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Exogenous estradiol and oxytocin modulate sex differences in hippocampal reactivity during the encoding of episodic memories

Marie Coenjaerts[a,*], Isabelle Trimborn[a], Berina Adrovic[a], Birgit Stoffel-Wagner[b], Larry Cahill[c], Alexandra Philipsen[d], René Hurlemann[e,f], Dirk Scheele[g,*]

[a] Division of Medical Psychology, Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn 53105, Germany
[b] Institute for Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn 53105, Germany
[c] Department of Neurobiology and Behavior, University of California, Irvine, CA 92697-3800, United States
[d] Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn 53105, Germany
[e] Department of Psychiatry, School of Medicine & Health Sciences, University of Oldenburg, Oldenburg 26129, Germany
[f] Research Center Neurosensory Science, University of Oldenburg, Oldenburg 26129, Germany
[g] Department of Social Neuroscience, Faculty of Psychology, Ruhr-University Bochum, Bochum 44780, Germany

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ABSTRACT

Considerable evidence supports sex differences in episodic memory. The hormones estradiol and oxytocin both affect episodic memory and may contribute to these sex differences, but possible underlying hormonal interactions have not been tested in a sample involving both sexes. To this end, we conducted a randomized, placebo-controlled, parallel-group functional magnetic resonance imaging (fMRI) study including healthy free-cycling women (n = 111) and men (n = 115). The fMRI session was conducted under four experimental conditions: 1. transdermal estradiol (2 mg) and intranasal oxytocin (24 IU), 2. transdermal placebo and intranasal oxytocin, 3. transdermal estradiol and intranasal placebo, 4. transdermal placebo and intranasal placebo. Participants were scanned during the encoding of positive, neutral, and negative scenes. Recognition memory was tested three days following the scanning sessions without additional treatments. Under placebo, women showed a significantly better recognition memory and increased hippocampal responses to subsequently remembered items independent of the emotional valence compared to men. The separate treatments with either hormone significantly diminished this mnemonic sex difference and reversed the hippocampal activation pattern. However, the combined treatments produced no significant effect. Collectively, the results suggest that both hormones play a crucial role in modulating sex differences in episodic memory. Furthermore, possible antagonistic interactions between estradiol and oxytocin could explain previously observed opposing hormonal effects in women and men.

1. Introduction

Sex differences in memory have been reported repeatedly (Andreano and Cahill, 2009; Cahill, 2003; Loprinzi and Frith, 2018). Metanalytical evidence indicates that women tend to outperform men in episodic memory functions (Andreano and Cahill, 2009; Asperholm et al., 2019; Herlitz et al., 1997; Herlitz and Yonker, 2002; Loprinzi and Frith, 2018), including autobiographical and recognition memory (Fuentes and Desrocher, 2012; Heisz et al., 2013). The magnitude of this sex difference is moderated by the type of task and stimulus material, with a female superiority found for tasks based on verbal abilities and a male advantage observed for tasks in which spatial processing is required (Asperholm et al., 2019; Loprinzi and Frith, 2018). The female advantage in verbal episodic memory appears to be stronger in recall than recognition tasks (Hirnstein et al., 2022). However, women also outperform men in some non-verbal tasks such as the recognition of faces, which may be related to increased scanning behavior (i.e. more fixations) at encoding in females (Heisz et al., 2013). Moreover, women have been found to remember more highly arousing negative pictures than men (Canli et al., 2002), although it has been proposed that sex differences in emotional memory may be related to feminine and masculine traits rather than actual sex per se (Cahill et al., 2004). Emotional hypermnesia is partially mediated through activation of the amygdala (Aikins et al., 2010; Hamann et al., 1999) and imaging studies revealed a sex-related hemispheric lateralization of the amygdala in response to emotional stimuli: right amygdala activation while viewing emotional stimuli is more significantly related to subsequent memory for the images in men than women, whereas the reverse sex difference is evident for the left amygdala (Cahill, 2006; Cahill et al., 2001; Canli et al., 2002, 2000).

* Corresponding authors.
E-mail addresses: m.coenjaerts@mail.de (M. Coenjaerts), dirk-scheele@gmx.de (D. Scheele).

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Potential biological mechanisms explaining these sex differences include the effects of sex hormones on memory function and neuroplasticity (Andreano and Cahill, 2009; Cahill, 2006; Cover et al., 2014; Duarte-Guterman et al., 2015; Herlitz and Yonker, 2002; Loprinzi and Frith, 2018). In particular, the role of estradiol (EST) as the most potent and prevalent circulating estrogen is discussed. As EST elicits effects on the memory consolidation in fear extinction learning, the regulating function of mnemonic brain regions, such as the hippocampus, has been highlighted (Taxier et al., 2020). Previous studies in rodents and humans have shown that hippocampal function is sensitive to changes in estrogens that occur across the reproductive cycle, pregnancy, or aging (Daniel, 2013; Duarte-Guterman et al., 2015; Pawluski et al., 2009). EST affects the dendritic spine density in the hippocampus (Loprinzi and Frith, 2018; Taxier et al., 2020) and enhances neuronal growth by promoting the formation of new synaptic connections (Cooke and Woolley, 2005). Several studies in female rodents have shown that the infusion of EST before or immediately after a training improves memory performance (Boulware et al., 2013; Fernandez et al., 2008; Luine et al., 2003; Pereira et al., 2014; Tuscher et al., 2019), but accumulating evidence indicates that EST also enhances cognition in male rodents (Taxier et al., 2020). In humans, correlative studies of natural hormonal fluctuations during the menstrual cycle found that estrogen levels are associated with greater episodic memory performance, but estrogen exposure has not been consistently shown to correlate with memory parameters in all studies (Loprinzi and Frith, 2018). For instance, some studies observed that higher levels of circulating EST correlate with better working memory performance (Hampson and Morley, 2013), whereas other studies reported changes in neither working memory nor delayed recall across the menstrual cycle (Mihalj et al., 2014). The mnemonic effects of EST might be task-dependent and vary with emotional valence and dose (Bayer et al., 2018; Luine, 2014). Despite the established sex differences in memory, there is little work directly comparing EST effects in women and men (Loprinzi and Frith, 2018).

Sex-specific behavioural and limbic effects have also been observed for the hypothalamic peptide oxytocin (OXT) (Gao et al., 2016; Luo et al., 2017; Rilling et al., 2014; Scheele et al., 2014). For instance, a dose of 24 IU intranasal OXT reduces amygdala responses to fearful faces in men (Spengler et al., 2017), but the same dose of the peptide increases amygdala activation in women (Lieberz et al., 2020). Likewise, OXT has been found to improve empathic accuracy in more socially proficient men but had no significant effect in women regardless of the social proficiency (Bartz et al., 2019). Considering the peptide's prosocial and anxiolytic effects, together with its high tolerability, OXT has evolved as a potential candidate compound for treating various mental disorders (Heinrichs et al., 2009; Herpertz and Bertsch, 2015; Meyer-Lindenberg et al., 2011). In male rodents, OXT plays a critical role in mediating social memory, with OXT receptors in the hippocampus (Raam et al., 2017), and amygdala (Ferguson et al., 2000) being necessary for social recognition. However, findings regarding OXT effects on human memory encoding have been inconsistent, with reports ranging from memory impairment (Bate et al., 2015; Heinrichs et al., 2004) to enhancement (Acevedo-Rodriguez et al., 2015; Guastella et al., 2008; Rimmele et al., 2009; Savaskan et al., 2008) via modulation of insula activity (Striepens et al., 2012). Of note, OXT effects may be moderated by inter-individual variables such as attachment insecurity (Bartz et al., 2010) or contextual factors including valence of the stimulus material (Bartz et al., 2011; Gao et al., 2016; Heinrichs et al., 2004; Wagner and Echterhoff, 2018). In addition, it has been discussed whether OXT primarily facilitates the processing of social cues (Guastella and MacLeod, 2012), but it is more and more recognized that OXT can modulate social and non-social behavior (Quintana and Guastella, 2020).

Inconsistent and sometimes opposing effects of OXT in women and men may result from interactive effects with EST. Evidence for interactions between OXT and EST derives from animal studies, showing extensive coexpression of EST receptor ß in OXT neurons of the paraventricular nucleus of the hypothalamus (Suzuki and Handa, 2005) and combinatorial modulation of synaptic plasticity in the medial nucleus of the amygdala in male rats (Frankiensztajn et al., 2018). The EST receptor additionally binds in a dimerized form to the composite hormone response element of the OXT promotor gene and may thus induce the production of OXT (Acevedo-Rodriguez et al., 2015; McCarthy et al., 1996; Young et al., 1998). In fact, orally administered EST induced an increase in OXT plasma levels in bulimic and healthy women (Chiodera et al., 1991). Importantly, in humans, possible OXT-EST interactions have been proposed for various domains including migraine attacks (Krause et al., 2021) and social anxiety (Schneider et al., 2021). An intriguing notion is that both hormones may antagonistically interact in a way that yields opposing effects on limbic reactivity in women and men (Lieberz et al., 2020).

