and interact with progesterone across the menstrual cycle. During the follicular phase, when the egg is developed, estrogen levels gradually increase starting from menstruation, while progesterone levels remain low. During the luteal phase, when the uterus is being prepared for fertilization, progesterone increases while estrogen fluctuates at a lower level. Both drop off steeply prior to menstruation (Gava et al., 2019).

Estrogens have pleomorphic biological actions, which in turn have significant neurological impacts. These include neuroprotection, anti-inflammatory actions, increasing endothelial nitric acid synthesis, as well as acting as a neuromodulator (Luine, 2014). Significantly, they are also implicated in neurotransmitter functioning, particularly acetylcholine (Gibbs, 2010), which is essential in memory, and the monoamines, such as dopamine, norepinephrine, and serotonin (Amin et al., 2015; Hwang et al., 2021). These monoamines are instrumental neurotransmitters in various forms of psychopathology and pharmacotherapy. Dopamine is most germane to ADHD. In reproductive biology, progesterone generally opposes the action of estrogen but, given the limited studies regarding its non-reproductive functions, it is de-emphasized here. Estrogen stimulates dopamine synthesis in the nucleus accumbens, induces dopamine release in the striatum, and

prolongs neurotransmission by reducing dopamine transporters (Almay et al., 2015; Barth et al., 2015: Hwang et al., 2021).

Cognition, Mood, and Psychopathology

Given the broad distribution of estrogen receptors in the central nervous system and its impact on key neurotransmitters, it is no surprise that estrogen levels are associated with higher order neural functioning. Converging lines of research in animals and humans indicate that low estrogen levels may lead to impaired cognition. For instance, women who undergo oophorectomy prior to menopause exhibit postoperative decline in verbal memory (Sherwin, 2003; Au et al., 2016). Literature reviews regarding the cognitive impact of natural menopause also reported lower scores on verbal measures, such as delayed verbal memory and phonemic fluency (Luine, 2014). Low estrogen levels have been implicated in the etiology of dementia in women. Women than men have Alzheimer's disease (AD) which is not accounted for by their greater longevity. Additionally, women who have undergone surgical removal of ovaries at a young age have increased risk of dementia, and there is substantially reduced risk for AD in women who receive postmenopausal hormone therapy (Sherwin, 2003; Luine, 2014; Au et al., 2016). High estradiol levels during menstrual phases led to improved spatial WM, as did replacement in postmenopausal women (Hwang et al., 2021).

Hormonal transitions across the reproductive lifespan and within cycles predispose women to mood disturbances; they have a heightened risk of developing depression following puberty (Martel et al., 2009). Thereafter, most women of reproductive age describe cycle-dependent increases in symptoms of negative mood, such as irritability, anxiety and depression. A subset of these women met DSM-5 criteria for a more severe clinical syndrome called premenstrual dysphoric disorder (PMDD), which usually begins 2-3 days before onset of menstruation and ends with onset of menses. Following childbirth, women can develop postpartum depression, thought to be triggered by the rapid drop in both estrogen and progesterone. Similarly, during the perimenopausal transition period when most female hormones decrease significantly, there is a high rate of new-onset major depression (Barth et al., 2015).

Lastly, there are notable gender differences in the rates of psychiatric illnesses and symptom expression, attributable to both female and male sex hormones. Men have higher rates of schizophrenia and more symptoms of antisocial traits and aggression. By contrast, women have a higher incidence of negative symptoms such as apathy and anhedonia. In addition, men have a single peak of onset of schizophrenia in their early 20s, while women have two: one after menarche and the second post menopause. This has led to the hypothesis that the neuroprotective actions of estrogen may reduce symptom severity and susceptibility, which shifts onset and progression of illness. Similarly, women tend to present bipolar disorder later in life than men, but have faster cycling of mania and depression, which is often associated with periods of hormonal fluctuation. Women also have higher prevalence of major depressive disorder (MDD), and its risk for suicide. Moreover, MDD is associated with low estrogen.

Together, this review indicates that changes in the levels and forms of estrogen can have profound effects on many of the processes associated with ADHD including memory, attention, executive functioning and mood regulation, as well as on neurotransmitters and other neural structures which mediate them. Moreover, given estrogen's impact on other mental illnesses, it follows that estrogen likely impacts the expression of ADHD in females significantly as well.

FLUCTUATIONS IN ESTROGEN AND PRESENTATIONS IN ADHD

An emerging body of research suggests that, in females with ADHD, the fluctuations of ovarian hormones across the menstrual cycle affect a wide range of behaviors. These studies shed light on why adolescent girls are particularly vulnerable to the development of psychopathology following a post-pubertal surge of estrogen (Martel et al., 2009; Murray et al., 2019). The surprisingly strong similarities on various outcome measures suggests the salience of cycling hormones in the experience of women with ADHD.

