Psychoneuroendocrinology 87 (2018) 20–26

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Neural activity during traumatic film viewing is linked to endogenous estradiol and hormonal contraception

Stephan F. Miedl[a,*,1], Melanie Wegerer[a,b,1], Hubert Kerschbaum[c], Jens Blechert[a,d], Frank H. Wilhelm[a]

[a] Department of Psychology, Division of Clinical Psychology, Psychotherapy, and Health Psychology, & Clinical Stress and Emotion Lab, University of Salzburg, Austria
[b] University Clinic of Psychiatry and Psychotherapy, Medical University of Vienna, Austria
[c] Department of Cell Biology, University of Salzburg, Austria
[d] Centre for Cognitive Neuroscience, University of Salzburg, Austria

ARTICLE INFO

Keywords:
Affective neuroscience
Neuroendocrinology
Estradiol
Hormonal contraception
Medial prefrontal cortex
Anterior cingulate cortex
Intrusion
Posttraumatic stress disorder

ABSTRACT

Women are at higher risk for Posttraumatic Stress Disorder (PTSD) and recent research has highlighted a modulating role of female sex hormones for cognitive and emotional processes potentially underlying PTSD symptoms. However, studies combining fMRI recordings of brain activity during trauma film viewing with assessment of female sex hormones are missing. The trauma film paradigm – a widely used experimental analogue for trauma exposure – confronts healthy participants with traumatic film clips and thus allows studying peritraumatic processing under laboratory conditions. Following this paradigm, the current fMRI study examined the role of endogenous estradiol and synthetic sex hormones for the neural processing of traumatic (i.e., depicting interpersonal violence) vs. neutral films in 53 healthy women (mean age 22.3 years; 23 using hormonal contraception, HC). As predicted, traumatic films strongly activated areas of the fear processing network, such as amygdala, insula, and dorsal anterior cingulate cortex. Estradiol levels in women not using HC were positively correlated with ventromedial prefrontal activity. Furthermore, women using HC as compared to women without HC demonstrated heightened insula and dorsal anterior cingulate cortex activity during traumatic film viewing. These experimental results highlight the effects of both gonadal hormone status and HC intake on peritraumatic processing in neural regions relevant for emotion generation and regulation that have been found to be abnormal in PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a highly disabling condition with women being at higher risk (Breslau et al., 1997). Cognitive-behavioral models state that peritraumatic processing plays an essential role for the occurrence and persistence of PTSD symptoms including intrusive memories (Ehlers and Clark, 2000). This assumption is supported both by investigations in trauma-exposed individuals (Ozer et al., 2003) as well as healthy subjects experiencing experimental stressors – such as traumatic film clips – in the laboratory (Holmes and Bourne, 2008). General neural models of PTSD propose amygdala, insula, and dorsal anterior cingulate cortex (dACC) to be hyperreactive and positively correlated with PTSD symptom severity, whereas the ventromedial prefrontal cortex (VMPFC, including rostral anterior cingulate cortex, rACC) are typically hypoactivated, thereby possibly releasing control over the amygdala (Fragkaki et al., 2016; Pitman et al., 2012; Rauch et al., 2006).

Recent research suggests that female sex hormones might play a modulatory role for cognitive-emotional processes underlying PTSD. It has been observed that PTSD symptom severity varies across menstrual-cycle phase (Bryant et al., 2011; Nillni et al., 2015). This might be due to estradiol – the predominant circulating estrogen during reproductive years – as suggested by laboratory based experimental research on analogue models of PTSD (Maeng and Milad, 2015; Stockhorst and Antov, 2015). Fear conditioning studies – modelling acquisition and extinction of fear as it occurs during and after a traumatic event – found a beneficial effect of higher estradiol levels for both extinction and retention of extinction memory in healthy participants (Graham and Milad, 2013; Wegerer et al., 2014) and PTSD patients (Glover et al., 2012). Fittingly, higher estradiol levels were also observed to be related

* Corresponding author at: Department of Psychology, Division of Clinical Psychology, Psychotherapy, and Health Psychology University of Salzburg, Hellbrunnerstrasse 34, 5020 Salzburg, Austria.
E-mail address: stephan.miedl@sbg.ac.at (S.F. Miedl).
[1] These authors contributed equally to this work

http://dx.doi.org/10.1016/j.psyneuen.2017.10.006
Received 29 March 2017; Received in revised form 26 September 2017; Accepted 5 October 2017

to fewer and weaker intrusive film memories that healthy women reported two days after having watched traumatic film clips embedded as unconditioned aversive stimuli in a fear conditioning paradigm (Wegerer et al., 2014). On the neural level, Zeidan et al. (2011) showed that estradiol modulated VMPFC and amygdala activity during fear extinction and its maintenance. These results correspond with findings by Goldstein et al. (2005) reporting enhanced emotional arousal as well as activity in stress-related brain circuits including the amygdala, dACC, and VMPFC/orbitofrontal cortex during viewing of negative vs. neutral pictures in women during the (low-estradiol) early follicular as compared to the (high-estradiol) midcycle phase. A protective effect of estradiol for emotional processing is also suggested by Albert et al. (2015) reporting that estradiol modulated hippocampal activity and attenuated negative mood in response to stress. Finally, Engman et al. (2016) observed lower amygdala connectivity with dorsal ACC in women with high estradiol, which they interpreted in terms of a potential beneficial effect of estradiol in emotion regulation. Critically, estradiol is proposed to exert its effects through a number of interactions with other endocrine (such as the hypothalamic-pituitary-adrenal axis) and neurotransmitter systems (including serotonin) and estrogen receptors are widely expressed in neural structures of the emotion regulation circuit including the PFC, amygdala, and hippocampus (Briscione et al., 2017; Montague et al., 2008; Östlund et al., 2003).