To date, no study has simultaneously probed the modulatory mnemonic effects of both hormones and possible interactions in women and men. Therefore, we conducted a randomized, placebo-controlled, parallel-group functional magnetic resonance imaging (fMRI) study to test the effects of EST, OXT, and their interaction on emotional memory and to elucidate the neural mechanisms involved in mnestic sex differences (see Fig. 1). Healthy men and free-cycling women were scanned under four experimental conditions: 1. transdermal placebo gel and intranasal placebo (PLC_{tra} & PLC_{int}), 2. transdermal placebo and intranasal OXT (24 IU) (PLC_{tra} & OXT_{int}), 3. transdermal EST (2 mg) and intranasal placebo (EST_{tra} & PLC_{int}), and 4. transdermal EST and intranasal OXT (EST_{tra} & OXT_{int}). As we were primarily interested in the effects of sex, EST, and OXT and their interaction on memory encoding, the participants received their treatment prior to being scanned. During fMRI, participants viewed positive, neutral, and negative scenes. A surprise recognition task three days later was used to classify encoding trials as remembered or forgotten.

Our first hypothesis was that the EST_{tra} administration would trigger an increase in the endogenous OXT levels (Acevedo-Rodriguez et al., 2015). Due to the previously observed correlation between higher EST and enhanced memory performance, we hypothesized that an EST_{tra} treatment prior to encoding would increase recognition memory of the encoded emotional material and encoding activity in the hippocampus and amygdala, in both sexes (Loprinzi and Frith, 2018; Taxier et al., 2020). Based on previous findings about valence- and sex-specific effects of OXT (Lieberz et al., 2020; Striepens et al., 2012), we expected that the pre-encoding OXT_{int} treatment would increase recognition memory of negative stimuli and insula activity to subsequently remembered negative items in men and that it would produce the opposite effect in women (Rilling et al., 2014). Additionally, the potential antagonistic relation between EST and OXT in women (Schneider et al., 2021) and the observed opposing effects of OXT on limbic reactivity in women and men (Lieberz et al., 2020; Schneider et al., 2021), led to the hypothesis that the effects of OXT_{int} in the combined treatment group would be reduced or even inverted in women and more pronounced in men. In additional explorative analyses, we examined possible sex-related hemispheric lateralization effects of the amygdala in response to remembered emotional stimuli (Cahill, 2006; Cahill et al., 2001; Canli et al., 2002, 2000) and probed whether OXT differentially modulated the encoding of subsequently remembered social and non-social stimuli (Guastella and MacLeod, 2012; Quintana et al., 2019).

2. Material and methods

2.1. Ethics and enrolment

The study was part of a larger project and was approved by the institutional review board of the Medical Faculty of the University of Bonn and carried out in accordance with the latest revision of the Declaration of Helsinki. The study was registered in the ClinicalTrials.gov database (Identifier: NCT04330677) and the data analyses were preregistered (https://osf.io/hvknp/). The current paper focuses on the effects

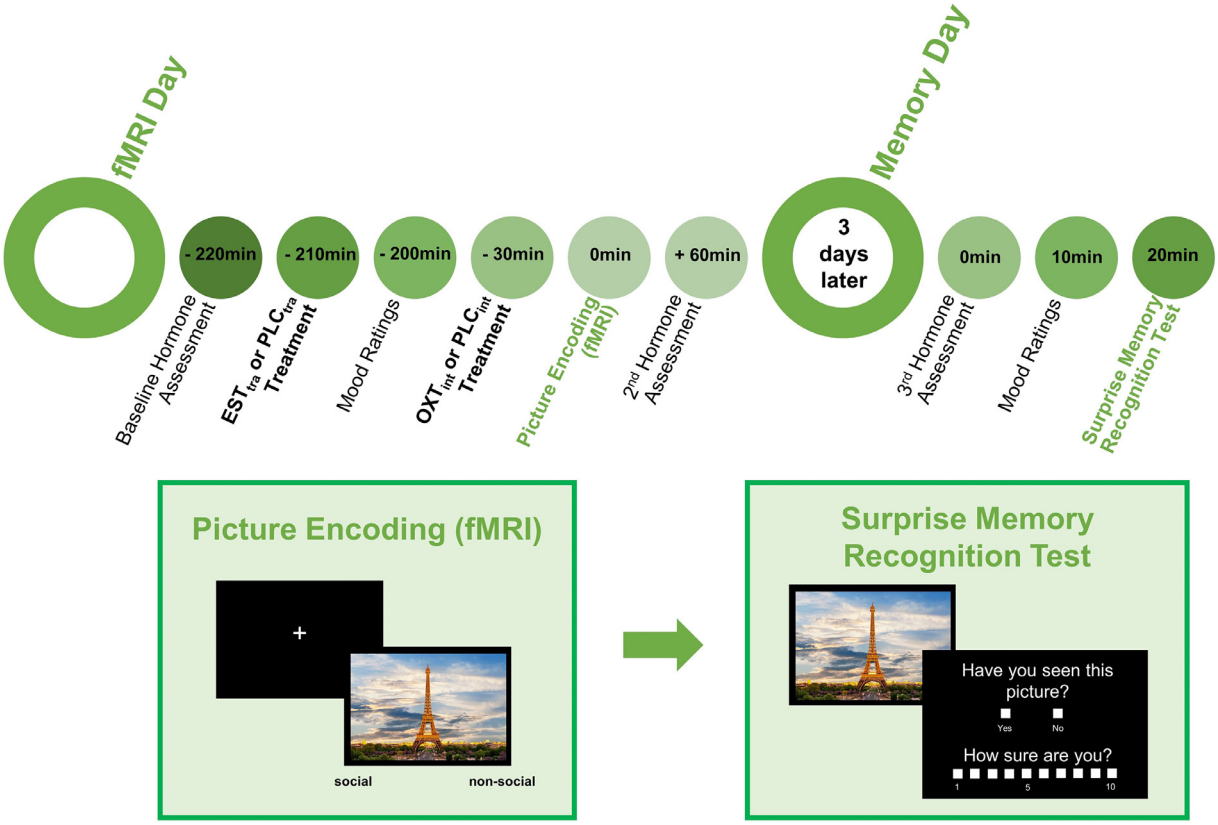

Fig. 1. *Study Design.* The functional magnetic resonance imaging (fMRI) day commenced with gel administration. Nasal sprays were administered 3 h after the gel treatment and a high-resolution structural MRI scan was conducted 30 min after the nasal spray administration. Functional imaging data collection commenced 45 min after nasal spray treatment and included a picture encoding task. Participants viewed emotional and nonemotional scenes in a randomized order and had to press a button to indicate whether the picture's context was social (i.e., if a human person was shown). Blood samples were collected at baseline and immediately after the fMRI testing session (approx. 4.5 h after the gel administration). Three days later a surprise memory recognition task was administered in a second testing session and a third blood sample was collected. The recognition task included the 120 pictures shown in the scanner and 60 new distractor pictures. Participants had to rate whether they had seen the picture in the MRI task (yes/no) and their level of confidence on a 10-point Likert scale.

of EST_{tra} and OXT_{int} on the encoding of subsequently remembered or forgotten stimuli (i.e. hypotheses 4a-h of the preregistration). The results of additional tasks and hypotheses will be reported elsewhere. The participants were enrolled in the study after giving written informed consent, and they received a monetary reimbursement of 100€ after completing the study.

2.2. Power analysis

We used G*Power 3 (Faul et al., 2007) to conduct an a-priori power analysis for the project. As we started planning the project in 2016, we were not aware of any study testing the effects of exogenous EST on memory in women and men. Therefore, we based the power analysis on the effect size obtained in our OXT dose-response study (Spengler et al., 2017). Regarding the effect of intranasal oxytocin (24 IU at a latency of 45 min) on the amygdala response to high intensity fearful faces we observed an effect size of $dz = 0.56$ in a within-subject design. To detect an oxytocin effect of this size (with $\alpha = 0.05$ and power = 0.75), we needed to test at least 48 participants in a between-subject design (i.e. 24 male participants in the placebo group and 24 male participants in the OXT group). Thus, we planned to include at least 24 participants in each treatment group (1. PLC & PLC; 2. PLC & OXT; 3. EST & PLC; 4. EST & OXT) separately for both sexes (1. female; 2. male). In total, 122 healthy women and 124 healthy men were included in the study to control for drop-outs and exclusions. The final sample included 44 participants (25 women) in the PLC_{tra} and PLC_{int} group, 56 participants (29 women) in the PLC_{tra} and OXT_{int} group, 54 participants (25 women) in the EST_{tra} and PLC_{int} group, and 48 participants (24 women) in the EST_{tra} and OXT_{int} group.