Differential rates of eating and substance abuse disorder, as well as of mood disorders, are examples of the former. For instance, there is a relationship between cycling ovarian hormones, eating disorders, and women with ADHD. Both ADHD and eating disorders are linked to impulsivity and rely on dopaminergic signaling (Ptacek et al., 2016), while binge-eating, bulimic symptoms, and body dissatisfaction peak during the mid-luteal/premenstrual phases. This low estrogen/high progesterone state appears to be associated with the phase of greatest impulsivity for women with ADHD. These findings suggest that the fluctuations in ovarian hormones may predict changes in emotion-motivated eating across the menstrual cycle (Lester et al., 2003; Klump et al., 2008).

High trait impulsivity is a core symptom of ADHD, and is sensitive to the effects of cycling ovarian hormones (Barkley, 2010). Paloyelis et al. (2010) report that impulsivity peaks during the phase of concurrent high progesterone. Delay discounting behavior also varies across the menstrual cycle, mediated by the interaction of estrogen and frontal dopamine (Haimov-Kochman & Berger, 2014). They found that when estrogen and dopamine levels dropped in tandem, impulsive women with ADHD were more likely to choose smaller short-term rewards, contrary to men with ADHD who chose larger delayed rewards (Doidge et al., 2021).

The risk for developing a substance use disorder (SUD) is higher for all individuals suffering from ADHD, including those with childhood history of either internalizing or externalizing disorders. Sex differences between the more abused substances suggest

that there may be differential reward processing in response to ovarian hormones throughout the menstrual cycle (Groenman, 2020). Some studies suggest that females with ADHD, with or without comorbidities, are more likely to develop a SUD (Ottosen et al., 2016) than males with ADHD. This may be particularly the case for alcohol and tobacco, though they are equally likely to suffer from SUD for other substances, including illicit ones (Elkins, I. & Iacono, W.G., 2020).

Roberts et al. (2018) studied the direct impact of hormonal fluctuations during the menstrual cycle on women with ADHD. Via daily saliva tests, they were able to monitor changing levels of estradiol (E2), progesterone (P4) and testosterone. This allowed them to examine how these hormones affect executive function, impulsivity, depression, and anxiety, as well as multiple other variables. They found that when estrogen was high and progesterone low, ADHD females exhibited improved cognition and mood, in addition to diminished ADHD symptoms. However, ADHD symptoms and comorbid impairments worsened in response to low estrogen/high progesterone states, with the most severe impairments experienced by ADHD women with high trait impulsivity. Their findings further suggested increases in ADHD symptoms during the early follicular (increasing estrogen and little to no progesterone), early luteal (decreasing estrogen and increasing progesterone) and post-ovulatory (low levels of both) phases, indicating the importance of estrogen/progesterone *ratio*, rather than simple differences between levels of each. They concluded that in women, ADHD symptoms may be variable across the menstrual cycle, and that clinicians may need to inquire about cycle phase, hormonal profile and the use of birth control.

Compared to control women, women with ADHD also have a higher risk of severe PMDD symptoms during the luteal phase (low estrogen, high progesterone) of the menstrual cycle, are more likely to experience postpartum depression after the birth of their first child, (resulting in a sharp drop of both hormones), and are likely to experience more severe climacteric symptoms (Dorani et al., 2021). Highly-impulsive ADHD women may be particularly sensitive to these hormone-related depressive disorders, and are at an increased risk for suicidality (Owens & Eisenmohl, 2018).

Lastly, another recent study by Sahin et al. (2018) evaluated the effects of estrogen and G protein-coupled estrogen receptor 1 on ADHD symptoms in both male and female children with ADHD. Using blood samples to monitor multiple hormone-related variables, they found that symptom expression was a function of G protein-coupled estrogen receptor levels (related to the GPR30 receptors discussed previously), rather than estrogen levels alone, irrespective of sex. This indicates that the *type* of estrogen receptor, rather than absolute levels of estrogen, determines the degree of ADHD symptoms. This somewhat paradoxical finding underlines how the complexity of estrogen and its receptors can moderate its impact on ADHD, and likely other hormone driven conditions.

Taken together, these studies have several themes in common: girls with ADHD are particularly vulnerable to the development of mood-based comorbidities in early adolescence and substance abuse (particularly of alcohol and tobacco) during adulthood. Additionally, fluctuating ovarian hormone levels, as well as types of estrogen receptors, influence the severity of ADHD symptoms and comorbidities across the lifespan. Impulsive women with ADHD appear to be particularly vulnerable to the effects of cycling ovarian hormones.

