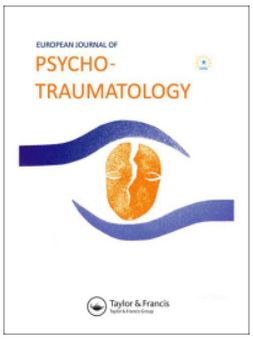

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Effects of oral contraceptives on intrusive memories: a secondary analysis of two studies using the trauma film paradigm in healthy women

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ABSTRACT

Background: Women are more likely to develop post-traumatic stress disorder (PTSD) than men. Recent research suggests an impact of oral contraceptive (OC) intake on PTSD and intrusive memories, a hallmark symptom of PTSD. Although a majority of women use OCs at some point in their lives, the effects on PTSD pathogenesis are only poorly understood.
Objective: In the current paper, we aimed to investigate the impact of OC intake on the acquisition and consolidation of intrusive memories in healthy women after watching a trauma film paradigm.
Methods: We performed a secondary analysis of a pooled dataset ($N = 437$) of two previously conducted and published studies investigating the effect of oxytocin on the development of intrusive memories.
Results: Women taking OCs showed an attenuated decline of intrusive memories over time after having watched the trauma film compared to naturally cycling women ($F(2.75, 1167) = 3.79$, $p = .03$, $\eta_p^2 = .01$).
Conclusion: These findings indicate that the intake of OCs is associated with the development of intrusive memories after a trauma film paradigm. This indication emphasizes the need to further investigate the complex impact of OCs and gonadal hormones on fear learning processes and PTSD.

Efectos de los anticonceptivos orales sobre los recuerdos intrusivos: un análisis secundario de dos estudios que utilizan el paradigma de la película de trauma en mujeres sanas

Antecedentes: Las mujeres son más propensas a sufrir Trastorno por estrés postraumático (TEPT) que los hombres. Recientes estudios sugieren que la ingesta de anticonceptivos orales (ACO) tendría un impacto en el TEPT y en los recuerdos intrusivos, un síntoma clásico de este trastorno. Aunque la mayoría de las mujeres utilizan ACO en algún momento de sus vidas, los efectos en la patogénesis del TEPT son escasamente comprendidos.
Objetivo: En el presente estudio, apuntamos en evaluar el impacto del consumo de ACO en la adquisición y consolidación de los recuerdos intrusivos en mujeres sanas, después de ver un paradigma de película sobre trauma.
Método: Realizamos un análisis secundario de un pool de datos ($N = 437$) de dos estudios previamente realizados, que investigaban el efecto de la oxitocina en el desarrollo de los recuerdos intrusivos.
Resultados: Las mujeres que consumían ACO mostraron una disminución atenuada de los recuerdos intrusivos con el tiempo después de haber visto una película sobre trauma, en comparación a las mujeres que ciclaban de forma normal ($F(2.75, 1167) = 3.79$, $p = .03$).
Conclusión: Estos hallazgos indican que el consumo de ACO, está relacionado con el desarrollo de recuerdos intrusivos después de un paradigma de una película de trauma. Esta indicación enfatiza en la necesidad de realizar nuevas investigaciones sobre el complejo impacto de los ACO y de las hormonas gonadales, sobre los procesos de aprendizaje del miedo y del TEPT.

口服避孕药对闯入性记忆的影响：两项对健康女性使用创伤电影范式研究的二次分析

背景：女性比男性更容易患创伤后应激障碍（PTSD）。最近研究表明，口服避孕药（OC）的摄入量对创伤后应激障碍（PTSD）和闯入性记忆（创伤后应激障碍的标志症状）有影

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Posttraumatic stress disorder; PTSD; intrusive memories; estradiol; oral contraceptives; HPA axis; cortisol

PALABRAS CLAVES
Trastorno por estrés postraumático; recuerdos intrusivos; estradiol; anticonceptivos orales; eje HHA; cortisol

关键词
创伤后应激障碍; PTSD; 闯入性记忆; 雌二醇; 口服避孕药; hpa轴; 皮质醇

HIGHLIGHTS

- The objective of the current study was to analyze the effect of oral contraceptives on the development of intrusive memories after a trauma film paradigm by conducting a secondary analysis of previously published data.
- Women taking oral contraceptives show an attenuated decline of intrusive memories after watching a trauma film paradigm compared to naturally cycling women in the luteal phase.
- Women using oral contraceptives show higher basal saliva cortisol levels.