2.3. Participants

In total, 295 participants (160 women) were invited to a screening session prior to the testing session. The 246 participants (122 women) who met the inclusion criteria (see below) were tested. The participants were randomly assigned to one of four experimental conditions: (1. PLC_{tra} & PLC_{int}; 2. PLC_{tra} & OXT_{int}; 3. EST_{tra} & PLC_{int}; 4. EST_{tra} & OXT_{int}). We had to exclude 44 participants from all analyses. The data of 11 participants were not completely recorded due to technical errors: the logfiles of the fMRI task were not completely saved for 4 participants and the synchronization of the MRI scanner and the computer used to display the stimuli failed in 7 participants. Furthermore, 3 participants did not finish the study, because they did not return to the last testing day due to scheduling issues. Additional 6 participants were excluded due to hormonal ($n = 4$) or anatomical ($n = 2$) abnormalities, resulting in a sample of 226 participants (PLC_{tra} & PLC_{int}: 25 men, 26 women; PLC_{tra} & OXT_{int}: 33 men, 31 women; EST_{tra} & PLC_{int}: 32 men, 27 women; EST_{tra} & OXT_{int}: 25 men, 27 women). In accordance with our preregistered analysis of the data, we had to exclude additional 24 participants from the neural and behavioral analyses, who remembered all or none of the stimuli in at least one valence category. Thus, our final sample for the neural and behavioural analyses included 202 participants (PLC_{tra} & $PLC_{int:}$ 19 men, 25 women; PLC_{tra} & OXT_{int}: 27 men, 29 women; EST_{tra} & PLC_{int}: 29 men, 25 women; EST_{tra} & OXT_{int}: 24 men,

24 women). For demographic and psychometric baseline characteristics see **Supplementary Table S7**.

2.4. Screening session and exclusion criteria

Screenings of the participants were conducted prior to the test sessions. Participants were free of current or past physical or psychiatric illnesses assessed by self-report and the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). In addition, participants were naive to prescription-strength psychoactive medication, and had not taken any over-the-counter psychoactive medications in the 4 weeks prior to the study. The participants were right-handed, nonsmoking and between 18 and 40 years old. Furthermore, the participants were asked to maintain their regular bed and waking times and to abstain from alcohol intake on the day of the experiment. Additional exclusion criteria were current pregnancy, MRI contraindications and the use of hormonal contraceptives. All women completed the fMRI testing session simultaneously with the onset of their menstruation (days 1–6). Thus, the women were tested in their early follicular phase of their menstrual cycle. The onset of their menstruation was measured via self-report, which was further validated by blood assays obtained on the testing day. Female participants ($n = 4$) showing estradiol pre-treatment values larger than 300 pg/ml were excluded, because it can be assumed that they were not in the follicular phase of their menstrual cycle (Kratz et al., 2004).

2.5. Experimental design

We used a randomized, double-blind, placebo-controlled parallel-group study design (see Fig. 1). After a screening session, the participants completed the fMRI testing session. Three days later a surprise memory recognition task was administered in a second testing session. The fMRI day commenced with the gel administration. In accordance with our pharmacokinetic pre-study (see **Supplementary Information** [**SI**]), the OXT_{int} or placebo spray was administered 3 h after gel administration. Functional imaging data collection commenced 45 min after nasal spray administration, because it was found to be the most effective dose-test interval for OXT_{int} (Spengler et al., 2017). The imaging data collection included a high-resolution structural MRI scan and an emotional subsequent memory task. To validate the cycle phase and control for baseline differences in gonadal hormone levels, blood samples were collected at baseline, immediately after the fMRI testing session (approx. 4.5 h after gel administration), and three days following the treatment. In addition, questionnaires assessing mood (Positive and Negative Affect Schedule [PANAS] (Watson et al., 1988)) were administered twice, first immediately following the EST_{tra} or PLC_{tra} treatment at the beginning of the testing session and after the fMRI session (see **SI**).

2.6. Treatments

2.6.1. Estradiol / placebo gel treatment

On the fMRI testing day, the participants received either EST_{tra} gel (Estramon, 2 mg EST, Hexal AG, Holzkirchen, Germany) or placebo gel (2 mg ultrasonic gel), which was transdermally applied to the participants' backs. In line with a pharmacokinetic study (Eisenegger et al., 2013), a 2 mg dose was chosen to reduce the possibility of side effects. The same dose has also been found to increase emotional vicarious reactivity in men when watching a distressed other (Olsson et al., 2016).

2.6.2. Intranasal oxytocin / placebo treatment

Via a nasal spray, the participants self-administered 24 International Units (IU) of synthetic OXT_{int} (Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Rome, Italy) or placebo prior to the fMRI scanning in line with the standardization guidelines (Guastella et al., 2013) and under supervision of a trained research assistant. There is compelling evidence that OXT_{int} bypasses the blood-brain barrier, elevates OXT concentrations in the cerebrospinal fluid (Lee et al., 2018; Striepens et al., 2013) and brain (Lee et al., 2020), and thus is a valid approach to target the brain's oxytocin system (Martins et al., 2022). The placebo was equivalent to the OXT_{int} solution without the peptide itself. The amount of administered substance was weighed and supplemented until 24 IU were reached. The puffs were balanced between the nostrils to allow the solution to be absorbed by the nasal epithelium and an interpuff interval of approx. 45 s was chosen.

2.7. Emotional subsequent memory task

2.7.1. fMRI task

During the fMRI, participants viewed a picture set (see **SI**) of negative ($n = 40$), neutral ($n = 40$), and positive ($n = 40$) scenes in a randomized order. Each picture was presented for 4 s with a randomized inter-stimulus-interval of minimal 4 to maximal 6 s. The content of the pictures was either social (defined as the presence of a depicted human) or non-social, which were equally distributed across valence categories. The selection of the stimuli was based on a pilot study and stimuli were chosen such that negative and positive stimuli produced comparable arousal ratings and sex differences were absent for all ratings (for further details see **SI**). The final picture set consisted of 20 pictures in each of the following categories: social negative (e.g. crying humans), nonsocial negative (e.g. trash or unwashed dishes), social neutral (e.g. humans with a neutral facial expression), non-social neutral (e.g. neutral objects like a cup), social positive (e.g. happy and laughing humans) and non-social positive (e.g. beautiful landscapes). Examples for each valence category can be found in the SI (see **Figure S1**). During fMRI, as an attention control, the participants had to press a button, if the picture's context was social (i.e., a human person was shown) or non-social (i.e., no human person was shown). The participants could choose their responses using an MRI-compatible response grip system (NordicNeuroLab AS, Bergen, Norway). The paradigm was written in Presentation code (Neurobehavioral Systems, Albany, CA) and the stimuli were presented on a 32-inch MRI-compatible TFT LCD monitor (NordicNeuroLab, Bergen, Norway) placed at the rear of the magnet bore.

2.7.2. Surprise recognition task

The participants performed a surprise memory recognition task three days after the MRI scan to classify pictures as remembered and nonremembered. Based on our pharmacokinetic pre-study, the delay of three days was chosen to ensure that the neuroendocrine parameters return to baseline levels before the surprise recognition task. The recognition task included the 120 pictures shown in the scanner and 60 new distractor pictures (matched for valence and arousal ratings, see **SI**). The participants had to rate whether they had seen the picture in the MRI task (yes/no) and their level of confidence on a 10-point Likert scale.

2.8. Data analysis

2.8.1. Memory performance

Stimuli were classified as remembered if the picture was included in the emotional subsequent memory task and correctly identified in the recognition task (see **SI** for further information). In accordance with our preregistration, the participants had to rate their confidence for an item as ≥ 2 on the 10-point Likert scale to be classified as remembered. The participants who remembered all or none of the stimuli in at least one valence category were excluded from the analysis ($n = 24$), because a minimum of one trial was required in every valence category for the neural and behavioral model estimation. For the behavioral model, we calculated d prime (d') by subtracting the z-standardized false alarm rate from the z-standardized hit rate. The hit rate was the mean of the correctly identified stimuli used in the fMRI paradigm. The false alarm rate was the mean of the distractors in our recognition paradigm, which were incorrectly identified as seen by the participant, although

they were not included in the fMRI task. When the hit rate or false alarm rate equals zero or one, the corresponding z-score would be -/+∞. Thus, we adjusted *d'* according to the loglinear method (Stanislaw and Todorov, 1999) by adding 0.5 to both the number of hits and the number of false alarms and adding 1 to both the number of signal trials and noise trials, before calculating the hit and false alarm rates (Hautus, 1995). A high *d'* indicated that the signal was easily detected (Haatveit et al., 2010).

2.8.2. fMRI data acquisition and analysis

All fMRI data were acquired using a 3T Siemens TRIO MRI system (Siemens AG, Erlangen, Germany) with a Siemens 32-channel head coil. fMRI data were preprocessed and analysed using standard procedures in SPM12 software (Wellcome Trust Center for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (MathWorks).

