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Low estradiol is linked to increased skin conductance, but not subjective anxiety or affect, in response to an impromptu speech task

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ABSTRACT

Low estradiol is associated with impaired extinction of conditioned physiological fear responses (e.g. skin conductance) in females. As fear extinction is the laboratory basis of exposure therapy for anxiety disorders, it has been speculated that estradiol may be related to the effectiveness of treatment for anxiety. The present study extended past research by examining whether estradiol is related to physiological and subjective fear responses during the impromptu speech task, where participants perform a surprise speech to camera. This task elicits psychosocial fear, and thus has relevance for social anxiety disorder (SAD). We used a quasi-experimental design with two groups of women: 39 naturally cycling women, and 19 women taking hormonal contraceptives. Based on the measured serum levels, naturally cycling women were further divided into women with higher- vs. lower estradiol levels. Compared to those with higher estradiol, women with lower estradiol, and those using hormonal contraceptives (chronically suppressed estradiol) displayed higher speech-elicited skin conductance yet reported no differences in subjective anxiety or affect. Conversely, irrespective of estradiol status, compared to those with low self-reported social anxiety, participants with higher social anxiety exhibited greater subjective anxiety and affect, yet no differences in skin conductance. These results demonstrate that the relationship between estradiol and physiological fear responses extends to psychosocial tasks. However, the dissociations between physiological and subjective measures highlight the need to consider the relevance of different response outputs so that the potential impact of estradiol on the treatment of anxiety disorders can be better understood.

1. Introduction

Anxiety disorders are characterized by impaired fear regulation. Exposure therapy is the most effective psychotherapeutic treatment for anxiety (Vervliet et al., 2013), involving exposure to situations that evoke fear, leading to a reduction in this emotion. Evidence suggests sex hormones modulate fear extinction, the laboratory basis of exposure therapy, which involves repeated non-reinforced exposure to a fear-eliciting conditioned stimulus (CS; i.e., a stimulus that was previously paired with an aversive unconditioned stimulus; US, like shock). Low estradiol has been linked to impaired extinction learning (slower reduction in fear during extinction training) and/or impaired extinction recall (heightened fear when re-presented with the extinguished CS) in female rodents (Chang et al., 2009; Graham and Daher, 2016; Graham and Milad, 2013; Graham and Scott, 2018; Milad et al., 2009; Milligan-Saville and Graham, 2016; Zeidan et al., 2011) and women (Antov and Stockhorst, 2014; Glover et al., 2012; Graham and Milad, 2013; Li and Graham, 2016; Milad et al., 2010; Milligan-Saville and Graham, 2016; Pineles et al., 2016; Wegerer et al., 2014; White and Graham, 2016; Zeidan et al., 2011). As extinction involves new learning (Quirk and Mueller, 2008), estradiol may influence the molecular processes underlying memory consolidation (Cover et al., 2014). It has been speculated that reduced estradiol may increase women's vulnerability to anxiety, or impact exposure therapy (Cover et al., 2014; Glover et al., 2015; Li and Graham, 2017). Indeed, we have reported that spider phobic women with higher estradiol responded more favorably to exposure therapy relative to women with lower estradiol (Graham et al., 2018).

Human research in this area has generally used physiological measures of fear, primarily skin conductance response (SCR; e.g. Antov and Stockhorst, 2014; Li and Graham, 2016; Milad et al., 2010; Pineles et al., 2016), although two studies have found similar results with fear-potentiated startle (FPS; Glover et al., 2012, 2013). The few studies that have assessed subjective measures (e.g. US expectancy) have reported dissociations between physiological and subjective responses, with lower estradiol associated only with heightened physiological, but not subjective, responses (Glover et al., 2013; Li and Graham, 2016; White and Graham, 2016). It is therefore difficult to determine whether

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estradiol-related differences in SCR during extinction are reflective of, or independent from, the fear response. This question is difficult to address using fear extinction protocols as these studies typically assess CS-US contingency awareness, rather than subjective emotional state. One way to investigate this further is to use an alternative task with strong connections to the pathology and treatment of anxiety to provide convergent evidence that estradiol is linked to fear responses. For example, the impromptu speech task, in which participants perform an improvised speech to video camera or audience, is used in research as a psychosocial stressor (e.g. Lam et al., 2009), as a tool to evoke fear in non-clinical participants (e.g. Wong and Moulds, 2009) and as an exposure procedure in clinical populations, including SAD (e.g. Hofmann and Otto, 2008; Niles et al., 2015). Indeed, fear of public speaking is the most common fear in SAD (Kessler et al., 1998), and is prevalent in the general population (Stein et al., 1996). Considering its use as a strategy in exposure therapy, both the speech task and fear extinction may activate common clinically relevant processes. For example, undergoing the speech may elicit new learning that the predicted catastrophic consequences do not occur, similar to the new learning that takes place during extinction. This task also incorporates other benefits of being a non-tactile fear stimulus, unlike the shock predominantly used in studies of hormonal effects on extinction (but see Glover et al., 2012; Wegerer et al., 2014). As pain thresholds change across the menstrual cycle (Riley et al., 1999), the link between estradiol and extinction could be explained by estradiol-related changes in pain sensitivity rather than differences in fear responses.