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响。尽管大多数女性在一生中的某个阶段都会使用口服避孕药，但其对 PTSD 发病机制的影响却知之甚少。
目的：在本文中，我们旨在调查观看创伤电影范式后，摄入 OC 对健康女性闯入性记忆的获取和巩固的影响。
方法：我们对先前进行并发表的两项研究的汇总数据集（$N = 437$）进行了二次分析，这些研究考查了催产素对闯入性记忆发展的影响。
结果：与自然循环的女性相比，服用 OC 的女性在观看创伤影片后，随着时间的推移，闯入性记忆的下降程度有所减弱 ($F(2.75, 1167) = 3.79$，$p = .03$）。
结论：这些研究结果表明，口服避孕药的摄入与创伤电影范式后闯入性记忆的发展有关。这一迹象强调需要进一步研究 OC 和性腺激素对恐惧学习过程和 PTSD 的复杂影响。

1. Introduction

Being a woman has been identified as a vulnerability factor for post-traumatic stress disorder (PTSD) (Shalev et al., 2017), a complex psychiatric disorder (American Psychiatric Association, 2013), with long-term adverse outcomes for those affected and high individual and societal burden (Kessler et al., 2017; McGowan, 2019; von der Warth et al., 2020). Women suffer from higher severity and chronicity of PTSD and show higher comorbidities with other diagnoses (Atwoli et al., 2015; Charak et al., 2014; McLean et al., 2011). Higher rates of PTSD in women have been suggested to be a consequence of higher rates of revictimization (Yehuda et al., 2015) and greater exposure to interpersonal violence in women than in men (Hegadoren et al., 2006); however, sex differences in PTSD development stay evident, even when studies control for greater exposure in women and trauma type (Tolin & Foa, 2008; Yehuda et al., 2015). These differences certainly have multifactorial etiologies. Besides psychological factors, evidence implicates sex differences in underlying neurobiological mechanisms associated with PTSD (Olff et al., 2007) and a potential role of female gonadal hormones (Garcia et al., 2018).

Intrusive memories are a hallmark criterion of PTSD and represent recurring distressing involuntary recollections of the traumatic event (American Psychiatric Association, 2013). Although most individuals develop intrusive memories after traumatic events, only a minority do not recover from them and develop PTSD (de Quervain et al., 2009). Maladaptive neurocognitive processes, such as fear conditioning and impaired extinction of traumatic memories, have been proposed to be underlying mechanisms of PTSD and intrusive memories (Amstadter et al., 2009; Blechert et al., 2007; Wessa & Flor, 2007). Fear conditioning and impaired fear extinction learning are sex dimorphic (Goldstein et al., 2010; Inslicht et al., 2013; Lebron-Milad & Milad, 2012; Ramikie & Ressler, 2018) and have been shown to be influenced by gonadal hormones, such as estrogen (Hwang et al., 2015; Taxier et al., 2020). Estrogen levels differ between sexes (Edelstein et al., 2010) and in women across the lifespan and within the menstrual cycle (Gandara et al., 2007); however, the underlying mechanisms of their effects are not yet sufficiently understood.