In a first model, twelve conditions (valence (negative, neutral, positive) x memory (remembered, forgotten) x sociality (social, non-social)) were modeled by a stick function convolved with a hemodynamic response function. In a second model, the factor "sociality" was aggregated, resulting in six conditions (valence (3) x memory (2)). Button presses were included as regressors of no interest. On the first level, task-specific effects were modelled (details see **SI**). On the second level, a full factorial design with the between-subjects variables "OXT_{int} treatment", "EST_{tra} treatment", and "sex" was conducted. Based on previous findings (Aikins et al., 2010; Hamann et al., 1999; Striepens et al., 2012; Taxier et al., 2020), analyses were conducted focusing on the anatomically defined amygdala, hippocampus, and insula cortex based on the WFU PickAtlas as regions of interest (ROIs). The significance threshold for the ROI analyses was set to $p < 0.05$, familywise error-corrected for multiple comparisons based on the size of the ROI. In addition, an exploratory whole-brain analysis was performed (cluster defining threshold $p < 0.001$; significance threshold $p_{FWE} < 0.05$ at peak level). Parameter estimates of significant contrasts were extracted using MarsBaR (https://www.nitrc.org/projects/marsbar, RRID: SCR_009605) and further analysed in SPSS 25 (IBM Corp., Armonk, NY). For further analyses and details see SI.

2.9. Statistical analyses

Behavioural, neuroendocrine, and demographic data were analysed in SPSS 25 using standard procedures including analyses of variances (ANOVAs) and post-hoc *t*-tests. Based on the view that main and interaction effects cannot be interpreted separately if the interaction effect is significant (Schnuck and Nisic, 2020; Mayerl and Urban, 2019), we report the significant main effects in the results section, but we abstain from interpreting them. Post hoc *t*-tests were Bonferroni-corrected (p_{cor}). In general, two-tailed *p* values < 0.05 were considered significant, except for directional hypotheses, in which case one-tailed t-tests were calculated. If the assumption of sphericity was significantly violated, a Greenhouse-Geisser correction was applied. As measures of effect sizes, partial eta-squared and Cohen's d were calculated. Furthermore, frequentist inference was complemented by computing Bayes factors (BFs) with default priors via JASP (version 0.14.1.0). For Bayesian *t*-tests, BF_{10} is reported. A BF_{10} larger than 1 can be interpreted as evidence in favor of the alternative hypothesis given the current data. For Bayesian ANOVAs, BF_{incl} (with fixed seed = 1) was calculated, which compares the performance of all models that include the effect to the performance of all the models that do not include the effect. Mixed-design ANOVAs with between-subjects variables "OXT_{int} treatment" (OXT_{int}, placebo nasal spray), "EST_{tra} treatment" (EST_{tra}, placebo gel) and "sex" (women, men) and the within-subject factors "valence" (negative, neutral, positive) and "sociality" (social, non-social) were conducted for the outcome "memory" (*d'*). In a second and third model, either the factor "sociality" or the factor "valence" was aggregated. In a fourth model, both factors "valence" and "sociality" were aggregated to provide an overall *d'* that represented the general memory performance of the participants irrespective of valence and sociality. Changes in hormone concentrations were examined with mixed-design ANOVAs with the between-subject factors "OXT_{int} treatment", "EST_{tra} treatment", and "sex" and the within-subject variable "time" (baseline, after treatment, and three days after treatment; for OXT changes: baseline vs. after treatment). Furthermore, to explore the potential moderating effects of treatment-induced hormonal changes, the magnitude of the increases in hormone concentrations (levels of EST, OXT, testosterone, and progesterone after the fMRI session minus baseline) were considered covariates in the main analyses with significant behavioural (*d'*) and neural outcomes (i.e., parameter estimates of significant contrasts of interests).

3. Results

3.1. Neuroendocrine parameters

Two sample t-tests showed that women at baseline had significantly higher EST concentrations ($t_{(117.24)} = -5.70$, $p < 0.001$, $d = -0.80$; $BF_{10} = 206{,}050.22$), but lower testosterone ($t_{(98.31)} = 27.09$, $p < 0.001$, $d = 3.89$; $BF_{10} = 9.96 \times 10^{64}$) and OXT levels ($t_{(196)} = 2.75$, $p < 0.01$, $d = 0.39$; $BF_{10} = 5.04$) than men. The progesterone baseline concentrations were comparable between the two sexes ($t_{(98.72)} = -1.76$, $p = 0.08$, $d = -0.25$; $BF_{10} = 0.65$). Importantly, all baseline levels were comparable between treatment groups in women and men (all *p*s > 0.05; $BF_{10} < 1$).

The EST_{tra} administration significantly increased blood EST levels in both sexes (see Fig. 2 **and Supplementary Table S4**; mixed-design ANOVA: time * EST_{tra} treatment: $F_{(1.00, 182.64)} = 265.92$, $p < 0.001$, $\eta_p^2 = 0.60$; $BF_{incl} = 1.14 * 10^{79}$), with women exhibiting a significantly larger increase than men (time * sex * EST_{tra} treatment: $F_{(1.01, 182.645)} = 16.30$, $p < 0.001$, $\eta_p^2 = 0.08$; $BF_{incl} = 742{,}418.03$). There were no significant main or interaction effects of the OXT_{int} treatment on EST levels (all *p*s > 0.05; $BF_{10} < 0.2$), indicating that the OXT_{int} treatment did not modulate the EST increase.

OXT_{int} administration significantly increased blood OXT levels in both sexes (see Fig. 2 **and Supplementary Table S5**; mixed-design ANOVA: time * OXT_{int} treatment: $F_{(1.00,190)} = 215.77$, $p < 0.001$, $\eta_p^2 = 0.53$; $BF_{incl} = 2.43 * 10^{31}$). There were no significant main or interaction effects of the EST_{tra} treatment on the OXT levels (all *p*s > 0.05; $BF_{10} < 0.4$), indicating that the EST_{tra} treatment did not modulate the OXT increase. To specifically test our first hypothesis that the EST_{tra} administration would trigger an increase in the endogenous OXT levels, we computed an additional mixed-design ANOVA with the between-subject factor treatment (EST_{tra} & PLC_{int} vs. PLC_{tra} & PLC_{int}), the within-subject factor time (pre vs. post), and the OXT level as dependent variable. In contrast to our first hypothesis, we did not find a significant main ($p = 0.58$; $BF_{incl} = 0.39$) or interaction effect ($p = 0.44$, $BF_{incl} = 0.28$) of the EST_{tra} treatment on blood OXT levels, indicating that the EST_{tra} treatment did not induce a significant OXT increase. The Bayes factors provide moderate evidence that the EST_{tra} administration had no effect on OXT levels.

To examine whether the changes in OXT_{int} and EST_{tra} levels moderated behavioural and neural treatment effects, we included the hormonal changes (after treatment minus baseline) as separate covariates in the analyses and all sex * treatment interactions remained significant. Furthermore, the treatments did not significantly alter the participants' mood (see **SI** and **Supplementary Table S6**).

3.2. Results for hypothesized valence-specific effects

Recognition memory was significantly better for emotional than neutral items (main effect valence: $F_{(2.00,388)} = 13.18$, $p < 0.001$, $\eta_p^2 = 0.06$; $BF_{incl} = 3054.02$) and for social than non-social stimuli (main effect of sociality: $F_{(1.00,194)} = 7.59$, $p < 0.01$, $\eta_p^2 = 0.04$; $BF_{incl} = 5.29$). However,

