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Cortisol reactivity following pharmacological "clamp" exposes women's vulnerability to major depressive disorder

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Cortisol reactivity following pharmacological "clamp" exposes women's vulnerability to major depressive disorder

by

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Dedication

To my parents and my partner,

for their unconditional and boundless love, support and encouragement.

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Abstract

Cortisol reactivity following pharmacological "clamp" exposes women's vulnerability to major depressive disorder

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Stress-evoked hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis—typically measured via cortisol activity—is a major risk factor in the pathogenesis of major depressive disorder (MDD). However, the standard laboratory assessment of stress reactivity—the Trier Social Stress Test (TSST)—reveals no sex differences, despite the finding that women experience MDD at about twice the rate of men. One possibility is that HPA axis responses to the TSST are at or the near physiologic ceiling. If true, then down-regulation of the HPA axis prior to TSST administration might reveal the expected sex difference in HPA axis response. To this end, we hypothesized that suppression of HPA axis response using dexamethasone would reveal the sex difference in TSST-evoked cortisol reactivity, thus supporting the role of hypercortisolemia in the pathophysiology of MDD. Prior to TSST administration, 92 healthy, never-depressed participants (50% female) were randomized to receive either two placebo pills, or 2mg dexamethasone and 80mg propranolol. Cardiovascular (heart rate) and HPA axis (cortisol) responses were assessed before, during, and after TSST administration.

Replicating previous work, analyses revealed no sex differences in cortisol reactivity in the placebo condition. However, as hypothesized, relative to men, women showed greater TSST-evoked HPA axis reactivity in the drug condition. This sex difference was not explained by sex differences in depression, anxiety, anxiety sensitivity, or history of adverse childhood experiences. By describing conditions under which sex differences in acute-stress hyperreactivity will emerge, the current study lends support to the role of stress-evoked hyperreactivity in the pathophysiology of MDD.

Table of Contents

List of Tables

List of Figures

Cortisol Reactivity

Stress-evoked hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis—typically measured via cortisol activity—is a major risk factor in the pathogenesis of depression (Holsboer, 2000; Nemeroff & Vale, 2005; Plotsky, Owens, & Nemeroff, 1998; Schlesser, Winokur, & Sherman, 1980). It is puzzling however, despite the finding that women are about twice as likely to develop depression compared to men (Nolen-Hoeksema, 1987; 2001), there is an absence of clear and consistent sex differences in the literature on HPA reactivity to stress eliciting challenges (Kelly et al., 2008; Kirschbaum et al., 1999).

Physiologic Ceiling Effect

One possible explanation for this apparent paradox is that HPA axis responses to laboratory stressors may be at or near the physiologic ceiling, thus masking underlying sex differences. In support, Kirschbaum, Pirke and Hellhammer (1993), reporting no sex difference in cortisol response to the Trier Social Stress Test (TSST) also reported a mean peak value of salivary cortisol concentration of 16 nmol/L (5.80 ng/mL)—a value approaching the mean peak concentration of 22.95 nmol/L (8.32 ng/mL) as reported by Wust et al. (2000) in an assessment of the cortisol awakening response. This leads to the possibility that suppression of the HPA axis prior to acute stress induction might reveal a sex difference in stress reactivity, through the creation of physiologic "headroom."

Suppression of HPA axis activity is typically achieved through administration of dexamethasone, a powerful synthetic glucocorticoid (Carroll, 1982). Supporting the idea

that HPA axis suppression may aid in uncovering pathogenic cortisol activity, significantly greater stress-evoked cortisol reactivity was seen in depressed patients, relative to healthy controls after dexamethasone administration (Carroll, 1977), whereas no difference was seen in the absence of dexamethasone-induced HPA axis suppression (Young et al., 2000). Further support for a physiologic ceiling effect is reported by Morris, Rao, and Garger (2012), in a study in which cortisol reactivity predicted depression in a mixed sample of remitted depressives and healthy controls who were in a low stress control condition. In comparison, cortisol reactivity was not predictive of future depression in the high stress condition (TSST-induced), presumably due to a physiologic ceiling effect.