Estradiol, the primary estrogen in women of childbearing age, is mainly produced by the ovaries and is known to peak twice during the menstrual cycle: at the end of the follicular phase, before ovulation, and in the course of the luteal phase (Schmalenberger et al., 2021). The menstrual cycle is regulated by the hypothalamic-pituitary-gonadal (HPG) axis (for an overview, see Kovacs & Ojeda, 2011). Combined oral contraceptives (OCs) containing estradiol and progesterone act through a negative feedback loop on the HPG axis (Hampson, 2020). The intake of combined OCs is, therefore, associated with a reduction of endogenous production of progesterone and estradiol (Rivera et al., 1999), resulting in constantly decreased plasma concentrations of estradiol compared with naturally cycling women in the luteal phase (De Bondt et al., 2013; Pluchino et al., 2009). Estrogen receptors can be found throughout various brain regions involved in fear conditioning and memory consolidation processes (e.g. amygdala, hippocampus, prefrontal cortex) (Maioli et al., 2021), and estradiol is involved in a variety of cognitive functions such as learning and memory (Hammoud et al., 2020). Research consistently indicates that estradiol enhances memory consolidation (Taxier et al., 2020) and fear extinction learning (Bauer, 2022; Graham & Milad, 2013; Maeng & Milad, 2015) but shows mixed effects on fear acquisition (Bauer, 2022; Carvalho et al., 2021; Gupta et al., 2001; Jasnow et al., 2006; Matsumoto et al., 2018; Taxier et al., 2020). The administration of estradiol in rodent studies enhanced fear acquisition in some studies (Jasnow et al., 2006; Morgan & Pfaff, 2001) but showed the opposite effect in others (e.g. Gupta et al., 2001; Markus & Zecevic, 1997). A possible explanation for the contradictory results, suggested by Garcia, Walker and Zoellner (Garcia et al., 2018), is the robustness of fear acquisition, which is less vulnerable to being affected by hormonal levels compared to extinction learning, which is more susceptible to hormonal fluctuations (Craske et al., 2008). Furthermore, human studies applying a psychosocial stressor before encoding a

short story showed that stressed women with low endogenous estradiol levels showed diminished learning compared to women with high estradiol levels (Antov & Stockhorst, 2014, 2018). Although the effect of estradiol enhancing fear acquisition seems contradictory to the impact of enhanced fear extinction, these findings make sense if estradiol is considered a neuromodulator that facilitates learning mechanisms in general (Garcia et al., 2018; Taxier et al., 2020).

Studies directly analyzing the effect of the menstrual cycle or estradiol on intrusive memories also consistently found an association. The direction and pattern of the association, however, are less consistent: Some studies found that low endogenous estradiol levels in healthy women were associated with more intrusive memories after watching trauma film paradigms (Krinke et al., 2022; Wegerer et al., 2014), suggesting the involvement of lower estradiol levels in the susceptibility to PTSD symptoms after traumatic events. Accordingly, women with low estradiol levels showed an attenuated decline in intrusive memories after watching a trauma paradigm compared to women with high estradiol (Franke et al., 2022). Others, in turn, found that healthy women reported more intrusive memories after watching film clips during the luteal phase (high estradiol levels) compared to women in the follicular phase (low estradiol levels) (Ferree et al., 2011; Ferree & Cahill, 2009). Further, the probability of experiencing intrusive memories was higher for traumatized women if they were traumatized in their luteal phase (Bryant et al., 2011). Finally, higher levels of endogenous estradiol were positively associated with the number of intrusive memories of negative images in healthy women (Cheung et al., 2013).

Studies about the effect of progesterone on fear learning paradigms mostly failed to find significant effects (Milad et al., 2010; Wegerer et al., 2014; Zeidan et al., 2011), and progesterone and intrusive memory literature is scarce and inconclusive (Cheung et al., 2013; Ferree et al., 2011; Krinke et al., 2022; Wegerer et al., 2014). While two studies found that intrusions were associated with higher progesterone levels (Ferree et al., 2011; Krinke et al., 2022), two others found no association between progesterone and intrusions at all (Cheung et al., 2013; Wegerer et al., 2014).

The HPG axis is known to have a close and bidirectional interaction with the hypothalamic pituitary adrenal (HPA) axis (for a review, see Phumsatitpong et al., 2021), and this interaction is thought to be partially responsible for sex differences in the development of stress associated disorders (Kudielka and Kirschbaum 2005). Cortisol (a main stress hormone), for example, has been shown to have a sex-dimorphic effect on fear conditioning (Zorawski et al., 2006) and interact with estrogens to sex-dependently affect fear learning and fear extinction (Merz et al., 2013). Further, a blunted cortisol release after a psychosocial stressor during the follicular phase (low estradiol) of the menstrual cycle compared to the luteal phase (high estradiol) (Kajantie & Phillips, 2006; Kirschbaum et al., 1999) reflects the influence of the HPG axis on the HPA axis. Additionally and of particular interest for the current paper is the observation of a recent meta-analysis that OC intake increases basal salivary cortisol levels and dampens the stress response of the HPA axis (Gervasio et al., 2022).