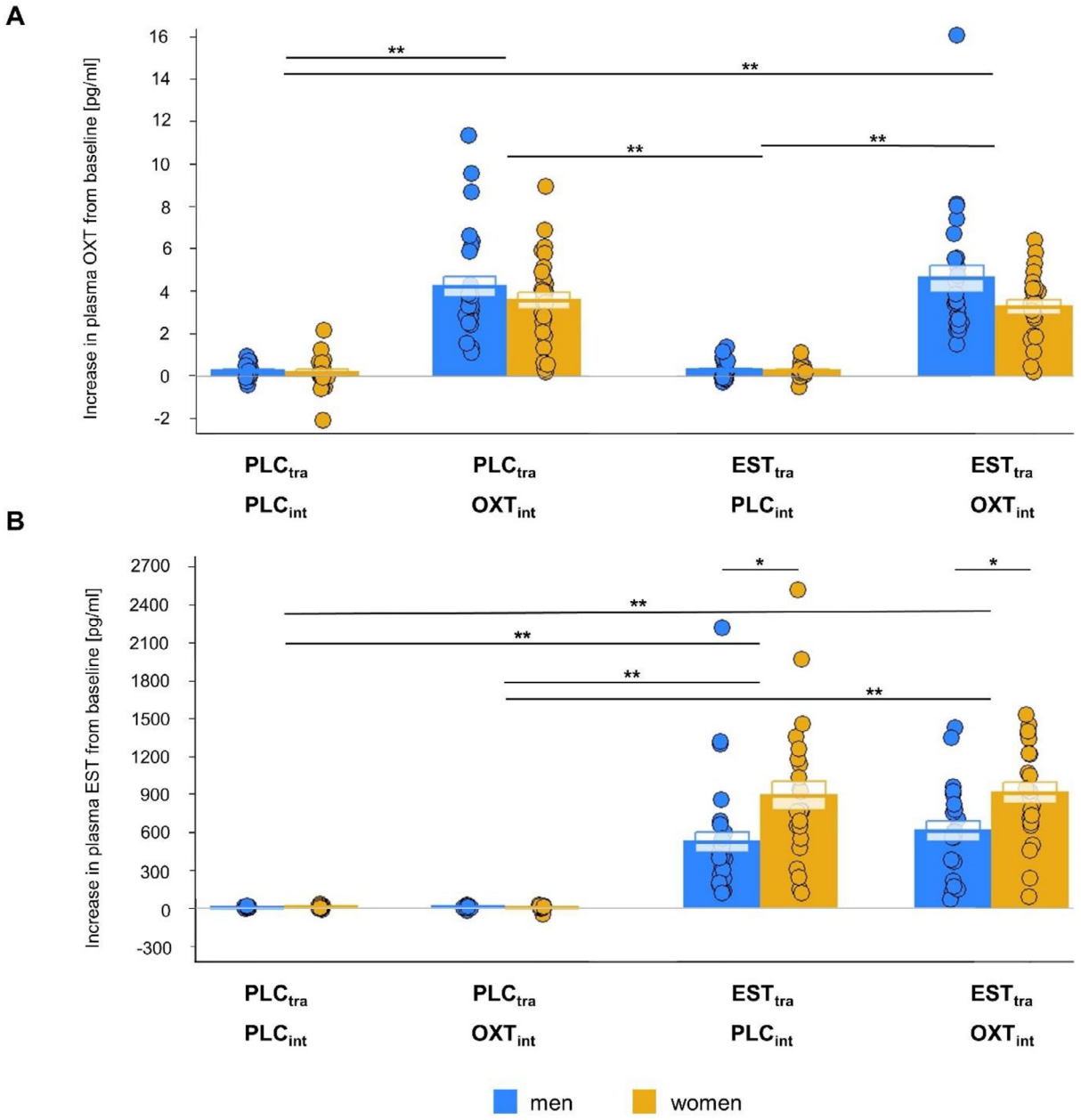

Fig. 2. *Treatment-induced changes (immediately after fMRI session minus baseline) in oxytocin and estradiol plasma levels.* **A** The administration of 24 international units (IU) of intranasal OXT_{int} induced a significant increase in blood oxytocin levels in both sexes. There was no significant interaction with the estradiol treatment. **B** The transdermal administration of 2 mg estradiol (EST_{tra}) significantly elevated blood estradiol levels in both sexes. EST_{tra} treatment induced a significantly stronger increase in women than in men, but there was no significant interaction with oxytocin treatment. PLC_{tra} = transdermal placebo gel; PLC_{int} = intranasal placebo; OXT_{int} = intranasal oxytocin; EST_{tra} = transdermal estradiol. $^{*}p < 0.05$, $^{**}p < 0.01$.

in contrast to our hypothesized effects of EST_{tra} or OXT_{int} on emotional memory, there were no significant interactions between these factors (valence and sociality) and sex or treatments ($BF_{incl} < 0.4$). We further hypothesized that the OXT_{int} treatment would increase the recognition memory of negative stimuli in men with placebo gel, whereas we expected a decrease in women. Furthermore, we expected that OXT_{int} would increase the activity in the insula cortex during the processing of subsequently remembered negative stimuli compared to forgotten items (i.e. [Negative $_{Remembered}$ > Negative $_{Forgotten}$]) in men with placebo gel and the opposite effect in women. We calculated two-sample *t*-tests to compare *d'* for negative stimuli and the insula responses to negative remembered stimuli compared to negative forgotten stimuli between the PLC_{tra} & PLC_{int} and PLC_{tra} & OXT_{int} groups separately for women and men. No significant group differences were detected (all *ps* > 0.05). Further mixed-design ANOVAs with EST_{tra} treatment and OXT_{int} treatment as between-subject factors and either *d'* for negative stimuli or the insula responses to negative remembered stimuli compared to negative forgotten stimuli as dependent variables separately for both sexes did not reveal any significant main or interaction effects of the treatment types (all *ps* > 0.05). Thus, in contrast to our hypotheses, we did not observe selective treatment effects for negative items.

3.3. Further behavioural results

Due to the missing significant interactions between valence and sociality and sex or treatments, the following exploratory analyses are

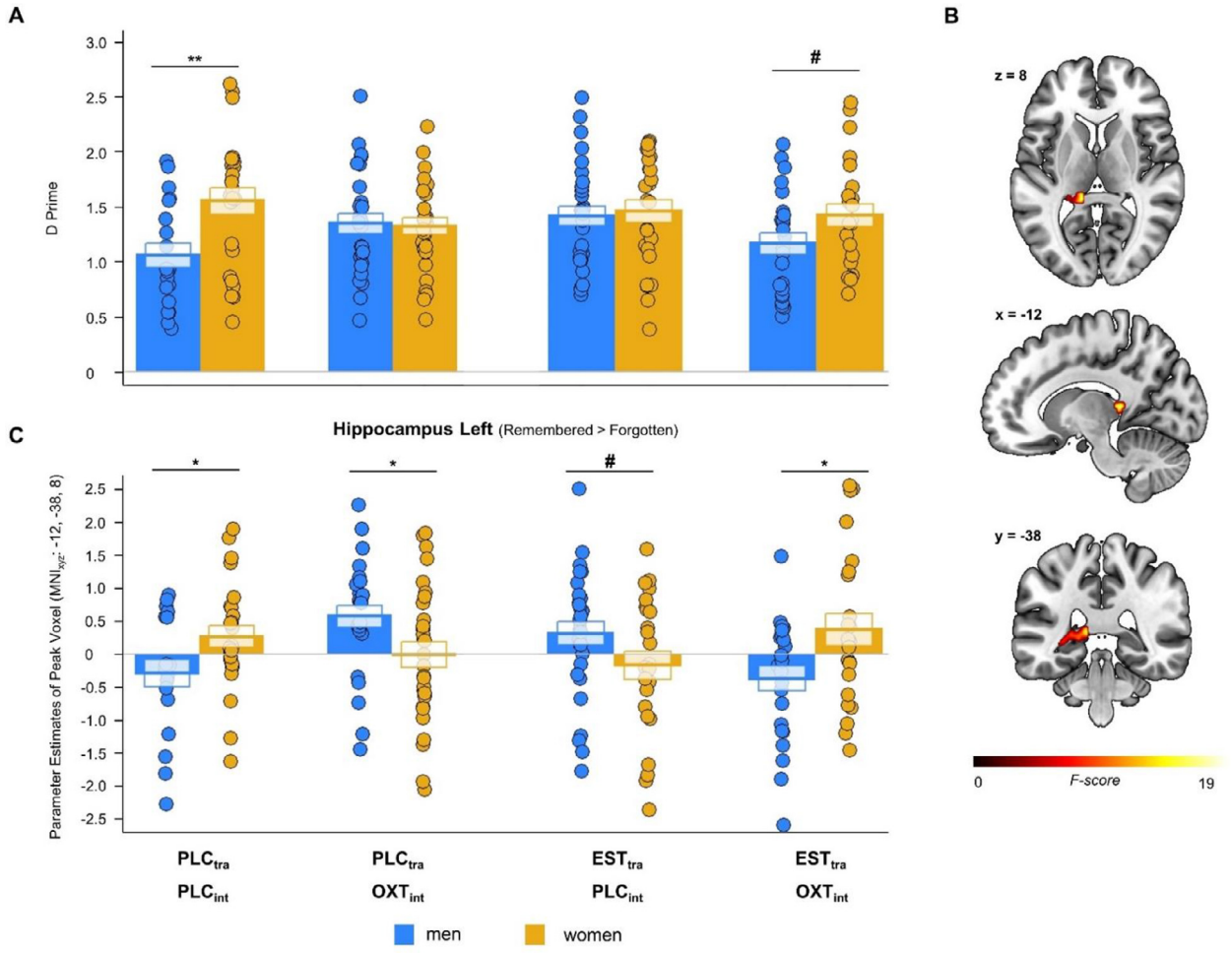

Fig. 3. *Treatment effects on mnemonic and hippocampal sex differences.* **A** Following placebo administration, women showed a significantly better memory performance (*d'*) than men, but there were no significant sex differences after single trandermal estradiol (EST_{tra}) or intranasal oxytocin (OXT_{int}) treatment. After the combined treatment, a trend similar to that observed in the placebo group was evident. **B** We observed a significant three-way interaction of sex, OXT_{int}, and EST_{tra} treatment in the left hippocampus responses to remembered compared to forgotten stimuli (MNI peak coordinates [x, y, z]: −12, −38, 8). **C** Further analyses of the parameter estimates for the left hippocampal responses revealed a similar pattern as that observed with memory performance. Women exhibited stronger left hippocampal responses to remembered items compared to forgotten items than men under placebo. This sex difference was reversed after either EST_{tra} or OXT treatment. Intriguingly, the same pattern as that observed in the placebo group was again evident in the combined treatment group. PLC_{tra} = transdermal placebo gel; PLC_{int} = intranasal placebo; OXT_{int} = intranasal oxytocin; EST_{tra} = transdermal estradiol. $^{\#}p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$.

based on *d'* averaged across valences and sociality. There were no significant treatment effects on the confidence ratings (for further details see SI).

