



# Hormonal contraception use alters stress responses and emotional memory

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## ARTICLE INFO

### Article history:

Received 24 April 2012

Accepted 22 October 2012

Available online 3 November 2012

### Keywords:

Hormonal contraception

Norepinephrine

Cortisol

Emotional memory

Salivary alpha-amylase

## ABSTRACT

Emotionally arousing material is typically better remembered than neutral material. Since norepinephrine and cortisol interact to modulate emotional memory, sex-related influences on stress responses may be related to sex differences in emotional memory. Two groups of healthy women – one naturally cycling (NC women,  $n = 42$ ) and one using hormonal contraceptives (HC women,  $n = 36$ ) – viewed emotionally arousing and neutral images. Immediately after, they were assigned to Cold Pressor Stress (CPS) or a control procedure. One week later, participants received a surprise free recall test. Saliva samples were collected and later assayed for salivary alpha-amylase (biomarker for norepinephrine) and cortisol. Compared to NC women, HC women exhibited significantly blunted stress hormone responses to the images and CPS. Recall of emotional images differed between HC and NC women depending on noradrenergic and cortisol responses. These findings may have important implications for understanding the neurobiology of emotional memory disorders, especially those that disproportionately affect women.

Published by Elsevier B.V.

## 1. Introduction

Hormonal contraception has been used by women worldwide for over 50 years, but its effects on hormone responses to different stressors and emotional memory have remained largely unexplored. Estrogen/progestin contraceptives utilize negative feedback to the hypothalamus to inhibit the mid-cycle gonadotropin-releasing hormone (GnRH) surge (Lobo and Stanczyk, 1994). In addition, these synthetic hormones suppress the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary to inhibit the gonadal production of endogenous estrogen and progesterone. The suppression of endogenous estrogen and progesterone likely disrupts stress hormone activity (Kudielka and Kirschbaum, 2005), sex/stress hormone interactions and subsequently, memory for emotionally arousing stimuli.

Evidence for the association between sex and stress hormone activity comes from studies demonstrating that hormonal contraception use significantly reduces stress hormone responses to a stressor. Kirschbaum et al. (1999) examined hypothalamic-pituitary-adrenal (HPA) responses to the Trier Social Stress Test (TSST) in men, naturally cycling women in both the follicular and luteal phases, and women on oral contraceptives. Women on oral

contraceptives had similar salivary cortisol responses to TSST compared to women in the follicular phase of the menstrual cycle, but significantly blunted responses compared to men and women in the luteal phase of the menstrual cycle. These findings suggest that oral contraceptive use can alter HPA activity in response to a psychosocial stressor, and these effects are likely due to the corticosteroid-binding globulin (CBG) enhancing effect of ethinyl estradiol (Fujimoto et al., 1986; Kirschbaum et al., 1999; Kumsta et al., 2007).

In addition, Otterstetter et al. (1999) reported that the use of hormonal contraception can also alter the reactivity of the sympathetic stress system; in response to a maximal exercise task, women on hormonal contraception had significantly lower post-exercise concentrations of plasma norepinephrine relative to naturally cycling women.

What remains unknown, however, is how these oral contraceptive-induced differences in cortisol and salivary alpha-amylase reactivity may affect memory for emotionally arousing stimuli. Several studies, however, have examined how sex and stress hormones interact to influence emotional memory among naturally cycling women. For example, Andreano et al. (2008) found that the relationship between a post-training release of cortisol and memory for an arousing story changed depending on levels of circulating sex hormones; cortisol positively correlated with story recall only for women in the mid-luteal (high progesterone) phase.

The notion that sex hormones influence stress effects on memory is further supported by human imaging studies. For example, Goldstein et al. (2005) demonstrated that women in the late

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follicular (high estrogen) phase showed significantly decreased responses in several limbic, frontal, and hypothalamic regions compared to those in the early follicular (low estrogen and progesterone) phase. Moreover, van Wingen et al. (2008) demonstrated that high levels of synthetic progesterone significantly increased amygdala responses to emotional images relative to neutral images. In addition to these studies showing sex hormone influences on memory, clear sex differences have been shown in stress response circuitry activation between men and naturally cycling women such that mid-cycle hormonal changes in women reduced subcortical arousal, which was coupled with a reduction in cortical arousal (Goldstein et al., 2010).

The findings by Goldstein et al. (2005, 2010) and van Wingen et al. (2008) were further supported by a study that examined the influence of sex hormones on amygdala and hippocampal activity. Andreano and Cahill (2010) scanned naturally cycling women in the early follicular (low estrogen and progesterone) and mid-luteal (high progesterone) phases of the menstrual cycle while they viewed emotional and neutral images. Results showed that women in the mid-luteal phase had significantly enhanced activity in response to emotional images in the hippocampus and amygdala as compared to those in the early follicular phase. When compared to the results from Goldstein et al. (2005), these findings suggest estrogen and progesterone may have different roles in modulating the brain's arousal circuitry and potentially, emotional memory processing.

Based on the aforementioned evidence suggesting that sex steroid hormones and stress hormones interact to influence memory, it seems very likely that hormonal contraception should influence memory for emotional material. A recent study from our lab provides preliminary evidence for such an association by demonstrating an association between the use of hormonal contraception and altered memory for information from an emotional story (Nielsen et al., 2011). These findings suggest that additional research is necessary to better understand the effects of hormonal contraception on both hormonal responses to different stressors and subsequently, memory for different types of emotional stimuli.

The purpose of the present investigation was twofold. First, we sought to better characterize the nature of the blunted stress hormone responses that the literature indicates occur with hormonal contraception. Second, we wished to further explore whether and how hormonal contraception influences memory for emotional material.