In the current secondary data analysis, we examined the effect of OC intake in healthy women compared to naturally cycling women in the luteal phase on the development of intrusive memories after watching a trauma film. For this purpose, we reanalyzed the dataset of two previously conducted and published studies (Maslahati et al., 2022; Schultebraucks et al., 2021) investigating the effect of oxytocin on the acquisition and consolidation of intrusive memories. As low levels of estradiol have been associated with enhanced memory consolidation and OCs result in reduced levels of estradiol, we hypothesized an increased number of intrusive memories in women using OCs compared to naturally cycling women (in the luteal phase) in the following four days after watching a trauma film paradigm. We also included cortisol as a stress marker in the analysis to factor in the bidirectional interaction of the HPA and HPG axis.

2. Materials and methods

The here analyzed data was collected in two separate studies, with a similar design analyzing the effect of oxytocin on the acquisition (Schultebraucks et al. 2021) and consolidation (Maslahati et al., 2022) of intrusive memories. The difference between the two studies was the timing of oxytocin administration. While oxytocin was administered before the trauma film in the first study (Schultebraucks et al., 2021), it was administered after the trauma film in the second study (Maslahati et al., 2022). Both studies were conducted within one year in the same room, with an identical setup at the Department of Psychiatry and Neurosciences, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin. Participants were allowed to participate only once and were instructed not to talk to any other potential participant about the study design. Cohort effects and order effects are, therefore, unlikely. The local ethics committee of Charité – Universitätsmedizin Berlin (EA4/144/16; EA4/162/18) approved study protocols and participants provided informed consent upon arrival in the laboratory. To account for circadian cortisol fluctuations (Kirschbaum & Hellhammer, 1989), the start of every testing was set for 2 pm More detailed test conditions have been

described and published formerly (Schultebraucks et al., 2019).

2.1. Participants

A pooled analysis of two studies with an identical design and a total of $N = 437$ healthy participants who report female sex and identify as women was analyzed. Participants in both studies were recruited via public postings or email lists. Because of the sexually dimorphic effect of oxytocin (Ditzen et al., 2013), only female participants were included. Eligibility criteria were assessed before participation and included mental and physical health-related aspects and have been described previously (Schultebraucks et al., 2019) and in the supplement information. To account for hormonal fluctuations during the menstrual cycle, which can impact intrusion formation (Bryant et al., 2011; Ferree et al., 2011), participants not taking oral contraceptives were tested during their luteal phase only. Each participant's menstrual cycle phase was calculated using self-report data about the first day of their last menstruation and the length of their cycle. HCG ULTRA pregnancy tests were applied to rule out pregnancy. All participants received an expense allowance and were contacted via phone four weeks after participation to ensure full recovery from the trauma film. In case of ongoing distress, participants were offered psychological care. In the second study (Maslahati et al., 2022), one participant reported ongoing intrusions and received six counselling sessions with a licensed psychologist. Associated distress and intrusions of the participant disappeared during aftercare.

2.2. Experimental phase

After filling in questionnaires, participants watched an analog trauma film paradigm. At the end of the session, they received instructions on filling out the intrusion diary over the following four days after participation at the end of the session. A detailed description of the study procedure has been published previously (Schultebraucks et al., 2021), and information about psychometric baseline assessment is provided in the supplementary material.

2.2.1. Trauma film

A well-established trauma film paradigm (Holmes et al., 2004; Holmes & Bourne, 2008; Weidmann et al., 2009), which reliably evokes intrusive symptoms (Rombold, Wingenfeld, Renneberg, Hellmann-Regen, et al., 2016; Schultebraucks et al., 2021; Weidmann et al., 2009), was presented in a dark room on a 2 × 2.5 m screen. The applied scene (14 min, 40 s) from the commercial film *Irreversible* directed by Gaspar Noë shows how a woman is attacked, brutally raped, and beaten up by a stranger in a pedestrian underpass. Prior to the movie, participants were instructed to allow any arising emotions. To verify that the participant watches the whole movie without visual (e.g. closing eyes) or acoustic (e.g. taking off headphones) avoidance, a trained investigator stayed in the room and controlled compliance with the rules.