3.3.1. Behavioural results: treatment effects

A mixed-design ANOVA with *d'* as the dependent variable and sex, EST_{tra}, and OXT_{int} as between-subject factors revealed that sex differences in recognition memory were significantly altered by both EST_{tra} and OXT_{int} treatments (significant three-way interaction: sex * EST_{tra} treatment * OXT_{int} treatment: $F_{(1.00,194)} = 6.96$, $p < 0.01$, $\eta_p^2 = 0.04$; $BF_{incl} = 5.55$; see Fig. 3 **and Supplementary Table S1**). To disentangle the observed three-way interaction, we examined the treatment effects separately for both sexes. Therefore, we calculated separate ANOVAs for both sexes with *d'* as dependent variable and the two treatment types as between-subject factors. We found a significant interaction between the OXT_{int} and EST_{tra} treatments in men ($F_{(1.00,95)} = 7.84$, $p < 0.01$ [$p_{cor} = 0.01$], $\eta_p^2 = 0.08$; $BF_{incl} = 6.94$), but not in women ($F_{(1.00,99)} = 0.93$, $p = 0.34$, $\eta_p^2 = 0.01$; $BF_{incl} = 0.40$). In men, OXT_{int} nonsignificantly improved recognition memory after PLC_{tra} treatment (PLC_{tra} & OXT_{int} vs. PLC_{tra} & PLC_{int}: $t_{(44)} = -2.01$, $p = 0.03$ [$p_{cor} = 0.1$], $d = -0.6$; $BF_{10} = 1.45$; one-tailed) and reduced performance after EST_{tra} treatment (EST_{tra} & OXT_{int} vs. EST_{tra} & PLC_{int}: $t_{(51)} = 1.95$, $p = 0.06$ [$p_{cor} = 0.23$], $d = 0.54$; $BF_{10} = 1.30$). However, in men, EST_{tra} treatment produced significantly better memory in participants who received PLC_{int} (EST_{tra} & PLC_{int} vs. PLC_{tra} & PLC_{int}: $t_{(46)} = -2.55$, $p < 0.01$ [$p_{cor} = 0.03$], $d = -0.75$; $BF_{10} = 3.75$; one-tailed), but the EST_{tra} effect was diminished in individuals who received OXT_{int} (EST_{tra} & OXT_{int} vs. PLC_{tra} & OXT_{int}: $t_{(49)} = 1.37$, $p = 0.18$, $d = 0.38$; $BF_{10} = 0.60$). Together, the Bayes factors indicate moderate evidence for an EST_{tra} * OXT_{int} interaction in men and moderate evidence for an EST_{tra}-induced memory improvement in men who had received PLC_{int}.

3.3.2. Behavioural results: sex differences

To further disentangle the observed three-way interaction, we examined sex differences within the treatment groups by applying post-hoc Bonferroni-corrected two-sample t-tests. Under placebo (PLC_{tra} & PLC_{int}), women showed significantly better memory performance than men ($t_{(42)} = -2.96$, $p < 0.01$ [$p_{cor} = 0.02$], $d = -0.90$; $BF_{10} = 8.31$), but there were no significant sex differences in the EST_{tra} & PLC_{int} group ($t_{(52)} = -0.32$, $p = 0.75$, $d = -0.09$; $BF_{10} = 0.29$) or the PLC_{tra} & OXT_{int} group ($t_{(54)} = 0.21$, $p = 0.83$, $d = 0.06$; $BF_{10} = 0.28$). The combined treatment (EST_{tra} & OXT_{int}) produced no significant effects, but the direction

of sex differences was comparable to that of the placebo group (women > men; $t_{(46)} = -1.87$, $p = 0.07$ [$p_{cor} = 0.28$], $d = -0.54$; $BF_{10} = 1.16$). Thus, the Bayes factors indicated moderate evidence for sex differences under placebo, moderate evidence for the absence of sex differences after single treatments and an inconclusive sex effect in the combined group.

3.4. Neural results

3.4.1. Whole-brain task effects

Across treatments and sexes, the remembered items compared to forgotten items induced activations in a wide network of brain areas (see **Supplementary Table S2**), including the bilateral hippocampus (left: Montreal Neurological Institute [MNI] peak coordinates [x, y, z]: −32, −18, −14, $F_{(1.00,194)} = 28.81$, on peak level $p_{FWE} < 0.02$; right: MNI peak coordinates [x, y, z]: 20, −6, −14, $F_{(1.00,194)} = 105.12$, on peak level $p_{FWE} < 0.001$). Furthermore, an emotional memory effect (i.e., [Emotional $_{Remembered>Forgotten}$ > Neutral $_{Remembered>Forgotten}$]) was evident in the left and right amygdala (left: MNI peak coordinates [x, y, z]: −20, −6, −14, $F_{(1.00,194)} = 18.12$, on peak level $p_{FWE} < 0.01$; right: MNI peak coordinates [x, y, z]: 22, −6, −12, $F_{(1.00,194)} = 13.96$, on peak level $p_{FWE} = 0.02$), as well as the left hippocampus (MNI peak coordinates [x, y, z]: −18, −6, −14, $F_{(1.00,194)} = 18.55$, on peak level $p_{FWE} < 0.01$) and the right insula (MNI peak coordinates [x, y, z]: 26, 22, −16, $F_{(1.00,194)} = 18.85$, on peak level $p_{FWE} = 0.01$; for additional activations, see **Supplementary Table S3**).

3.4.2. ROI analysis: treatment effects

We found a significant three-way interaction of sex, OXT_{int}, and EST_{tra} treatment in the left hippocampus responses to remembered stimuli compared to forgotten stimuli (MNI peak coordinates [x, y, z]: −12, −38, 8, $F_{(1.00,194)} = 17.80$, on peak level $p_{FWE} = 0.012$; see Fig. 3), but we did not observe a significant three-way interaction for this contrast for the insula or amygdala responses. To disentangle the observed three-way interaction in the left hippocampus, we examined the parameter estimates for left hippocampal responses to remembered items compared to forgotten items separately for both sexes. In a mixed-design ANOVA with the left hippocampal responses as dependent variable and OXT_{int} and EST_{tra} treatments as between-subject factors, we found a significant interaction between the OXT_{int} and EST_{tra} treatments in men ($F_{(1.00,95)} = 17.30$, $p < 0.001$ [$p_{cor} < 0.001$], $\eta_p^2 = 0.15$; $BF_{incl} = 316.43$), but not in women ($F_{(1.00,99)} = 3.92$, $p = 0.05$ [$p_{cor} = 0.10$], $\eta_p^2 = 0.04$; $BF_{incl} = 1.38$). Post-hoc two-sample t-tests revealed that OXT_{int} significantly increased the hippocampal response to remembered stimuli compared to forgotten stimuli in men who had received PLC_{tra} (PLC_{tra} & OXT_{int} vs. PLC_{tra} & PLC_{int}: $t_{(44)} = -3.30$, $p < 0.01$ [$p_{cor} < 0.01$], $d = -0.99$; $BF_{10} = 18.29$). Importantly, in accordance with our hypothesis, we found evidence for an interaction of OXT_{int} and EST_{tra}, but not in the expected direction. OXT_{int} had the opposite effect in men after EST_{tra} treatment and significantly decreased hippocampal responses (EST_{tra} & OXT_{int} vs. EST_{tra} & PLC_{int}: $t_{(51)} = 2.61$, $p = 0.01$ [$p_{cor} = 0.04$], $d = 0.72$; $BF_{10} = 4.24$). Likewise, EST_{tra} did not significantly affect hippocampal activation in men after PLC_{int} (EST_{tra} & PLC_{int} vs. PLC_{tra} & PLC_{int}: $t_{(46)} = -2.17$, $p = 0.02$ [$p_{cor} = 0.07$], $d = -0.64$; $BF_{10} = 1.88$; one-tailed), but significantly decreased hippocampal activation when combined with OXT_{int} treatment (EST_{tra} & OXT_{int} vs. PLC_{tra} & OXT_{int}: $t_{(49)} = 3.80$, $p < 0.001$ [$p_{cor} < 0.001$], $d = 1.07$; $BF_{10} = 67.05$). Thus, again, the Bayes factors indicated strong evidence for an EST_{tra} * OXT_{int} interaction in men. Furthermore, there was moderate-to-strong evidence for opposing effects of OXT_{int} on hippocampal activation depending on EST_{tra} pretreatment and strong evidence for an EST_{tra}-induced decrease when combined with OXT_{int}. Nevertheless, in contrast to our hypothesis, we did not detect a significant effect of EST_{tra} on encoding activity for all stimuli in the hippocampus and amygdala in women.