GONADAL MEDIATED SEX DIFFERENCES IN STRESS REACTIVITY

Women may be more stress-sensitive than men because of sex differences in several important steroid sex hormones. Women have higher levels of estrogen and progesterone than do men, and heightened stress-evoked cortisol reactivity has been linked to elevated levels of estrogen and progesterone. For example, Kirschbaum et al. (1996) showed that administration of an estradiol patch for 24 hours in healthy men resulted in a greater response to a social stressor. Furthermore, increased circulating levels of progesterone have also been shown to decrease the effects of glucocorticoids on HPA axis negative feedback (Keller-Wood, Silbiger, & Wood, 1988). Altemus et al. (1997) reported decreased cortisol suppression to dexamethasone during the luteal phase of the menstrual cycle, as compared with the follicular phase in the same women, presumably because estradiol and progesterone are elevated during luteal phase. In

humans, pregnancy is marked by increases in estrogen and progesterone concentrations, providing another model in which interactions between gonadal steroids and HPA axis activity may be examined (Demey-Ponsart et al., 1982; Carr et al., 1981; Nolten & Rueckert, 1981). Consistent with the idea that elevated levels of circulating estradiol and progesterone decrease cortisol suppression and thus increase cortisol reactivity, dexamethasone challenge studies conducted during pregnancy show diminished dexamethasone-induced negative feedback, relative to non-pregnant controls. On a cellular level, estradiol has been reported to decrease expression of glucocorticoid receptor mRNA in lymphocytes, causing a decrease in glucocorticoid receptor density in the luteal phase of the menstrual cycle, suggesting a hormonally-modulated genomic mechanism underlying the increased cortisol reactivity associated with women during the luteal phase (Altemus et al., 1997)

CURRENT AIMS

In light of these considerations, the aim of the present study was to evaluate sex differences in cortisol responses to the TSST following administration of dexamethasone in a healthy, nonclinical sample. Because depression is much more prevalent in women than men, we hypothesized that women would be more likely to show dexamethasone-induced hypercortisolemia in response to an acute laboratory stressor (Greden et al., 1983).

Method

Participants

In total, 92 participants (M_{age}=19.08, SD_{age}=1.17; M_{BMI}=24.04, SD_{BMI}=2.34; 50% female) completed the study. Exclusion criteria include daily recreational drug use (including, but not limited to, nicotine and alcohol); chronic psychological and physiological illness; anomalous body mass index (i.e., less than 18 and greater than 27); medication use that is known to affect either endocrine or sympathetic nervous system (SNS) functioning; and irregular menstrual cycles. In addition, all participants completed a 3-lead electrocardiogram in order to ensure safety associated with drug administration (CardioComm Solutions, Toronto, ON).

All female participants were scheduled during the estimated mid-luteal phase of their menstrual cycles (between 17th and 28th day following the onset of menstruation) in order to minimize the possible effects of cycling gonadal hormones on the SNS and the HPA axis. To assess cycle phase, female participants were asked to recall the first day of their most recent menstruation during a telephone screening. Male participants were scheduled according to the availability of laboratory facilities and the experimenter.

Drug Assignment

All participants were assigned to either the drug or the placebo condition in a stratified, randomized design. Previous research demonstrates that suppression of the HPA response led to compensatory response from the SNS (Andrews & Pruessner, 2013), thus in order to control for the response of the SNS all participants in the drug

condition were also supplied with propranolol, a non-selective β-antagonist in addition to dexamethasone.

STUDY PROCEDURES

Two weekday appointments were made for each participant. During the first appointment, the on-site experimenter obtained written informed consent from participants following a complete description of the study procedures, including any risks and benefits associated with participation along with the option to withdraw from the study at any time without penalty. Following informed consent, participants completed a questionnaire battery, including the Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977), Beck Depression Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988), Anxiety Sensitivity Inventory 3 (ASI-3; Taylor et al., 2007), and Risky Family Questionnaire (Taylor et al., 2004), to assess depressive symptoms, anxiety symptoms, fear of sensations associated with the experience of anxiety, and adverse childhood experiences, respectively.