2.2.2. Intrusion diary

After the experimental session, the participants were instructed to fill out an intrusion diary, used in previous studies (Schultebraucks et al., 2021; Rombold, Wingenfeld, Renneberg, Schwarzkopf, et al., 2016), for four consecutive days. Participants were asked to enter every film memory directly after occurrence. Subjects were instructed to transfer their records into an online diary daily to prevent data loss and ensure participation. They received a daily text message at 9 pm as a reminder. According to Holmes et al. (Holmes et al., 2004), participants had to indicate the suddenness of the film-associated memories, their content, frequency, and modality, which was classified as image-based, thought, or both, and degree of vividness and degree of distress (0 = not at all to 5 = very strong). Memories were classified as intrusive if they occurred spontaneously, included images, and had ratings of ≥ 1 in distress and vividness.

2.3. Statistical analysis

All statistical analyses were performed with SPSS version 29.0. We conducted two sample characteristic comparisons: first, we compared all participants of the first study with participants of the second study. Secondly, we compared all participants using OC with naturally cycling participants. For this purpose, we used Chi-square and Student's t-test or the non-parametric Mann-Whitney-U-test. Group differences were conducted to ensure there were no differences regarding cortisol, sample characteristics, and psychometric variables that have been shown to be associated with intrusion formation (Breslau et al., 1999; Maslahati et al., 2022): Childhood Trauma Questionnaire (Bernstein & Fink, 1998), state-trait anxiety inventory-trait subscale (Spielberger, 1983), Beck depression inventory-revised (Beck et al., 1996), emotion regulation questionnaire (Abler & Kessler, 2009).

To test the main and interaction effects of time, treatment condition (oxytocin before the trauma film; oxytocin after the trauma film; placebo), and participant group (OC intake; naturally cycling) on the number of intrusive memories, we conducted a repeated measures mixed design ANOVA. Oxytocin was a confounder due to the original study design and was included in the analysis to control for its variability. To analyze possible effects of baseline variables that significantly differ between participants taking OCs and

naturally cycling participants, we included these variables as covariates in the repeated measures mixed design ANOVA. Levene's statistic was used to assess the homogeneity of variance of the data, and Muchly's test was used to examine sphericity. If the assumption of sphericity was not met, Greenhouse-Geisser corrected *p-values* are reported.

3. Results

We included $n = 399$ of the $n = 437$ enrolled participants in the final analysis. Factors that led to the exclusion of participants included unreliable reports of intrusive memories and prolonged interruption of the experiment due to technical problems. A detailed report on the inclusion and exclusion of participants during the two studies has been published previously (Maslahati et al., 2022; Schultebraucks et al., 2021). Eight participants using OCs that only contained synthetic progesterone and four participants that did not give information about the kind of OC were additionally excluded from the current analyses, as participants could neither be assigned to the natural cycling group in the luteal phase nor the group with a chronic intake of combined OCs. One hundred twenty-seven of the included participants used OCs; the compositions of the included OCs are listed in Supplementary Table 1. Apart from baseline cortisol levels, there were no significant differences regarding the sample characteristics and psychometric assessment presented in Table 1 and Supplementary Table 2 neither between participants using OC ($n = 127$) and naturally cycling participants ($n = 272$) (Table 1), nor between the participants of the two studies ($n_1 = 199$; $n_2 = 200$) (Supplementary Table 2). Baseline cortisol levels were significantly higher in OC-taking participants than in naturally cycling participants (Table 1).

The longitudinal development of salivary cortisol, before and after the trauma film did not significantly differ between the OC group and naturally cycling participants ($F(1, 389) = 1.54$, $p = .22$, $\eta_p^2 = .01$) and is illustrated in Supplementary Figure 1.