Because of previous sex-related findings with both stress hormone responses and emotional memory, we examined whether hormone responses to emotionally arousing images and Cold Pressor Stress (CPS) differed between women on hormonal contraception and naturally cycling women. We selected these stressors to elicit a noradrenergic response at encoding (emotionally arousing images) and a post-training glucocorticoid response (CPS). To assess these hormone responses, we measured salivary alpha-amylase (sAA) as a biomarker for norepinephrine (Chatterton et al., 1996) as well as salivary cortisol levels. On the basis of prior research (Kirschbaum et al., 1999; Otterstetter et al., 1999), we predicted that women on hormonal contraceptives would have reduced cortisol responses to CPS and reduced sAA responses to the emotional images compared to naturally cycling women. We also investigated whether their memory for emotional slides differed with a surprise free recall test 1 week later. Since we wanted to explore differences between naturally cycling (NC) women and women on hormonal contraception (HC) who did or did not exhibit a stress hormone response to the emotional images or to the CPS, we also performed analyses with the women divided into "responder" and "non-responder" groups (Buchanan et al., 2006). Responder/Non-Responder criteria for sAA and cortisol responses will be discussed in the Methods.

To date, there has been limited work in humans on the relationships between norepinephrine, glucocorticoids, and memory consolidation in general (van Stegeren et al., 2007, 2010; Felmingham et al., 2012) and none with respect to potential sex hormone influences. However, based on previous research that identified sex influences on emotional memory (Andreano and Cahill, 2009), we hypothesized norepinephrine at encoding and post-training glucocorticoids would influence memory differently in naturally cycling women vs. women on hormonal contraception.

## 2. Methods

### 2.1. Participants

Ninety-eight female students from the University of California, Irvine between the ages of 18–35 ( $M=20.37$ ,  $SD=2.37$ ) participated in this study, which was approved by the University's Institutional Review Board. The subjects received course credit. All participants were non-smokers. Participants were asked to refrain from alcohol, caffeine, and cardiovascular exercise for 24 h prior to each experimental session to control for outside influences that could affect baseline salivary alpha-amylase and cortisol levels. To avoid contamination of salivary samples, participants were asked to fast 1 h prior to each experimental session as well as refrain from brushing teeth within the hour before their appointment.

Of the participants, 50 were NC women who reported having regular menstrual cycles and 45 were women currently on a combined HC regimen for at least 1 month. Of these, six women were excluded for not returning for the second experimental session (1 NC, 3 HC), for having baseline sAA levels more than three standard deviations above the mean (1 HC), and for having a cortisol response to CPS that was more than three standard deviations above the mean (1 HC). An additional 11 women (7 NC, 4 HC) were excluded from the final analyses because they exhibited a cortisol response to the control condition for Cold Pressor Stress (CPS).

The final analyses thus included data from 42 NC women (15 Follicular, 27 Luteal) and 36 HC women. All women reported that they were in good health, and the average body-mass-index (BMI) values for NC ( $M=21.78$ ,  $SD=2.71$ ) and HC ( $M=22.15$ ,  $SD=3.98$ ) women did not differ significantly. Of the women included in the final analyses, seven used prescription medications other than hormonal contraception (5 NC, 2 HC). Of the HC women, 25 took monophasic drugs and 11 used triphasic pills. All the HC women were on drugs that contained ethinyl estradiol, and the content of this synthetic estrogen varied between .015 mg and .03 mg/dose.

### 2.2. Procedures

All experimental sessions were conducted between the hours of 12:00 and 18:00 to minimize the effects of circadian rhythm on sAA and cortisol levels. During the first experimental session, participants filled out a screening questionnaire and three cognitive assessments including the BEM Sex Roles Inventory (BEM; Bem, 1981), the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), and the Mehrabian test (Mehrabian, 1994). The BEM was implemented to assess masculine and feminine influences/traits within each individual participant, whereas the PANAS was given to measure the participants' affect at the time of testing. The Mehrabian was implemented to assess levels of trait anxiety (Mehrabian, 1994).

Fifteen minutes after their arrival, participants provided a 1-mL saliva baseline sample ("pre-slideshow"/"pre-CPS" sample) using the "passive drool" collection method (Shirtcliff et al., 2001). Following the baseline saliva sample, participants moved into a solitary experimental room where they watched a slideshow comprised of twelve arousing positive images, twelve arousing negative images, and twelve neutral images from the International Affective Picture System (IAPS) (Lang et al., 1997). Each image was displayed for 10 s and slides were presented in random order. Following each image, participants were asked to rate the image on the degree of emotional arousal and valence; subjects had 5 s to make each rating using a 1–9 scale (Adolphs et al., 2001). The scale is described in Section 2.3. A second 1-mL saliva sample ("post-slideshow" sample) was taken immediately after the 12 min slideshow.

Participants were then randomly assigned to either a CPS (24 NC, 23 HC) or control condition. Those assigned to the CPS condition immersed their right hand in ice water (1–4 °C) for up to 3 min, whereas participants in the control condition immersed their right hand in warm water (37 °C) for the same length of time. Subjects in both conditions were informed prior to the test that they could remove their hand from the water at any time without penalty. Of the participants included in the final analyses, seven women removed their hand before the end of the 3-min CPS session (4 HC, 3 NC). These women were included in the final analyses because they completed at least 30 s of the CPS task. Upon completion of CPS or control condition, participants provided a third 1-mL saliva sample. All participants were instructed to refrain from any stressful activities for the remainder of the session. Additional samples were collected 15 and 25 after the CPS or control condition.

One week later, participants returned and provided one 1-mL saliva sample after a 15-min acclimation period. This sample was collected to maintain a consistent procedure across the two experimental sessions and was not analyzed for levels of sAA

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