Following the completion of the questionnaires, participants were supplied with either dexamethasone or placebo in the form of an oral capsule and instructed to ingest the capsule at bedtime the evening before their second appointment. Dexamethasone is ingested the night before to ensure an almost complete suppression of cortisol the next morning (De Kloet et al., 1974; Carroll, 1977). Participants were also given a second envelope containing either propranolol or placebo and were instructed to ingest the capsule 30 minutes prior to their second appointment, which took place between 8h00 and 9h00 the day following dexamethasone administration.

During their second appointment, all participants completed the standardized Trier Social Stress Task (TSST) 30 minutes following arrival to the laboratory: an acute psychosocial stressor designed to elicit both SNS and the HPA axis activation (Kirschbaum, Pirke, & Hellhammer, 1993). Participants were told via a pre-recorded message that they will be evaluated on their verbal and non-verbal skills (i.e., posture, facial expression) in an impromptu mock interview by a panel of behavioral experts. Furthermore, they were also instructed that their performances would be video recorded for subsequent in-depth analysis. Participants were given eight minutes to prepare their presentations in a quite room, and then asked to present their speech in front of the panel of one male and one female judges. When the five minutes allotted for their speeches elapsed, participants were asked to count down from 1,022 in decrements of 13, where they must begin from 1,022 once again if they produce an incorrect response at any point in the sequence. The experience of a social-evaluative threat in terms of being exposed to a potentially negative judgment by others and of anticipating an uncontrollable outcome performance have been associated with the largest and most reliable cortisol responses compared to other laboratory stressors (Dickerson and Kemeny, 2004). These stress effects seem to reflect the assumptions of Mason (1975), who considered novelty, uncontrollability, unpredictability and ego involvement as the most potent factors eliciting substantial HPA responses.

All participants completed seven visual analogue scales assessing state anxiety, five salivary cortisol samples through passive drool and seven physiological measures

including heart rate and blood pressure corresponding to baseline, anticipation, post-TSST, and recovery.

HORMONAL ANALYSIS

All saliva samples were immediately frozen following collection and stored at -25°C until analysis. Salivary cortisol concentrations were analyzed in-house with commercially available DRG enzyme immunoassay kits (DRG International, Springfield NJ). Frozen saliva samples were thawed completely and centrifuged for 15 minutes at 3000 rpm immediately prior to assay. All cortisol samples were assayed in duplicate. For cortisol, the test used 100 μL of saliva per determination, had a lower limit of sensitivity of 0.537 ng/mL, a standard curve range from 0.012 μg/dl, to 3.0 μg/dl, an average intra-assay coefficient of variation (CV) of 8.8% and an average inter-assay CV of 5.1%. Cortisol levels were in the normal expected range reported by DRG (M=5.754, *SD*=3.143). There was no significant difference in their pre-performance cortisol levels between males (M=5.71, *SD*=2.57) and females (M=5.79, *SD*=3.69), $t(44)=.09$, $p=.17$ in the placebo condition, or post-performance cortisol levels between males (M=6.62, *SD*=2.37) and females (M=5.99, *SD*=4.43), $t(44)=-.60$, $p=.12$ in the placebo condition.

Results

Independent samples *t*-tests demonstrated no significant differences between males and females for total scores on depression ($t(90)=1.45$, $p=0.15$), anxiety ($t(90)=1.22$, $p=0.22$), anxiety sensitivity ($t(90)=1.01$, $p=0.36$), and adverse childhood experiences ($t(90)=1.418$, $p=0.16$).

CORTISOL

A One-way Analysis of Variance (ANOVA) was used to examine whether participants' total cortisol production over the course of the study (i.e., area under the curve with respect to ground; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) differed across four groups: 1) female placebo, 2) female drug, 3) male placebo, and 4) male drug. See Table 1 for the means and standard deviations for each of the four groups.

