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Contribution of stress and sex hormones to memory encoding

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ABSTRACT

Distinct stages of the menstrual cycle and the intake of oral contraceptives (OC) affect sex hormone levels, stress responses, and memory processes critically involved in the pathogenesis of mental disorders. To characterize the interaction of sex and stress hormones on memory encoding, 30 men, 30 women in the early follicular phase of the menstrual cycle (FO), 30 women in the luteal phase (LU), and 30 OC women were exposed to either a stress (socially evaluated cold-pressor test) or a control condition prior to memory encoding and immediate recall of neutral, positive, and negative words. On the next day, delayed free and cued recall was tested. Sex hormone levels verified distinct estradiol, progesterone, and testosterone levels between groups. Stress increased blood pressure, cortisol concentrations, and ratings of stress appraisal in all four groups as well as cued recall performance of negative words in men. Stress exposure in OC women led to a blunted cortisol response and rather enhanced cued recall of neutral words. Thus, pre-encoding stress facilitated emotional cued recall performance in men only, but not women with different sex hormone statuses pointing to the pivotal role of circulating sex hormones in modulation of learning and memory processes.

1. Introduction

Stress and stress hormones exert tremendous effects on emotional learning and memory processes playing a crucial role in the pathogenesis of various mental disorders such as posttraumatic stress disorder (PTSD) or anxiety disorders (De Quervain et al., 2017; Merz et al., 2016). Importantly, these effects depend on the exact timing between stress and the respective memory phase. Sex hormones also critically modulate these relationships and contribute to the development, maintenance and treatment of mental disorders (Cover et al., 2014; Lebron-Milad and Milad, 2012; Merz and Wolf, 2017). Thus, the effects of stress and sex hormones need to be considered together when investigating learning and memory processes to understand their potential clinical relevance.

Stress triggers the activation of two systems: on the one hand, stress initializes the sympathetic nervous system (SNS) to release catecholamines such as norepinephrine and epinephrine. On the other hand, stress triggers activation of the hypothalamus-pituitary-adrenocortical (HPA) axis leading to a hormonal cascade ending in the secretion of glucocorticoids (GCs; mainly cortisol in humans). GCs and norepinephrine jointly modulate (emotional) learning and memory processes by acting on respective receptors especially located in the amygdala and hippocampus (De Kloet et al., 2005; Roozendaal et al., 2009).

While it has been consistently reported that stress hormones impair memory recall, but enhance memory consolidation (Schwabe and Wolf, 2013; Wolf, 2009), there is still no consensus how exactly stress hormones influence memory encoding. Several theories have been proposed to explain these discrepant findings (cf. Merz and Wolf, 2015b) including temporal proximity of stress and encoding (Akirav and Richter-Levin, 1999, 2002; Diamond et al., 2007; Joëls et al., 2006, 2011; Schwabe et al., 2012), time of day (Het et al., 2005), and emotionality of the learning material (e.g. Buchanan and Lovallo, 2001; Payne et al., 2007; Rimmele et al., 2003). Importantly, it has also been assumed that stress effects on memory encoding might critically depend on sex hormone status (Merz and Wolf, 2017).

The release of sex hormones (such as estradiol, progesterone, or testosterone) is under the control of the hypothalamus-pituitary-gonadal (HPG) axis and varies substantially in women over the course of the menstrual cycle. It is typically reduced during intake of oral contraceptives (OCs; Fleischman et al., 2010; Montoya and Bos, 2017), but can be modulated by different factors such as OC type and brand (D'Arpe et al., 2016; Elliott-Sale et al., 2013; London and Jensen, 2016). Likewise, sex hormones influence different brain structures such as the amygdala and the hippocampus by targeting their respective receptors (McEwen and Milner, 2017). Sex hormones also modulate the salivary cortisol response to a psychosocial stressor with a similar pattern in men and women in the luteal phase of the menstrual cycle (LU; high estradiol and progesterone levels) but reduced or blunted responses in

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women in the follicular phase (FO; low estradiol and progesterone levels) or taking OCs (Kirschbaum et al., 1999; see also Childs et al., 2010; Cornelisse et al., 2011; Espin et al., 2013; Rohleder et al., 2003). In the present report, this sex hormone status effect on the stress response will be investigated using a combination of a psychosocial and a physical stressor and its impact on memory encoding will be characterized.

Previous studies focusing on interactive effects of sex and stress hormones on memory encoding found partly discrepant results: While men remembered emotional pictures better in a recognition test when encoding took place after a psychosocial stress induction, this effect was absent for neutral pictures and in women (Cornelisse et al., 2011). More specifically, pre-encoding stress also led to a better immediate free recall of neutral material in men, but not in FO, LU, or OC women (Espin et al., 2013). Another study reported free recall of neutral words to be enhanced in men and OC women alike when free recall was tested one hour or one day after encoding (Schwabe et al., 2008a). Taken together with studies including men only (e.g. Nater et al., 2007; Quaedflieg et al., 2013; Tops et al., 2003; Wolf, 2012) or both sexes without explicitly testing the impact of different sex hormone status in women (e.g. Rimmele et al., 2003; Zoladz et al., 2011), pre-encoding stress effects seem to be more stable in men compared with women. However, available results need to be expanded to a detailed investigation of the relevance of sex hormone milieu concerning the impact of pre-encoding stress on delayed memory recall. Therefore, the current report contrasts men with FO, LU, and OC women in their delayed recall performance after being exposed to pre-encoding stress.