The speech task is one component of the Trier Social Stress Task (TSST; Kirschbaum et al., 1993), which is used to examine sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis responses to stress. Women generally exhibit lower HPA responses than men (Kajantie and Phillips, 2006); differences that are partly mediated by sex hormones (Barel et al., 2018; Juster et al., 2016). Although studies examining the menstrual cycle have produced inconsistent results, hormonal contraceptives suppress HPA responses during the TSST, likely due to increased corticosterone-binding globulin (Kajantie and Phillips, 2006; Kirschbaum et al., 1999). Fewer studies have assessed the relationship between sex hormones and SNS responses, although Barel et al. (2018) demonstrated that TSST-induced increases in alpha amylase (a molecular marker of SNS activity) were attenuated when sex hormone levels were statistically controlled for, suggesting hormonal regulation of the SNS. We are unaware of studies that have assessed the relationship between sex hormones, hormonal contraceptive use, and skin conductance (a physiological marker of SNS activity) during the TSST, although Merz (2017) demonstrated elevated blood pressure following the cold pressor task (a physical stressor) amongst women using hormonal contraceptives.

Given the above, the impromptu speech may be an effective tool with which to provide convergent insights to the dissociable relationship between estradiol, and physiological and subjective responses documented in previous extinction studies. In the current experiment, naturally cycling women with higher and lower levels of estradiol, plus women using hormonal contraceptives (which suppress endogenous estradiol), underwent a video-recorded impromptu speech task. Skin conductance, changes in self-reported state anxiety, and positive and negative affect were measured throughout. Based on research linking low estradiol with increased SCR during extinction (reviewed in Li and Graham, 2017), and research linking hormonal contraception with elevated stress-induced blood pressure (Merz, 2017) we predicted that women with low estradiol (naturally or due to hormonal contraceptive use) would show increased skin conductance compared to women with high estradiol. We further predicted that low estradiol women would report higher state anxiety, higher negative affect, and lower positive affect, as we expected that the differences in skin conductance would be concordant with subjective fear.

2. Method

2.1. Participants

Fifty-eight women (18–35 years old, mean age 21.8 years) were recruited from first-year psychology courses and community advertisements. Participants reported no history of DSM-V disorders and no history of endocrinological conditions (e.g. polycystic ovary syndrome). We used a quasi-experimental design with two groups of women: 39 naturally cycling women with regular menstrual cycles, and 19 women taking hormonal contraceptives (see Table S1 in supplement for contraceptive details). Based on the measured serum levels, naturally cycling women were further divided into women with higher- vs. lower estradiol levels. All procedures were approved by the University of New South Wales Human Research Ethics Committee, and written informed consent was obtained from all participants.

2.2. Measures

2.2.1. Pre-experimental subjective trait measures

A battery of standardized subjective measures was administered to participants at the start of the session, incorporating: (a) Fear of Negative Evaluation Scale (FNE; Watson and Friend, 1969), a 30-item true/false self-report measure of trait social-evaluative anxiety that is widely used in non-clinical populations to identify high and low socially anxious individuals; (b) Beck Anxiety Inventory (BAI; Beck and Steer, 1993), a 21-item scale that measures anxiety symptoms experienced during the past month. Items are rated using a 4-point scale (0 = *not at all,* 3 = *severely)*; (c) Beck Depression Inventory II (BDI; Beck et al., 1996), a 21-item scale that measures depression symptoms experienced during the previous two weeks. Items are rated using a 4-point scale (0 = *not at all,* 3 = *severely)*; (d) State-Trait Anxiety Inventory (Spielberger et al., 1983) Trait Version (STAI-T), a 20-item self-report measure that assesses predisposition to anxiety. Participants are asked to rate each item according to how they "generally feel", using a 4-point scale (1 = *almost never*, 4 = *almost always*).

2.2.2. Skin conductance recording and analysis

Skin conductance was recorded via an ADInstruments GSR amp (FE116) using constant voltage (22 mV_{rms} at 75 Hz) AC excitation through a stainless-steel dry bipolar electrode (MLT116 F) that was Velcro strapped to the distal phalanx of the index and middle fingers of the non-dominant hand. The analogue inputs were digitized by an ADInstruments Powerlab 8/35 data acquisition system (PL3508), then sampled and processed using LabChart software.

Skin conductance was continuously recorded from the start of the baseline period to the end of recovery. Event markers were used to identify each of the five key phases during the task: the three-minute baseline period (BASELINE), the period when participants were first told about the speech (INSTRUCTIONS), the one-minute preparation period (PREPARATION), the three-minute speech (SPEECH), and the three-minute recovery period (RECOVERY). All skin conductance values were square-root transformed to reduce heteroscedasticity.

Due to the restrictions of the GSR recorder, which forced participant skin conductance to be baselined to zero before data could be recorded, skin conductance levels were assessed as a change from *average* baseline skin conductance (i.e. as a change from average skin conductance level during the full three-minute baseline period). This ensured a more stable baseline measure was used for each participant, while also making the data more interpretable by minimizing the possibility of "negative" skin conductance values, due to skin conductance falling below the initial value of zero during the three-minute baseline period. Furthermore, given the large individual differences in skin conductance (Boucsein et al., 2012), the use of change scores also controlled for any variation in baseline skin conductance between participants.

Mean change from baseline was assessed during the *first* 30 s for