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Estradiol moderates the relationship between state-trait anxiety and attentional bias to threat in women☆

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ABSTRACT

Anxiety disorders are characterized by impaired fear extinction and heightened attentional allocation to threatening stimuli. The sex hormones estradiol and progesterone modulate fear extinction in female rats and women; whether these hormones are similarly related to attentional biases to threat has not been examined. In the present study 74 women (53 cycling, 21 using hormonal contraception), and a comparison group of 30 men, completed standard assessments of state-trait anxiety, as well symptoms of depression, anxiety and stress, followed by a computerized assessment of attentional bias, the dot-probe task. Women's endogenous estradiol and progesterone levels were ascertained by a blood sample. No differences in attentional bias were found dependent on sex or hormonal contraceptive use. Estradiol was the only variable measured that was independently positively correlated with attentional bias to threat. Regression analyses revealed a bi-directional relationship between state-trait anxiety, symptoms of anxiety and stress, and attentional bias that was moderated by estradiol, such that a positive relationship was observed amongst women with higher estradiol, and a negative relationship was observed amongst women with lower estradiol. Together, these results indicate that under conditions of anxiety and stress, women may attend to threat differently depending on endogenous estradiol levels, being avoidant when estradiol is lower, and vigilant when estradiol is higher. A more nuanced understanding of the role for attention in anxiety disorders amongst women may be developed by taking hormonal status into consideration.

1. Introduction

Considerable evidence suggests that many features of anxiety disorders are sexually dimorphic, with the prevalence, severity, and chronicity of anxiety being greater in females relative to males (Li and Graham, 2017). Sociocultural factors undoubtedly contribute to these dimorphisms (McLean and Anderson, 2009), although fluctuations in sex hormones also appear to impact anxious symptoms in women. For example, women's risk for anxiety increases during puberty (Paus et al., 2008), post-partum (Ross and McLean, 2006), and *peri*-menopause (Bromberger et al., 2013). Additionally, the severity of anxious symptoms fluctuates across the menstrual cycle (Li and Graham, 2017). Combined, these findings underscore the importance of considering sex and hormonal status as biological factors of interest when examining the pathogenesis of anxiety.

Two key psychological processes that are relevant to anxiety are fear extinction and the allocation of attention to threatening stimuli (Bishop, 2007). Fear extinction refers to the reduction in fear that results from repeated exposure to a fear-eliciting cue in the absence of aversive outcome. Not only does extinction form the basis of exposure therapy for anxiety disorders, but also, deficits in extinction are considered a hallmark of anxiety that contribute to its development and maintenance (Graham and Milad, 2011). In addition to impaired extinction, anxiety disorders are characterized by the preferential allocation of attention to threatening, relative to neutral, stimuli (Mathews and MacLeod, 2005). Biased attention to threat correlates positively with state and trait anxiety, and is generally not observed amongst individuals with low trait anxiety under conditions of mild threat (Bar-Haim et al., 2007). Like extinction, biases in the attentional processing of threatening stimuli are considered central to the development and maintenance of anxiety disorders, and evidence suggests that computerized attentional training interventions that promote preferential processing of positive or neutral stimuli reduce anxious symptoms (Hakamata et al., 2010). Importantly, fear extinction and attentional biases are easily measured using well-validated procedures, and thus represent clinically relevant processes that are highly amenable to laboratory investigation.

Recent research has established that sex hormones play a

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modulatory role in fear extinction, with female rats and women exhibiting better extinction (comparable to males) during periods of higher estradiol and progesterone, relative to periods of lower estradiol and progesterone (due to changing menstrual cycle phase, or hormonal contraceptive use; Chang et al., 2009; Graham and Daher, 2016; Graham and Milad, 2013; Graham and Scott, 2018; Gruene et al., 2014; Milad et al., 2009; Milad et al., 2010; Milligan-Saville and Graham, 2016; Pineles et al., 2016; Rey et al., 2014; White and Graham, 2016; Wegerer et al., 2014; Zeidan et al., 2011). Similar findings have been reported for women with spider phobia (Li and Graham 2016), and posttraumatic stress disorder (Glover et al., 2012; Pineles et al., 2016, although in the latter study a combination of higher progesterone and lower estradiol predicted impaired extinction). In contrast to extinction, sex has rarely been considered in studies of attentional bias, and if sex differences exist, they are subtle, and influenced by anxiety and stress. For example, in the dot-probe task, Carr et al. (2016) reported that women exhibited attentional avoidance of emotional faces under basal conditions, and attentional vigilance following stress. Men showed a small attentional vigilance under both conditions. In the spatial-cueing task, Waters et al. (2007) found that the emotional content of cues did not alter attentional responses in men. In contrast, threatening cues led to heightened attention to threat amongst high trait anxious women, and attentional avoidance amongst low trait anxious women. Similarly, Tan et al. (2011) reported that high trait anxious women showed difficulty disengaging attention from threat; in contrast, high trait anxious men exhibited attentional avoidance of threat. Finally, a recent meta-analysis of 23 studies using the dot-probe task revealed no differences in performance between men and women (Campbell and Muncer, 2017).