Another line of research has investigated a role of hormonal contraception (HC) for cognitive-emotional processes underlying PTSD. Combined oral contraceptives contain ethinyl-estradiol, as a synthetic agonist for estradiol receptors, and a progestin. HC exert their effect via inhibition of ovulation by decreasing ovarian production of estrogens and progesterone. Thus, endogenous estradiol and progesterone are tonically low under HC, while synthetic female sex hormones are high. With respect to relationships between HC and PTSD, Ferree et al. (2012) found that female sexual assault survivors that used HC at the time of assault reported less intrusive memories when being interviewed six months after the assault than women not using HC. Studies investigating effects of HC on processing of aversive stimuli in the laboratory, however, yielded mixed results. Several fear conditioning studies suggest alterations under HC, such as impaired recall of extinction memory (Graham and Milad, 2013) and enhanced conditioned responding during extinction as indexed by activation in amygdala, ACC, VMPFC, and thalamus (Hwang et al., 2015; Merz et al., 2011). Petersen and Cahill (2015), however, reported decreased bilateral amygdala reactivity in response to aversive pictures in HC-using women. Importantly, recent longitudinal data suggest that HC intake induces structural reorganization in the brain's emotion regulation circuit; i.e., left amygdala/anterior parahippocampal gyrus volume and changes in resting state functional connectivity of this region with dorsolateral prefrontal cortex after three months of HC intake (Lisofsky et al., 2016; see also Petersen et al., 2014). In sum, despite growing evidence, the direction of effects of HC on aversive processing and its neurobiological underpinnings are still rather unclear. Likewise, while effects of endogenous female sex hormones on brain physiology and structure are increasingly uncovered, the neuronal targets of their synthetic analogs contained in HC are still largely unknown. Importantly, a limitation of the existing studies on estradiol or HC-mediated neural effects is that they mainly used paradigms and stimuli (e.g., pictures or electric stimulation) that have relatively poor correspondence with real-life traumatic events and thus limited explanatory value for the formation of PTSD symptoms.

The present study combined fMRI recordings of brain activity during trauma film viewing with assessment of female sex hormones and HC status. By utilizing film clips depicting severe interpersonal violence (as compared to neutral content) and thus portraying potentially traumatic material, we expected activity in typical threat-processing brain regions such as amygdala, insula, and dACC. Based on the laboratory based research summarized above, we expected a positive correlation between estradiol levels and medial prefrontal (VMPFC, rACC) fear regulating activity in naturally cycling women. Furthermore, we predicted alterations in the fear processing network, including amygdala, insula, ACC, and VMPFC in HC users vs. naturally cycling women.

2. Materials and methods

2.1. Participants

A total of 53 healthy women (aged 18–34 years) participated in the study. Participants reported no current mental or neurological disorders, no current use of prescriptive medication except oral hormonal contraceptives (HC group; N = 23; see Table S4) and no current alcohol or drug dependence. Furthermore, participants who reported past experiences of severe interpersonal violence or excessive consumption of violent material by TV, films, or video games (more than 2–3 times per week) were not included in the study. All women in the HC group were using combined oral contraceptive pills including ethinylestradiol as well as a progestin for at least six months. Women in the NO–HC group (N = 30) had to report regular menstrual cycles and to be free of hormonal contraceptives for at least three months to preclude any influences of external hormonal administration. Free-cycling women were tested at any time point during their menstrual cycle. Still, menstrual cycle phase was assessed for descriptive purposes by asking women about the first day of their last menses. Additionally, onset of the next menses was evaluated at follow-up to confirm cycle phases. All participants read and signed an informed consent form that had been approved by the ethics committee of the University of Salzburg and received monetary compensation or course credit for participation.

2.2. Procedure

After being welcomed to the laboratory and providing informed consent, participants completed several questionnaires including the assessment of general medical and psychological health conditions (customized questionnaire including questions concerning participants' menstrual cycle, usage of hormonal contraception, neurological or psychological disorders) as well as trait anxiety (STAI-trait; Laux and Spielberger, 1981). Next, participants were asked to gently flush out their mouth with some water in preparation for the subsequent drawing of the saliva sample before they were placed in the MRT. The task included four blocks (two traumatic and two neutral). Traumatic and neutral film clips were closely matched with respect to number of actors, movements, number of film cuts, and sound pitch of background sounds. Traumatic film clips were extracted from commercial movies ("Antichrist", 2009, directed by Lars von Trier; "Hostel", 2005, directed by Eli Roth; "Scar", 2007, directed by Jed Weintrob) and depicted a severely violent attack of one person against another. The respective film clips have already been proven to elicit fear, arousal and subsequent intrusive memories in previous studies (Wegerer et al., 2013; Wegerer et al., 2014). Neutral film clips were taken from Internet sources and depicted two persons in a non-violent interaction (playing chess, making yoga exercises, or painting). Each block started with an information slide (2.5 s) referring to which video category ('traumatic' or 'neutral') was to be presented, and consisted of three videos (each 25 s) from that category. Each video was preceded by a jittered ITI (mean 16.5 ± 2.5 s) and was followed by ratings (via button box press during scanning) of valence and arousal (at least 10 s; visual-analogue scale 0–10; see Fig. 1). The order of film clips and blocks was counterbalanced across participants. The task was presented using Presentation software (version 14.8, Neurobehavioral Systems, Inc., Albany, USA). Finally, participants were debriefed and compensated for participation.