Table 1: Means and Standard Deviations of Total Cortisol Output.

Group	*n*	*Mean*	*SD*
Female, Placebo	23	411.72	246.08
Female, Drug	23	264.00	134.43
Male, Placebo	23	438.24	114.04
Male, Drug	23	168.68	67.56
Total	92	320.66	188.40

The one-way ANOVA of total cortisol output (see Table 2) revealed a statistically significant main effect, $F(3, 88)=15.438$, $p < .000$, indicating that not all four groups of resulted in the same total cortisol output.

Table 2: Analysis of Variance of Total Cortisol Output in Response to TSST.

Source	*SS*	*df*	*MS*	*F*	*p*
Between	1113768.11	3	371256.036	15.438	.000
Within	2116270.74	88	24048.531		
Total	3230038.85	91			

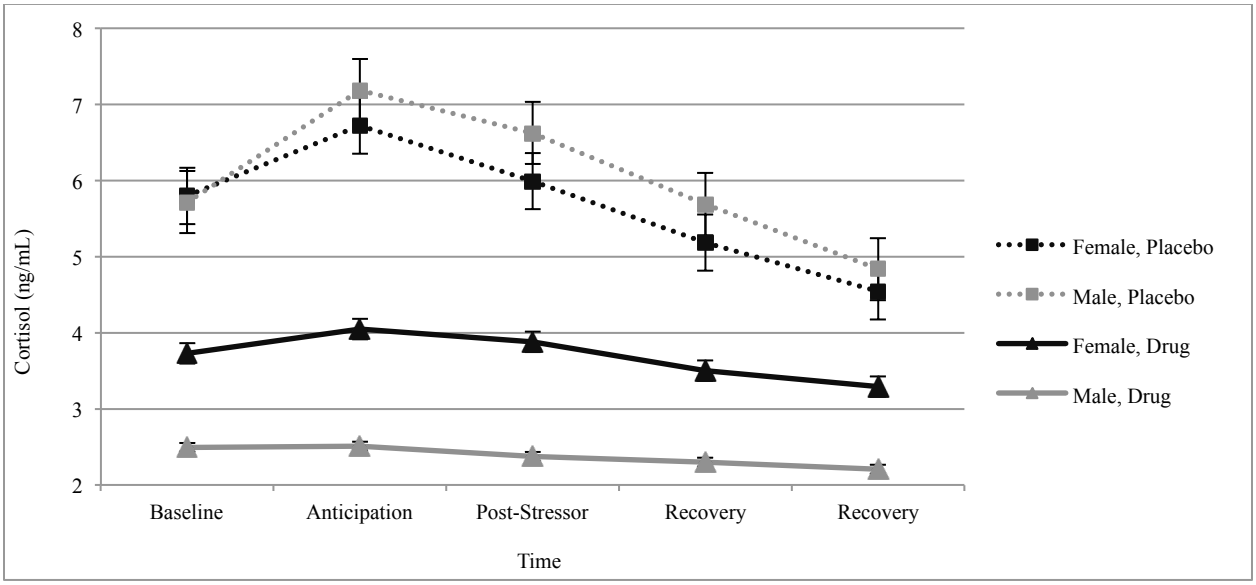
Post hoc comparisons using Fisher's least significant difference (LSD) procedures were used to determine which pairs of the four group means differed. These results are given in Table 3 and indicate that both male and female participants in the drug condition experienced a statistically significant suppression effect following dexamethasone administration compared to their placebo counterparts (Figure 1). While male and female participants in the placebo condition did not differ in total cortisol production in response to the TSST, female participants experienced significantly less suppression of cortisol compared to their male counterparts in the drug condition (p=.04).

Table 3: Post Hoc Results for Total Cortisol Output in Response to TSST.