Recently, the possibility that endogenous hormonal levels might contribute to variance in attentional processing has been examined. Masataka and Shibasaki (2012) reported that the faster detection of threatening versus neutral stimuli in a visual search task was exacerbated during the luteal phase of the menstrual cycle, relative to the early and late follicular phases. As estradiol and progesterone levels are higher in the luteal phase, this might indicate a hormonal-mediated enhanced detection of threat. This interpretation is consistent with a subsequent finding that, relative to the follicular phase, women in the luteal phase generated faster eye movements towards emotional facial stimuli, indicative of hypervigilance (Wolohan et al., 2013). However, no study has directly assessed the relationship between sex hormones and attentional bias, or whether sex hormones moderate the relationship between anxiety and attentional bias. Moreover, existing studies have not differentiated between potential contributions of estradiol and progesterone. In the present study we employed a standardized dot-probe procedure (MacLeod et al., 2007), and obtained measurements of estradiol and progesterone in female participants who were cycling or using hormonal contraceptives. A male comparison group was also included. All participants provided self-ratings of state-trait anxiety, and symptoms of depression, anxiety, and stress. Based on findings from Masataka and Shibasaki (2012), and Wolohan et al. (2013), the primary hypothesis was that estradiol and/or progesterone would positively correlate with biased attention to threat. Further, we speculated that the expected positive relationship between state-trait anxiety and attentional bias would be enhanced with heightened estradiol and/or progesterone.

2. Methods

2.1. Participants

One hundred and four participants (74 women) were recruited via a public online research participation system and paid $20 per hour, or received course credit, for their participation. Inclusion criteria included males and females aged 18–35 years old, with English language proficiency. Additionally, female participants were required to have regular menstrual cycles (n = 53) or be taking hormonal contraception (n = 21). In order to achieve wide variance in hormonal levels, cycling female participants were invited to participate in the experiment across all phases of the menstrual cycle. Based on serum estradiol and progesterone analyses, 52.8% of cycling women had values in the expected range for the early follicular phase, 24.3% had values in the expected range for the late follicular phase, and 22.6% had values in the expected range for the luteal phase. Although not the prime focus of the study, men were included for comparative purposes.

2.2. Questionnaires

To assess for trait and state levels of anxiety, participants were administered both forms of the State-Trait Anxiety Inventory (STAI-T, and STAI-S, respectively; Spielberger et al., 1983). The STAI consists of two 20-item self-report measures. The STAI-T assesses how participants "generally feel", and the STAI-S assesses how participants feel "right now, at this moment". The STAI has excellent internal consistency and the Trait form has excellent test-retest reliability (Barnes et al., 2002). To assess for symptoms of depression, anxiety, and stress over the preceding week, participants were administered the Depression Anxiety Stress Scales 21 (DASS21; Lovibond and Lovibond, 1995), which is a 21-item questionnaire with seven items per scale. The DASS21 possess high internal consistency, with reliability estimates slightly higher for the depression and stress scales compared to the anxiety scale (Henry and Crawford, 2005).

2.3. Stimulus words

The 96 word pairs used in experimental trials were those provided by MacLeod et al. (2007). Each pair consisted of one threat and one nonthreat word, matched for word length and frequency of usage. Stimuli used during practice trials were pairs of numbers, written as words. Although emotional pictures are frequently used as stimuli in the dot-probe task, given the novelty of the experimental focus (i.e., hormonal associations with attentional bias), we elected to use the word stimuli with which the paradigm that we employed was originally validated, to ensure the validity of our assessment of attentional bias. Indeed, evidence suggests that threat related words and pictures yield comparable attention biases in anxious individuals (Bar-Haim et al., 2007).

2.4. Equipment and attentional probe software package

BenQ computer monitors were set at 800 × 600 screen resolution. MacLeod et al.'s (2007) online version of the attentional Dot Probe software package was installed on INQUISIT 4 and the script was configured in line with their parameters. Briefly, each trial commenced with a 500 msec presentation of three adjacent crosses in the center of the screen, followed by a 500 msec presentation of a word pair. After the word pair disappeared, a probe stimulus (either the symbol " < " or " > ") appeared in the spatial location previously occupied by one of the items in the word pair, and participants were required to respond by pressing either the " < " or the " > " key, corresponding to the probe's identity. In total, 10 practice and 96 experimental trials were delivered, with an inter-trial-interval of 1000-msec. INQUISIT 4 recorded response times (RTs) for individual trials, calculated as the interval elapsing between the probe presentation and keypad response.

2.5. Serological assessment

A venous blood sample was drawn from each female participant approximately 15 min after completion of the dot-probe task at a pathology service located within walking distance from the University. Serum hormone concentrations were analyzed by Healthscope Pathology Services. Estradiol levels were analyzed using an ADVIA