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Reproductive steroids and ADHD symptoms across the menstrual cycle

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ABSTRACT

Although Attention-Deficit/Hyperactivity Disorder shows (ADHD) male predominance, females are significantly impaired and exhibit additional comorbid disorders during adolescence. However, no empirical work has examined the influence of cyclical fluctuating steroids on ADHD symptoms in women. The present study examined estradiol (E2), progesterone (P4), and testosterone (T) associations with ADHD symptoms across the menstrual cycle in regularly-cycling young women (N = 32), examining trait impulsivity as a moderator. Women completed a baseline measure of trait impulsivity, provided saliva samples each morning, and completed an ADHD symptom checklist every evening for 35 days. Results indicated decreased levels of E2 in the context of increased levels of either P4 or T was associated with higher ADHD symptoms on the following day, particularly for those with high trait impulsivity. Phase analyses suggested both an early follicular and early luteal, or post-ovulatory, increase in ADHD symptoms. Therefore, ADHD symptoms may change across the menstrual cycle in response to endogenous steroid changes.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common and impairing childhood neurodevelopmental disorder (APA, 2013; Bernfort et al., 2008; Pelham et al., 2007; Polanczyk et al., 2007; Sayal et al., 2017; Thomas et al., 2015) that often persists into adolescence and adulthood with a prevalence of approximately 3% in adults (Faraone and Biederman, 2005; Fayyad et al., 2017; Kessler et al., 2006; Wilcutt, 2012). ADHD is a heterogeneous condition, currently conceptualized theoretically using multiple pathway models (Nigg et al., 2004; Sonuga-Barke, 2005) and most accurately described using two continuous symptom dimensions of inattention and hyperactivity-impulsivity (Haslam et al., 2006; Larsson et al., 2012; Marcus and Barry, 2011). Although ADHD is more frequently diagnosed in males, females with ADHD often become particularly impaired and exhibit comorbid disorders beginning during adolescence (Biederman et al., 1999; Hinshaw et al., 2012; Hosain et al., 2012; Lahey et al., 1994; Quinn, 2005; Robison et al., 2008). The mechanisms of such sex differences remain unclear yet fundamental to understanding ADHD and sex differences in ADHD.

Prior work suggests a role for organizational testosterone (T) in ADHD symptoms in both sexes (Wang et al., 2017), but particularly males (Martel, 2009; McFadden et al., 2005). Women and girls are under-studied and in particular, activational hormonal effects remain essentially unstudied in ADHD. Case studies have suggested that ADHD symptoms may worsen the week before menstruation (during declining estrogen and progesterone; Quinn, 2005) and improve during pregnancy (during elevated estrogen and progesterone (Nadeau and Quinn, 2002), but empirical work is lacking.

Higher estradiol (E2) and progesterone (P4) have been generally linked to enhanced executive function (EF) and attention (e.g., Hatta and Nagaya, 2009), which appear to improve during cycle phases characterized by elevated E2 and P4 (Gogos, 2013; Howard et al., 1988; Jacobs and D'Esposito, 2011; Lord and Taylor, 1991; Rosenberg and Park, 2002; Segal, 2012; Vranić and Hromatko, 2008; Solís-Ortiz and Corsi-Cabrera, 2008; Solis-Ortiz et al., 2004). Further, verbal fluency, verbal learning and memory appear to improve with administration of T in women (Davison et al., 2011; Drake et al., 2000), whereas response inhibition performance decreases (Bjork et al., 2001). Given that weak EF is a prominent correlate and possible marker of ADHD, this prior work suggests a potential role for cycling reproductive steroids in daily ADHD symptom expression.

During adulthood, impulsivity appears to be a particularly prominent marker of ADHD that is underpinned by cyclical steroid effects (Barkley et al., 2010). Studies of adult ADHD suggest robust associations with components of impulsivity (Lynam et al., 2006), including Negative Urgency (negative affect-driven rash action), Lack of Perseverance (inability to persist on a task through completion), and Lack of

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Table 1
Partial (Controlling for Age and BMI) Spearman Rank Correlations Between Average Steroids, Variance in Steroids, Impulsivity Variables, and ADHD symptoms Across Observations (N = 32).

	1	2	3	4	5	6	7	8	9	10	11	12
1. Negative Urgency												
2. Positive Urgency	**0.85*****											
3. Sensation Seeking	**0.62*****	**0.66*****										
4. Lack Premeditation	**0.49****	**0.59*****	**0.37***									
5. Lack Perseverance	**0.54****	**0.51****	0.11	**0.67*****								
6. Testosterone Average	0.04	0.02	0.05	−0.20	−0.10							
7. Estradiol Average	−0.13	−0.05	−0.05	−0.20	−0.19	0.22						
8. Progesterone Average	−0.28	**−0.43***	**−0.37***	**−0.42***	−0.18	0.11	**0.55****					
9. Testosterone SD	0.28	**0.37***	**0.42***	0.07	0.03	**0.71*****	0.30	−0.02				
10. Estradiol SD	**−0.30***	−0.19	−0.10	−0.11	−0.07	0.12	**0.45***	0.17	0.01			
11. Progesterone SD	**−0.27***	**−0.39***	**−0.30***	−0.25	−0.07	0.07	**0.30***	**0.87*****	0.01	0.12		
12. Hyp/Imp Sx Average	**0.61*****	**0.42***	**0.50****	**0.51****	**0.46***	−0.22	−0.23	−0.18	−0.09	−0.20	−0.14	
13. Inattentive Sx Average	**0.58*****	**0.60*****	**0.55****	**0.51****	**0.41***	−0.22	**−0.36***	**−0.44***	0.01	−0.23	**−0.39***	**0.79*****

Bolded values represent $p < 0.05$.
Note.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 2a
Models Predicting Daily ADHD Symptoms Person-Standardized Recent Ovarian Steroid Levels.