Group	Mean	Mean Differences ($\bar{X}_i - \bar{X}_k$)			
		1	2	3	4
1. Female, Placebo	411.7215	–			
2. Female, Drug	264.0046	-147.7170*	–		
3. Male, Placebo	438.2398	26.51826	174.23522*	–	
4. Male, Drug	168.6809	-243.0407*	-95.32370*		–

*$p < .05$

Figure 1: Cortisol Reactivity Across Time by Sex and Drug Condition.



HEART RATE

A One-way ANOVA was used to examine whether participants' heart rate in response to the TSST (i.e., area under the curve with respect to ground) differed across four groups: 1) female placebo, 2) female drug, 3) male placebo, and 4) male drug. See Table 4 for the means and standard deviations for each of the four groups.

Table 4: Means and Standard Deviations of Total Heart Rate Output.

Group	*n*	*Mean*	*SD*
Female, Placebo	21	892.17	122.01
Female, Drug	23	767.14	128.49
Male, Placebo	23	836.63	130.81
Male, Drug	23	740.83	161.28
Total	90	810.13	145.90

The one-way ANOVA of heart rate (see Table 5) revealed a statistically significant main effect, F(3, 82)=5.308, p=.002, indicating that not all four groups of had the same cardiac response to the TSST.

Table 5: Analysis of Variance of Total Heart Rate Output in Response to TSST.

Source	*SS*	*df*	*MS*	*F*	*p*
Between	294212.208	3	98070.736	5.308	.002
Within	1515137.50	82	18477.287		
Total	1809349.71	85			

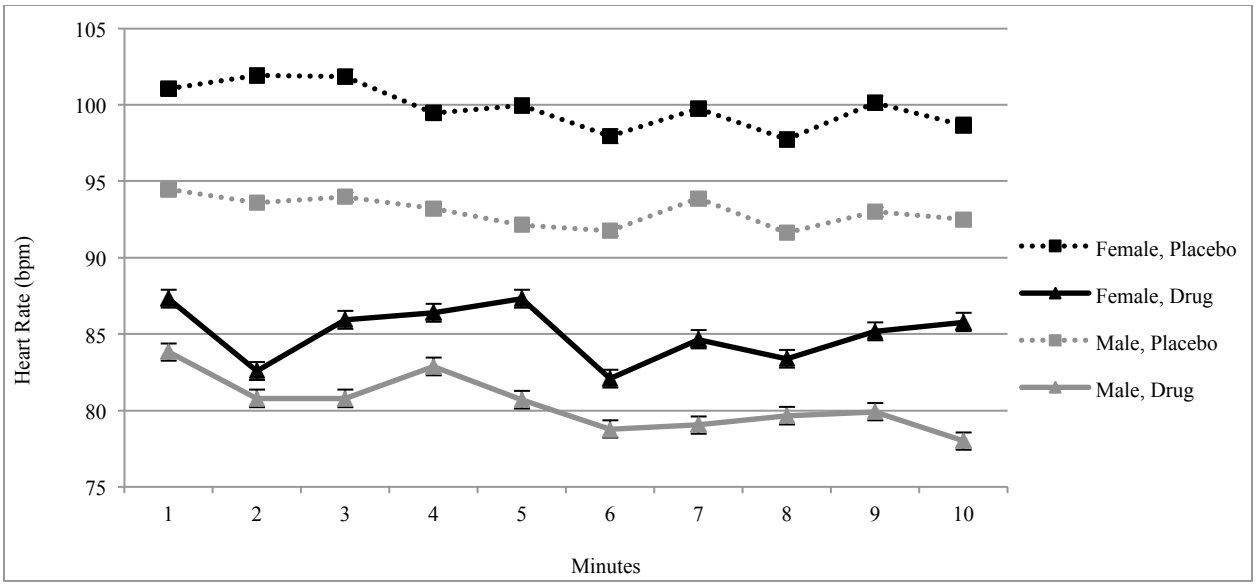
Post hoc comparisons using Fisher's least significant difference (LSD) procedures were used to determine which pairs of the four group means differed. These results are given in Table 6 and indicate that both male and female participants in the drug condition experienced a statistically significant suppression effect following propranolol administration compared to their placebo counterparts (Figure 2).