2. Material and methods

2.1. Participants

All participants were recruited through email announcements at the University of Trier, Germany, or by personal address. Most of them were students (117; 56 students of psychology), the remaining three participants were working at the university. To assess different sex hormone statuses, 30 men, 60 free-cycling women, and 30 OC taking women were included. Free-cycling women did not take any kind of contraceptives and reported to have a regular menstrual cycle. One half of them was invited in the early follicular phase (FO; 3rd–9th day after the onset of their last menstruation) and the other half in the luteal phase (LU; 3rd–9th day before the onset of their next menstruation) of the individual menstrual cycle. OC women were required to have been taking their birth control pill (only monophasic preparations with a 0.02–0.035 mg ethinylestradiol and a gestagenic component) for at least the last three months. Preparations included gestagenic components with androgenic (desogestrel, levonegestrel) and anti-androgenic properties (chlormadinone acetate, cyproterone acetate, dienogest, drospirenone). They were tested during the pill intake phase on both experimental days.

None of the participants was taking regular medication except OCs or reported a history of psychiatric or neurological treatment. Exclusion criteria covered somatic diseases (e.g., high blood pressure, Raynaud's disease or allergies), in particular endocrine diseases known to influence endogenous hormone levels (e.g., hyper-/hypothyroidism), and smoking more than five cigarettes/month. Inclusion criteria comprised an age between 18 and 35 years and a body mass index (BMI) between 18 and 28 kg/m^2. The final sample had a mean age of 23.22 (SD = 2.92) years and a mean BMI of 21.96 (SD = 2.49) kg/m^2.

The study was approved by the local ethics committee of the University of Trier.

2.2. Procedure

On two consecutive days, experimental sessions were run between 1 and 6 p.m. and participants had to be awake for at least three hours before testing in order to control for circadian fluctuations in salivary cortisol (Kudielka et al., 2009). They were instructed to refrain from intense physical exercise, smoking, eating, and drinking anything but water for at least ninety minutes before the start of the experiment.

After arrival on day one, participants received a detailed explanation of the general procedure and gave written informed consent. They were then instructed to provide a first saliva sample (S1) and demographical details as well as a second saliva sample (S2) after a resting phase of ten minutes; both saliva samples served the determination of sex hormone status (see 2.3). After that, a third saliva sample (C1) for the determination of baseline cortisol concentrations was required (see 2.4). Then, blood pressure was measured and participants from each sex hormone status group were randomly assigned to one of two experimental conditions comprising 15 persons each (stress condition: socially evaluated cold-pressor test (SECPT)) vs. warm water control condition; (Schwabe et al., 2008b). Both conditions required participants to immerse their dominant hand up to the elbow into water, with a temperature between 0 and 3 °C in the stress condition and between 36 and 37 °C in the control condition. A neutral female experimenter (only present for the duration of the SECPT) videotaped and observed participants during the SECPT while blood pressure was recorded simultaneously. In the control condition, neither videotaping nor observation took place. In both conditions, participants were instructed to remove their arm from the water after three minutes. If they did not manage to keep their arms in the ice water in the SECPT for this duration, they were instructed to hold their hands above the water for the remaining time. After cessation, participants answered three questions concerning their subjective appraisal of the task (see 2.4). The fourth saliva sample (C2) was provided and blood pressure was measured eight minutes after onset of the experimental condition. Twenty minutes after stress onset, participants were asked for a fifth saliva sample (C3), followed by memory encoding and immediate recall (see 2.5). Thirty minutes after stress onset, participants provided the sixth saliva sample (C4).

At the beginning of day two, participants provided two saliva samples (S3, C5) before free and cued memory recall (see 2.5) was tested in a different room than on day one. Ten minutes after the first saliva sample and after free memory recall, the next saliva sample (S4) was collected. After cued recall, participants gave the last saliva sample (C6) and finally received either partial course credits or 20€ as a monetary compensation for their attendance.

2.3. Measurement and analysis of sex hormones

Eppendorf tubes were used for the collection of saliva samples required for the determination of the sex hormones estradiol, progesterone, and testosterone (samples S1-S4). These four samples were pooled before analyses, thus generating one concentration for each sex hormone subserving to check for expected differences between men, FO, LU, and OC women (cf. Merz et al., 2012). All saliva samples were stored at −20 °C until assayed. Commercially available enzyme-linked immunosorbent assays (for estradiol and testosterone: Demeditec, Kiel, Germany) and enzyme imunoassays (for progesterone: Salimetrics, Newmarket, Suffolk, UK) were used to measure free hormone concentrations. Intra-assay coefficients of variations (CV) for all analyses were below 8% with inter-assay CV below 11%. Data of one OC woman in the control condition could not be analyzed for progesterone and testosterone concentrations, since hormonal levels were outside the measurable range of the assay. Except for analyses of progesterone and testosterone levels, the respective data were included.

All data were analyzed using the SPSS 20.0 software (SPSS Inc., Chicago, USA) with the significance level set to $\alpha = .05$. Estradiol, progesterone, and testosterone were subjected to separate analyses of variance (ANOVA) with the between-subjects factors stress (stress vs. control condition) and sex hormone status (men vs. FO vs. LU vs. OC women). Where appropriate, Greenhouse-Geisser degrees of freedom