3.1. Mean group differences

The mean numbers of intrusive memories of both groups (OC vs. Naturally Cycling) over four days are shown in Figure 1. While the number of intrusive memories expectedly significantly declined over time ($F(2.75, 1167) = 135.43$, $p < .001$, $\eta_p^2 = .26$), there was no significant main effect of OC ($F(1, 389) = .00$, $p = .95$, $\eta_p^2 = .00$); however, we found a significant interaction of time and OC ($F(2.75, 1167) = 3.79$, $p = .03$, $\eta_p^2 = .01$), with OC users showing an attenuated decline of intrusive memories compared to naturally cycling women (cf. Figure 1). The interaction of OC and oxytocin (oxytocin before the trauma film; oxytocin after the trauma film; placebo) was not significant ($F(3, 389) = .73$, $p = .53$, $\eta_p^2 = .06$). As participants taking OCs showed significantly heightened baseline cortisol levels, we included baseline cortisol levels as a covariate in the analysis. This addition did not change the results.

4. Discussion

This secondary analysis aimed to investigate the impact of OC intake on the acquisition and consolidation of intrusive memories in healthy women after watching a trauma film. The intake of OCs significantly influenced the decline of intrusive memories in interaction with time. Women taking OCs showed an attenuated decline of intrusive memories compared to naturally cycling women in the luteal phase.

Considering that OC intake is associated with reduced endogenous estradiol levels (De Bondt et al., 2013; Pluchino et al., 2009), the result of the current study replicates findings of a previously published

Table 1. Sample characteristics.

Characteristics	Hormonal contraception ($n = 127$) M (SD) or *n*	No hormonal contraception ($n = 272$) M (SD) or *n*	Statistics
Age	23.38 (4.76)	24.35 (4.86)	$t(397) = 1.87$, $p = .06$, $d = 0.20$ (95% CI [−0.05, 1.98])
BMI	22.29 (2.69)	21.78 (2.53)	$t(397) = -1.86$, $p = .06$, $d = -0.02$ (95% CI [−1.06, .0.03])
CTQ	30.24 (6.14)	32.15 (8.23)	$U = 14{,}783.50$, $Z = -2.33$, $p = .06$
STAI-T	1.60 (0.28)	1.66 (0.34)	$U = 15{,}912$, $Z = -1.04$, $p = .30$
BDI-II	3.69 (3.94)	4.17 (3.91)	$U = 16{,}052.5$, $Z = -1.14$, $p = .25$
ERQ reappraisal	29.66 (4.91)	29.14 (5.43)	$t(397) = -.92$, $p = .09$, $d = -0.26$ (95% CI [−1.64, 0.59])
ERQ suppression	11.33 (4.18)	11.47 (4.14)	$t(397) = 0.31$, $p = .76$, $d = 0.03$ (95% CI [−0.74, 1.01])
Participants who had seen the film before	8	21	$\chi 2(1) = 0.24$, $p = .62$, $\varphi = 0.03$
Baseline cortisol (nmol/l)	2.98 (1.99)	2.63 (1.76)	$t(397) = -1.81$, $p = .04$, $d = 0.19$ (95% CI [−0.75, −0.31])

M = mean, SD = standard deviation, BMI = body mass index, CTQ = Childhood Trauma Questionnaire, STAI-T = state-trait anxiety inventory-trait subscale, BDI-II = Beck depression inventory-revised, ERQ = emotion regulation questionnaire (subscales reappraisal and suppression).