Additionally, we did not observe a significant three-way interaction for the social memory effect in the hippocampus, insula or amygdala (i.e., [Social $_{Remembered>Forgotten}$ > Non-social $_{Remembered>Forgotten}$]). However, we found a significant two-way interaction of sex and OXT_{int} treatment in the left and right amygdala responses (left: MNI peak coordinates [x, y, z]: −24, −4, −16, $F_{(1.00,194)} = 11.31$, on peak level $p_{FWE} = 0.048$; right: MNI peak coordinates [x, y, z]: 20, −4, −16, $F_{(1.00,194)} = 18.98$, on peak level $p_{FWE} = 0.002$). To disentangle the treatment effects of OXT_{int}, two-sample *t*-tests were calculated to compare the amygdala responses across the EST_{tra} treatments in the PLC_{int} (PLC_{tra} & PLC_{int} and EST_{tra} & PLC_{int}) and OXT_{int} (PLC_{tra} & OXT_{int} and EST_{tra} & OXT_{int}) groups separately for women and men. There were no significant OXT_{int} treatment effects in men. However, in women OXT_{int} significantly decreased bilateral amygdala responses compared to PLC_{int} (OXT_{int} vs. PLC_{int}: left: MNI peak coordinates [x, y, z]: −24, −4, −16, $F_{(1.00,101)} = 4.31$, on peak level $p_{FWE} = 0.002$; right: MNI peak coordinates [x, y, z]: 20, −2, −14, $F_{(1.00,101)} = 4.28$, on peak level $p_{FWE} = 0.002$). We found no further significant main or interaction effects of sex and treatment types for the hippocampus, insula and amygdala responses for the social memory effect (all *p*s > 0.05).

3.4.3. ROI analysis: sex differences

We observed a significant main effect of sex in the left amygdala responses to positive remembered stimuli compared to positive forgotten stimuli (MNI peak coordinates [x, y, z]: −28, −2, −24, $F_{(1.00,204)} = 12.37$, on peak level $p_{FWE} = 0.03$; see Fig. 4) and in the right amygdala responses to negative remembered stimuli compared to negative forgotten stimuli (MNI peak coordinates [x, y, z]: 28, 4, −16, $F_{(1.00,205)} = 12.23$, on peak level $p_{FWE} = 0.03$), but there were no significant interactions between sex and either treatment type. We extracted the parameter estimates from the significant main effect and analyses revealed that across treatments men exhibited significantly increased right amygdala responses to negative remembered stimuli relative to negative forgotten stimuli compared to women ($t_{(200)} = 3.16$, $p < 0.01$, $d = 0.45$; $BF_{10} = 15.17$). In contrast, women showed a stronger activation than men in response to positive remembered stimuli relative to positive forgotten stimuli in the left amygdala ($t_{(200)} = -2.85$, $p < 0.01$, $d = -0.40$; $BF_{10} = 6.50$).

To further disentangle the observed three-way interaction in the left hippocampus, we examined sex differences in the parameter estimates for left hippocampal responses to remembered items compared to forgotten items separately for the treatment groups. Post-hoc two-sample t-tests of the extracted parameter estimates revealed that women exhibited nonsignificantly stronger hippocampal responses to remembered items than men under placebo (PLC_{tra} & PLC_{int}; $t_{(42)} = -2.10$, $p = 0.04$ [$p_{cor} = 0.17$], $d = -0.64$; $BF_{10} = 1.68$). This sex difference was reversed (i.e., men > women) in both the EST_{tra} & PLC_{int} group ($t_{(52)} = 1.77$, $p = 0.08$, [$p_{cor} = 0.33$], $d = 0.48$; $BF_{10} = 0.99$) and the PLC_{tra} & OXT_{int} group ($t_{(54)} = 2.25$, $p = 0.03$ [$p_{cor} = 0.11$], $d = 0.60$; $BF_{10} = 2.13$). Interestingly, the same pattern observed in the placebo group was again evident in the combined treatment group (women > men; $t_{(46)} = -2.42$, $p = 0.02$ [$p_{cor} = 0.08$], $d = -0.7$; $BF_{10} = 2.93$). Notably, a similar sex * EST_{tra} treatment * OXT_{int} treatment interaction emerged for the emotional memory effect in the left hippocampus ([Emotional $_{Remembered>Forgotten}$ > Neutral $_{Remembered >Forgotten}$]; MNI peak coordinates [x, y, z]: −14, −40, 10, $F_{(1.00,194)} = 16.66$, on peak level $p_{FWE} = 0.02$; see **SI**).

As an additional control analysis, we used a median-dichotomization and excluded EST_{tra}-treated women with large EST increase. In this subsample, the treatment-induced increases in EST levels were comparable between women and men within the treatment groups (all *p*s > 0.05; $BF_{10} < 0.6$) and the main behavioral and neural analyses yielded a similar pattern of results. In line with our reported main findings, we also found a significant three-way interaction of sex, OXT_{int}, and EST_{tra} treatment in the left hippocampus responses to remembered stimuli compared to forgotten stimuli (MNI peak coordinates [x, y, z]: −12, −38, 8, $F_{(1.00,165)} = 15.01$, $p < 0.01$ [$p_{cor} < 0.01$], $\eta_p^2 = 0.08$; $BF_{incl} = 208.56$), as well as a significant three-way interaction for the recognition mem-

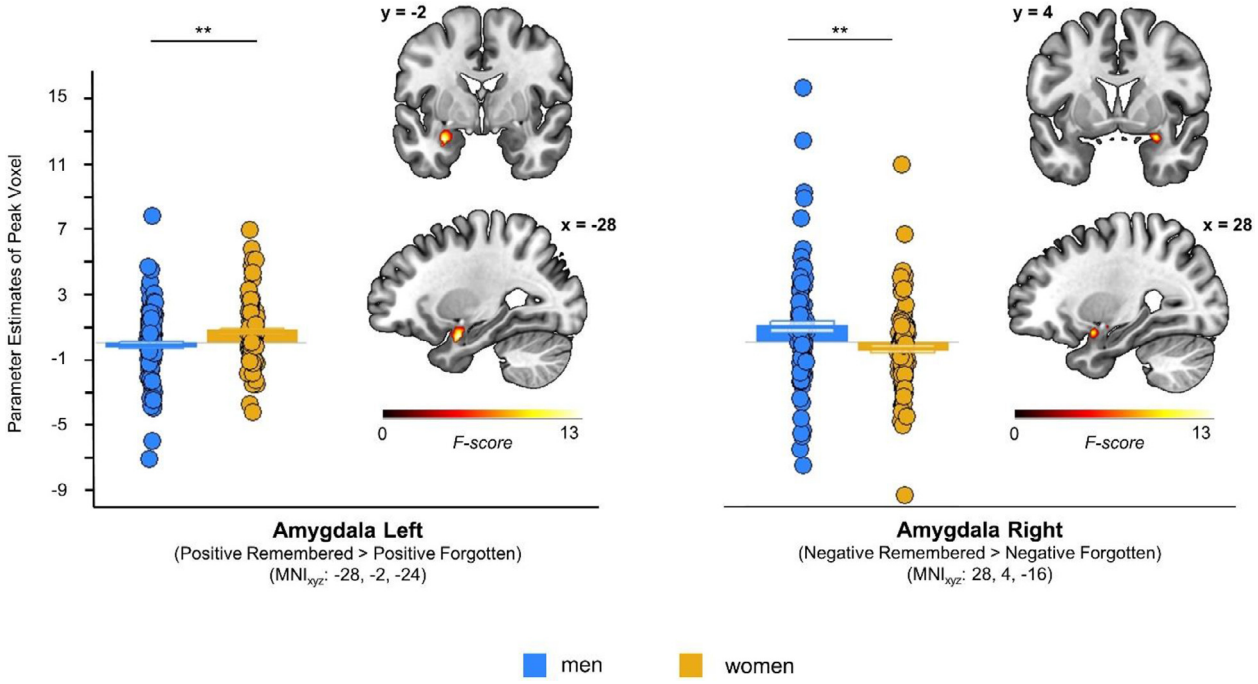

Fig. 4. *Sex-specific lateralization of amygdala activation.* Significant main effects of sex emerged in left amygdala responses to positive remembered stimuli compared to positive forgotten stimuli (MNI peak coordinates [x, y, z]: −28, −2, −24) and for right amygdala responses to negative remembered stimuli compared to negative forgotten stimuli (MNI peak coordinates [x, y, z: 28], 4, −16). Across treatments, analyses of the extracted parameter estimates showed that men exhibited significantly greater right amygdala responses to negative remembered stimuli relative to negative forgotten stimuli than women. However, the pattern in the left amygdala was reversed. Women showed a stronger activation than men in response to positive remembered stimuli compared to positive forgotten stimuli. There were no significant interactions between sex and either treatment type. $^{**}p < 0.01$.

ory ($F_{(1.00,165)} = 6.24$, $p = 0.01$, $\eta_p{}^2 = 0.04$; $BF_{incl} = 5.05$). Further analyses of the extracted parameter estimates revealed results that were comparable to our reported main findings (see **SI** and **Supplementary Figure S2**).