Parameter	Daily Outcome			
	Hyperactive/Impulsive Symptoms		Inattentive Symptoms	
	Estimate	*SE*	*Estimate*	*SE*
Intercept	0.13	0.03	0.16	0.05
BMI	0.04	0.03	0.04	0.05
E2	−0.02	0.02	0.00	0.02
P4	0.02	0.02	−0.01	0.02
T	0.00	0.02	0.02	0.02
E2 × P4	−0.01	0.02	0.00	0.02
E2 × T	−0.02	0.01	−0.01	0.02
P4 × T	0.01	0.02	0.00	0.02

Note. E2 = Estradiol, P4 = Progesterone. T = Testosterone. Significant fixed effects are shown in bold.

Table 2b
Models Predicting Daily ADHD Symptoms from the Interaction of Negative Urgency and Recent Ovarian Steroid Levels.

Parameter	Daily Outcome			
	Hyperactive/Impulsive Symptoms		Inattentive Symptoms	
	Estimate	*(SE)*	*Estimate*	*(SE)*
Intercept	0.12	0.03	0.17	0.04
BMI	0.00	0.03	−0.01	0.04
E2	−0.02	0.01	−0.01	0.02
P4	**0.04****	0.01	0.00	0.02
T	−0.01	0.01	0.00	0.02
E2 × P4	**−0.03***	0.01	**−0.05****	0.02
E2 × T	0.00	0.01	−0.01	0.02
P4 × T	0.00	0.01	0.04	0.03
Negative Urgency (NU)	**0.10****	0.03	**0.14****	0.05
NU × E2	**−0.03***	0.02	−0.01	0.02
NU × P4	**0.05****	0.02	0.00	0.02
NU × T	0.01	0.01	0.02	0.02
NU × E2 × P4	**−0.04***	0.01	**−0.05***	0.02
NU × E2 × T	0.01	0.01	0.01	0.02
NU × P4 × T	0.00	0.02	0.01	0.02

Note. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. E2 = Estradiol, P4 = Progesterone. T = Testosterone. Significant fixed effects are shown in bold.

Planning (action without careful thinking; Miller et al., 2010; Pedersen et al., 2016; reviewed by Berg et al., 2015) with Negative Urgency potentially related to fluctuations in E2 and P4 through its links with affect (Eisenlohr-Moul et al., 2015). Sensation-Seeking (tendency to seek adventure) may be more specifically associated with hyperactivity-impulsivity (Lopez et al., 2015), as well as related to higher T (Campbell et al., 2010; Daitzman and Zuckerman, 1980; Roberti, 2004). Overall, trait impulsivity appears prominently associated with both adult ADHD symptoms and steroid effects. Therefore, in line with rodent research (Löfgren et al., 2009), impulsivity may be a marker or a route to adult ADHD that is particularly sensitive to steroid effects. Thus, the possibility that steroid effects on ADHD may be apparent particularly for women with high trait impulsivity (particularly Negative Urgency and Sensation-Seeking) was examined herein.

1.1. Goals of the present study

The present study was conducted with the intention of examining the within-person covariations of reproductive steroids, including E2, P4, and T, with daily ADHD symptoms across the menstrual cycle. Based on prior work on E2 associations with EF, it was hypothesized that 1) between-women, lower average E2 across the entire menstrual cycle would be associated with higher ADHD symptoms, 2) within-person declines in E2 (i.e., lower-than-average E2 for a given woman) would be associated with increases in ADHD symptoms, and that 3) within-person declines in E2 would be more strongly associated with increased ADHD symptoms, particularly for those with higher levels of trait impulsivity. Additionally, given the evidence for interactive effects of E2 and P4 in other externalizing psychopathologies (Eisenlohr-Moul et al., 2015; Klump et al., 2008, 2013). P4 was included as an exploratory moderating variable given established antagonistic effects on E2, and T was also included as an exploratory moderating variable due to associations of T with ADHD symptoms (Martel, 2009; McFadden et al., 2005) and sensation seeking (Campbell et al., 2010; Daitzman and Zuckerman, 1980; Roberti, 2004). Finally, 4) cycle phase effects were examined to more easily compare results to previous studies and to evaluate whether ADHD risk may be heightened during particular parts of the menstrual cycle exhibiting characteristic hormone profiles, such as the early luteal phase and the perimenstrual timeframe (see Appendix A).