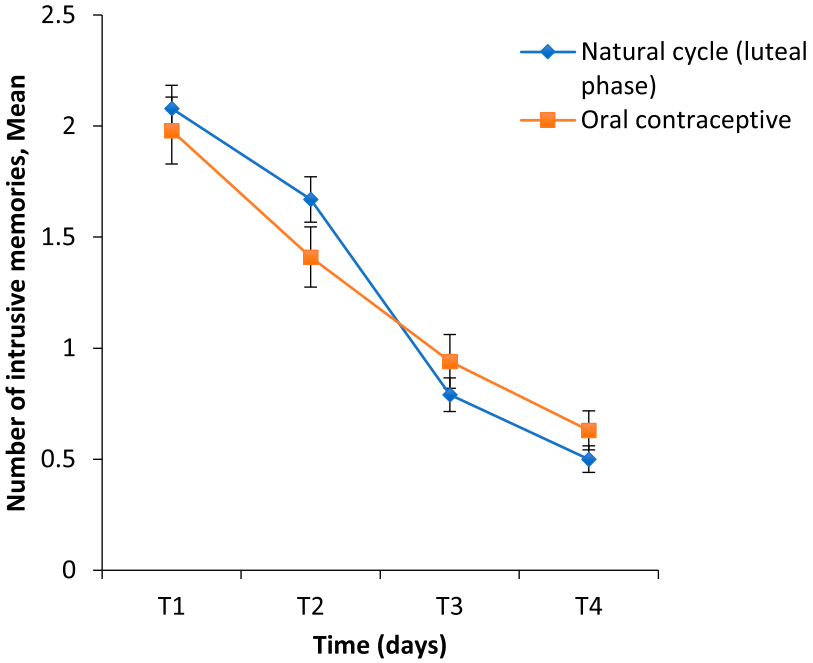

Figure 1. Number of intrusive memories of naturally cycling women in the luteal phase and women using oral contraceptives over four days. Points are means, with standard errors represented by vertical bars.

study showing that lower peritraumatic estradiol levels were associated with a blunted decrease of intrusive memories after watching a trauma film (Franke et al., 2022). The results are further in accordance with studies showing an adverse effect of low estradiol levels on intrusive memories (Helpman et al., 2023; Krinke et al., 2022; Wegerer et al., 2014). One possible underlying mechanism of OC intake impairing the decline of intrusive memories may be due to reduced endogenous estradiol levels. Low levels of estradiol, due to OC intake or natural fluctuations, have consistently been shown to impair fear extinction processes (Bauer, 2022; Graham & Milad, 2013; Maeng & Milad, 2015; White & Graham, 2016), which in turn have been proposed to be associated with the maintenance of intrusive memories (Miedl et al., 2020). In a review of the mechanisms of estradiol on fear circuity, Cover et al. (Cover et al., 2014) proposed that estradiol impacts fear circuity through different cellular pathways, influencing gene expression and learning-induced neuronal plasticity.

The result that OC intake significantly increases basal salivary cortisol levels in our analysis aligns with previous research (Gervasio et al., 2022; Mordecai et al., 2017), but is also in contrast to earlier studies showing lower levels of salivary cortisol in OC users compared to naturally cycling participants (Lewis et al., 2019). The latter effect has been attributed to ethinyl estradiol (Wiegratz et al., 2003), the estrogen compound in OCs triggering the hepatic production of cortisol-binding globulin (CBG). CBG is associated with decreased levels of free cortisol concentrations, measured in saliva (Kumsta et al., 2007); however, specific synthetic progesterone compounds in OCs have been shown to alter this effect (Hammerstein et al., 1993; Wiegratz et al., 1995, 1998). While Ethinyl estradiol is the most widely contained form of estrogen in OCs, the type of progestogen varies across OC types (Goldzieher & Stanczyk, 2008). Equally, in our studies, all participants used OCs that contain ethinyl estradiol as an estrogen, but the synthetic progesterone of the included OCs comprised eight different types (Supplementary Table 3). The variation of progesterone types used in OCs may contribute to varying effects of OCs on stress responsivity across studies and may be the reason why we did not find a blunted cortisol response to the trauma film in participants using OCs compared to naturally cycling participants as indicated in a recent review by Jentsch et al. (2022). To better understand the underlying mechanism of this association, further research is needed.

Contradictory findings exist on the influence of OCs on PTSD symptoms in traumatized individuals. Ferree, Wheeler and Cahill (2012) found that women taking OCs at the time of the trauma (sexual assault) showed significantly lower intrusive symptoms 5 to 7 months post-trauma than naturally cycling women. Further, Engel et al. (2019) found that women using OCs showed a stronger decrease in PTSD symptoms from 1.5 to 6 months post-trauma compared to naturally cycling women. The current study analyzed differences between healthy women using OCs that contain estradiol and progesterone and healthy naturally cycling women in the luteal phase in the direct aftermath of watching a trauma film. The results of the two before-mentioned studies may be divergent from ours, as the study samples consisted of traumatized women, and the examination time was several months post-trauma. Further, the two studies included

different kinds of OCs (also including OCs, that contain progestogen only) and did not control for the menstrual cycle phase in naturally cycling women. These two aspects are fundamental, as estradiol levels are differently influenced by different kinds of OCs (Elliott-Sale et al., 2013) and are known to fluctuate during the menstrual cycle (Schmalenberger et al., 2021). The latter has further been shown to impact intrusive memories (Ferree et al., 2011).