IMPLICATIONS

Despite sharing features with ADHD males, females with ADHD exhibit significant differences in their presentations and associated problems. As a result, they are under-recognized and under-treated. Here we have outlined ways the ovarian hormones, particularly estrogen, may moderate presentations and treatment response. This review suggests that pubertal girls and women with ADHD may experience hormone-related impairments, which exist on a continuum, shifting in response to ovarian hormone levels as they fluctuate across the menstrual cycle. In addition, impulsive females may be particularly sensitive to these hormonal effects. A number of implications grow out of these considerations.

Differences in hormonal status likely contribute to the under-identification of pre-pubertal females and misdiagnosis of those that have reached puberty. In addition, due to hormone fluctuation during perimenopause and eventual estrogen depletion during menopause, some of these women may receive a first-time diagnosis of ADHD in adulthood, probably incorrectly. As discussed above, a drop off in estrogen may lead to multiple cognitive changes, which include core ADHD symptoms such as impaired working memory, executive dysfunction and even poor sleep. Thus, hormonal changes during perimenopause and menopause may contribute to the population of so-called 'adult-onset' ADHD.

Estrogen fluctuations also have implications regarding treatment. Although the research is minimal at this time, we need to clarify understanding of the effect size of these observations, as well as possible modes of measuring hormone levels practically. In addition, when females have fluctuating symptoms or poor responses to stimulants, hormonal status and/or the point in the woman's menstrual cycle may be usefully considered. In some cases, estrogen replacement and/or birth control may be an option.

Until recently, females with ADHD have been the focus of relatively few studies, and the majority of those have focused on girls. To improve long-term outcomes for women, more research is needed to clarify and explore the impact of cycling ovarian hormones on ADHD symptoms and related impairments in post-pubescent females with this disorder. Shifting the diagnostic model to accommodate internalizing symptoms and common comorbidities may better identify a wider range of females who suffer from ADHD at all

ages. Psychoeducation can then address the complexity of female presentations and may further facilitate identification. Revising assessment tools is necessary in order to allow more females to be recognized.

Further topics for research may include an exploration of the ways in which impulsivity mediates the impact of cycling ovarian hormones and an exploration of the neuroprotective actions of estrogen as they affect ADHD in women. Studies are also needed to explore the treatment potential of hormone replacement therapy to enhance cognitive and mood deficits in women with ADHD, from perimenopause throughout the climacteric period. Although outside the scope of this review, future studies could also explore how other hormones interact with estrogen and progesterone, such as testosterone, thyroxine, and cortisol.

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Implications of the Executive Function—Self-Regulation (EF-SR) Theory of ADHD for Estimates of Persistence and Prevalence

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Keywords: executive function, self-regulation, age declines, DSM criteria, prevalence

EF-SR THEORY

On the surface, ADHD as described in the DSM-5 appears to be a disorder merely comprised of inattention, impulsivity, and hyperactivity. However, it is far more than that set of behaviors, as ample research has shown. Calling ADHD an attention disorder, in my opinion, is like referring to autism spectrum disorder as hand flapping or stereotyped movement: to do so is to define the disorder by its more obvious, but more superficial, behaviors. Beyond those surface symptoms, ADHD , in my—longstanding—opinion, is actually a disorder of self-regulation (SR), making it an SR-deficit disorder (SRDD). Self-regulation relies on executive functioning (EF) and its underlying brain networks, therefore one might also just as accurately refer to ADHD as EFDD (Barkley, 2012a, 2015b). I prefer the term SRDD here, because that is what I believe is evident and inarguable in people with this condition. Deficits in EF create the SR-deficient phenotype, but those deficits, being largely private or mental activities, are not so visible in the patient with ADHD, especially by adulthood. It is the repeated failure to demonstrate self-regulation that is most apparent to those with ADHD, their families, and clinicians.

Researchers disagree on the exact definition of EF—I found more than 20 when writing my book on EF in 2012. This is one reason why the field of EF has made so little conceptual progress during my career, and why some authors, such as Koziol (2014), have called for its abandonment. Most investigators recognize that EF involves mental abilities necessary for goal-directed action, an intentional stance toward the future. While that may be, it is hardly an operational definition. Investigators also differ in explaining what makes a mental function executive in nature, if they explain it at all, or just how many functions fall under the meta-construct of EF. There is general agreement on the seven most likely EFs, which are commonly cited in research papers on EF to date. These are self-awareness, inhibition, nonverbal and verbal working memory, emotional self-regulation, self-motivation, and planning/problem solving. Left unsaid is what these seven functions share that makes them EFs, while other mental abilities (such as long-term memory, visuospatial abilities and speech/language) are not?

The core EFs are essential for the contemplation of a hypothetical future, and consequently, the formation of a goal. The construction of plans and behavioral sequences to attain that future, and their guidance over time by mental representations about this plan are achieved by these seven EFs. The quintessential function of the EFs and