Table 6: Post Hoc Results for Total Heart Rate Output in Response to TSST.

Group	Mean	Mean Differences ($\bar{X}_i - \bar{X}_k$)			
		1	2	3	4
5. Female, Placebo	982.1667	–			
6. Female, Drug	767.1364	-125.0303*	–		
7. Male, Placebo	836.6304	-55.53623	69.49407	–	
8. Male, Drug	740.8250	-151.3417*	-26.31136	-95.80543*	–

*$p < .05$

Figure 2: Heart Rate Across Duration of the TSST by Sex and Drug Condition.



Discussion

The purpose of this study was to examine, in a nonclinical healthy sample, possible sex differences in response to a combined psychological stress challenge and drug administration. Results demonstrate that while men and women had similar cortisol response to the stressor in the placebo condition, women failed to suppress cortisol to the same degree as men in the drug condition, suggesting vulnerability of the HPA axis. These differences are not accounted for by sex differences in depression, anxiety, anxiety sensitivity, or by a history of adverse childhood experiences.

The lack of observed sex differences in HPA axis reactivity to laboratory stress in the placebo condition is consistent with several previous studies (Kirschbaum et al., 1999, 1992). To the best of our knowledge this is the first study to demonstrate sex differences in cortisol suppression in a combined psychological stress challenge and dexamethasone administration, highlighting possible linkage between sex differences in the prevalence of unipolar depression and women's hypercortisolemia due to resistance to glucocorticoid-mediated feedback.

Women's resistance to glucocorticoid feedback may be one critical biological factor contributing to the greater incidence and prevalence of depression in women (Young, 1998). In animal studies, estrogens enhance HPA axis activity (Viau & Meaney, 1991; Burgess & Handa, 1992) and, in response to stress females have consistently shown greater increases in ACTH and corticosterone compared with males (Kitay, 1961; Handa et al., 1994; & Armario et al., 1995). There is evidence in preclinical models that estradiol modulates mineralocorticoid (MR) and glucocorticoid (GR) receptors and thus

modifies cortisol negative feedback within the HPA axis (Peiffer et al., 1991; Burgess & Handa, 1992; Handa et al., 1994). Specifically, in estrogen treated rats, an increase in the magnitude and the duration of the corticosterone response to stress has been shown, suggesting an impairment of the GR-mediated negative feedback (Burgess & Handa, 1992).

The identification of the moderating role of sex on HPA axis response to stress has significant implications. Standard pharmacological treatment has proven to have limited efficacy in the treatment of major depression and related disorders (Joffe, 2011). For example, up to half of patients treated for major depression will have an antidepressant response, and only approximately one third will achieve remission of symptoms (Joffe, 2011). The possibility that a reduction in cortisol levels may be of benefit for the treatment of the symptoms of depression has been explored using cortisol biosynthesis inhibitors (see Murphy, 1997 for review). These studies have demonstrated that treatment with cortisol biosynthesis inhibitors does result in improvement of the depressive symptoms in the majority of patients. The results from the present study point to an important area of further research in both the prevention and treatment of depression.

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Vita

Shuo (Ellie) Jin obtained her Bachelor of Arts degree in Psychology at McGill University in Montreal, Canada. While at McGill, she completed her senior honors thesis under the supervision of Dr. Jens Pruessner where she examined sex differences in acute stress reactivity. Presently, Shuo's research explores the role of hormones in the pathogenesis of disorders such as anxiety, depression, and post-traumatic stress disorder. Outside of the laboratory, Shuo coordinates the Summer Undergraduate Research Experience (SURE) program for students traditionally underrepresented in the field of psychology, as well as the Psychology Department Graduate Student Diversity Committee. Shuo's clinical training has primarily focused on cognitive-behavioral therapy, interpersonal therapy and family systems theory. Clinically, Shuo enjoys working with students struggling with anxiety and depression using a variety of evidence based treatments.

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This thesis was typed the by the author, Shuo Jin.