4.1. Strengths and limitations

One limitation of the findings is the conduction of a secondary analysis of studies that were originally not conducted to analyze the effects of OCs on intrusive memories and correspondingly did not include measurements of gonadal hormone levels. Nevertheless, the results add to rising evidence that OCs have important effects on the brain (Brønnick et al., 2020) and that gonadal hormones play a role in memory processes, particularly in women (Glover et al., 2012; Lebron-Milad et al., 2012).

A main strength of this secondary analysis is the high internal validity due to high experimental control, strict inclusion criteria, the inclusion of healthy women only, and the clear operationalization of intrusive memories. At the same time, including young, healthy women without any previous traumatic experiences poses a limitation. The results cannot be generalized to more vulnerable individuals with psychiatric disorders and lifetime experiences of traumatic events. Although increasing evidence suggests a similarly important role of estrogen on memory processes in men (Taxier et al., 2020), the current results can also not be transferred to men. Results must be extended to a more heterogeneous sample, including both sexes.

Translational research suggests that the leading effect of OCs on fear circuity is mainly led by the reduction of estradiol levels (Graham & Milad, 2013); however, it is unlikely that estradiol acts in isolation; fluctuations in other hormones such as progesterone may also impact the effect of estradiol on the formation of intrusive memories and should be further investigated. As described earlier, studies of progesterone mostly failed to find an impact on fear learning processes or intrusive memories (Garcia et al., 2018). Nevertheless, the issue of disentangling the effect of estrogen and progesterone on intrusive memories remains complex and future studies should analyze potential independent and interacting effects.

Although combined OCs, containing estradiol and progesterone, are thought to chronically (but not irreversibly) reduce endogenous cycling estradiol (De Bondt et al., 2013; Pluchino et al., 2009), we cannot be certain about the gonadal hormone levels of the participants, as we did not analyze them. Like other studies (e.g. Ferree et al., 2012; Engel et al., 2019) we included different brands of OCs. To improve internal validity, we only included participants taking OCs that contain a combination of estradiol and progestogen. Nevertheless, different brands of OC may have different intake instructions, different modes of action (Elliott-Sale et al., 2013), and varying types of progesterone. Potential diversity among different OC effects may be obscured when putting them together (Hampson, 2020). We further relied on self-reporting data for assessing the menstrual cycle phase. We only included naturally cycling participants in the luteal phase, a common approach, when factoring in cycle effects (Ney et al., 2019; Green & Graham, 2022); However, the luteal phase is characterized by strong hormonal fluctuations (Schmalenberger et al., 2021). In order to improve research on OC and cycle effects, future studies should consider brands of OCs and apply consistent methods to operationalize the menstrual cycle phase, as suggested by Schmalenberger et al. (2021).

Finally, investigating PTSD symptoms using a trauma film paradigm should be listed as a study limitation. The trauma film is a relatively mild stressor compared to real traumatic events, and it is not clear if the current data allow any conclusions about the development of intrusions in patients with PTSD. Nonetheless, applying actual traumatic events for research is ethically unjustifiable. Trauma film paradigms, therefore, offer an ethically justifiable method to investigate pre- and peri-traumatic PTSD vulnerability and risk factors (James et al., 2016).

5. Conclusion

The presented results show that OC usage is associated with the development of intrusive memories after a trauma film paradigm. The interpretation of the effects of OC usage and endogenous gonadal hormone levels on intrusive memories is complex. Although the majority of women use OCs at some point in their lives (Darroch 2013), and gonadal hormones are strongly suggested to impact PTSD (Garcia et al., 2018), the effects on PTSD pathogenesis are only poorly understood. The findings here contribute to the existing literature and emphasize the need to further investigate the impact of OCs and gonadal hormones on fear learning processes and PTSD.

When investigating the effect of gonadal hormones and OCs, studies should choose a homogenous subphase of the menstrual cycle (e.g. early follicular phase) in naturally cycling women, consider different compositions of OCs and incorporate measurements of blood or salivary gonadal hormone samples of the participants and cortisol measurements, in order to

facilitate understanding of underlying hormonal mechanisms.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author, TM, upon reasonable request.

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