4. Discussion

The goal of the current study was to elucidate the effects of EST_{tra} and OXT_{int} and their interaction on the encoding of emotional and non-emotional scenes in healthy women and men. In contrast to our hypotheses, the treatments did not selectively affect the recognition memory of emotional material and we did not find significant treatment effects on amygdala or insula responses. Instead, we detected effects of EST_{tra} and OXT_{int} on the overall *d'* representing the general memory performance accompanied by neural changes in the hippocampus, but not in the amygdala or insula. Our results showed that under placebo women exhibited a better recognition memory than men and increased hippocampal responses to subsequently remembered items irrespective of emotional valence. Separate treatments with either EST_{tra} or OXT_{int} significantly diminished this mnemonic sex difference and reversed the hippocampal activation pattern. However, the combined treatments produced no significant effect, indicating an antagonistic effect of the two hormones at the administered doses. This pattern was also evident in a subsample with comparable treatment-induced EST increases in women and men. Given significant memory differences between the sexes in the placebo group, our data are consistent with the reported advantage of women in episodic memory (Andreano and Cahill, 2009; Fuentes and Desrocher, 2012; Heisz et al., 2013; Herlitz et al., 1997; Herlitz and Yonker, 2002; Loprinzi and Frith, 2018). The preponderance of studies with exclusively female samples to examine the effects of the "female" sex hormone EST_{tra} and exclusively male samples in the case of OXT_{int} might have obfuscated the contribution of these hormones to sex differences in episodic memory (Hammes and Levin, 2019; Taxier et al., 2020). Our study included both sexes and indicated an essential role of EST_{tra} and OXT_{int} as modulators of episodic memory in women and men.

In men, separate treatment with either EST_{tra} or OXT_{int} prior to encoding increased hippocampal activation and improved subsequent recognition memory, although the EST_{tra} effects on hippocampal activation and the behavioral OXT_{int} memory effect did not survive correction for multiple comparisons. Previous studies show that EST and OXT receptor signaling in the hippocampus regulate neuronal excitability, synaptic plasticity, and memory formation in male mice and rats (Frick et al., 2018; Lin and Hsu, 2018). For instance, EST induced spinogenesis in the hippocampus (Jacome et al., 2016) and improved long-term memory following pretraining administration of EST_{tra} in male rats (Locklear and Kritzer, 2014; Vázquez-Pereyra et al., 1995). Likewise, OXT has been found to enhance cortical information transfer in the hippocampus irrespective of sex by exciting fast-spiking interneurons (Owen et al., 2013). Furthermore, conditional deletion of OXT receptors in the hippocampus of male mice impaired the persistence of long-term social recognition memory (Lin et al., 2018), and treatment with OXT_{int} after experiencing a stressful event rescued recognition memory and hippocampal long-term potentiation in male rats (Park et al., 2017). In humans, some studies found improved recognition memory after an OXT_{int} administration before encoding (Guastella et al., 2008; Rimmele et al., 2009), while other studies observed the opposite effect (Heinrichs et al., 2004; Herzmann et al., 2012). In our study, the behavioral effect of the OXT_{int} administration did not survive correction for multiple comparisons, indicating that the mnemonic effects of 24IU OXT_{int} administration in men are not very robust. By contrast, EST_{tra} treatment significantly improved recognition memory in men independent of the emotional valence. We are not aware of any study probing the effects of exogenous EST_{tra} on memory performance in men, but our study provides first evidence that mnemonic EST effects in men are not emotion-specific.

Intriguingly, a single EST_{tra} treatment produced similar effects as OXT_{int}, but the OXT_{int}-induced increase in hippocampal activation was absent after EST_{tra} pretreatment. One possible explanation for this pattern of results is that EST_{tra} may have increased OXT receptor binding (Johnson et al., 1991), thereby mirroring the opposing effects previously observed for higher OXT_{int} doses in men (Spengler et al., 2017). Interestingly, EST_{tra}*OXT_{int} interactions may have contributed to the modulatory effects of hormonal contraception (Scheele et al., 2016) and to the sex-specific effects of OXT_{int} that have been found in various domains, including fear-related amygdala reactivity (Lieberz et al., 2020), the perception of competition (Fischer-Shofty et al., 2013), moral decision-making (Scheele et al., 2014), and emotional responses to couple conflict (Ditzen et al., 2013). In both sexes, we did not find the expected increase of endogenous OXT_{int} following the EST_{tra} treatment 4.5 h after gel administration, but there is preliminary evidence that EST_{tra}-induced OXT secretion would be most pronounced after 18–36 h (Chiodera et al., 1991). Thus, the chosen timepoint of the second blood sample was possibly too early to detect a potential increase in endogenous OXT levels.

The absence of a significant EST_{tra} effect in women may reflect sex-specific dose-dependent mechanisms. The EST_{tra} treatment produced a significantly larger increase in peripheral EST concentrations in women than in men, yielding concentrations comparable to the EST levels in pregnancy (Gressner and Arndt, 2013). Thus, the nonsignificant decrease in hippocampal activation is consistent with the notion of an inverted U-shaped dose-response function of EST_{tra} in women (Bayer et al., 2018). EST_{tra} levels within physiological ranges have been found to stimulate hippocampal activity, while levels within supraphysiological ranges can have the opposite effect. While low levels of EST were shown to activate the high-affinity receptor ERα, thus inducing synaptogenesis and enhancing blood oxygen level-dependent (BOLD) responses, high levels of EST also activated the low-affinity receptor ERβ, which in turn reduced synaptogenesis (Foster, 2012; Szymczak et al., 2006). As such, the EST_{tra}-enhanced anxiolytic action of OXT_{int} previously observed in female mice may also be dose-dependent (Young et al., 1998). In contrast, sex-specific effects of OXT_{int} on the amygdala response to fearful faces in women have been reported across a range of doses (Lieberz et al., 2020). Significant OXT_{int} effects in men, but no-significant effects in women, have been previously observed for hippocampal responses to cooperative interactions (Rilling et al., 2014) and chemosensory stress signals (Maier et al., 2019). Intranasal OXT administered after acquisition improved recognition memory of faces in a combined sample of 36 women and men (Savaskan et al., 2008), suggesting that the peptide's mnemonic effect may be modulated by the stimulus material or may differ between encoding and consolidation.

Similar time-sensitive effects have been found for other domains, with OXT_{int} increasing both fear conditioning (Eckstein et al., 2016) and fear extinction (Eckstein et al., 2015) in men depending on whether the peptide is administered before or after the fear learning. Nevertheless, a strong impact of OXT_{int} on consolidation processes in our study seems unlikely considering the kinetics of OXT_{int}. Limbic effects of OXT_{int} were already attenuated 75 min after nasal spray administration (Spengler et al., 2017) and blood OXT concentrations return to baseline 3–4 h after the treatment (Gossen et al., 2012). To account for the longer half-life time of EST_{tra} (~37 h, (Naunton et al., 2006)), we implemented a delay of 3 days between the encoding and the surprise recognition test. Furthermore, the recognition test was unannounced and we can therefore exclude that the treatments interacted with intentional memory strategies during the consolidation phase. Nevertheless, residual OXT or EST effects on consolidation processes may have contributed to the observed results and future human studies should apply OXT and EST immediately following encoding to further disentangle their roles in memory encoding and consolidation.

In addition, we replicated the sex-specific lateralization of amygdala recruitment (Cahill, 2006; Cahill et al., 2001; Canli et al., 2002, 2000), but there was no significant interaction of the treatments for the emotional memory effect in the amygdala. The effects of EST_{tra} and OXT_{int} on amygdala activation have been well established in animal studies (Acevedo-Rodriguez et al., 2015; Knobloch et al., 2012; Viviani et al., 2011), but translation to humans may depend on methodological details such as task design and stimulus material. Furthermore, while the availability of aromatase, the enzyme that catalyzes testosterone to estradiol, is comparable in the amygdala between women and men, higher aromatase availability was associated with lower memory performance in men, but not women (Alia-Klein et al., 2020). Thus, the effects of and interactions with other gonadal steroids should be taken into consideration. For instance, testosterone treatment shifted amygdala lateralization towards the right hemisphere in transgender boys (Beking et al., 2020) and exogenous progesterone increased amygdala responses to emotional faces in women (Van Wingen et al., 2008).

Our data replicated the known memory effect of emotional valence of the stimulus material, evident in better recognition memory of emotional vs. neutral images. In contrast to our hypotheses, however, the treatments did not selectively affect the recognition memory of emotional material and we did not find an emotion-specific female memory advantage. Null effects of EST on emotional memory performance have been previously observed after exogenous administration (Bayer et al., 2018) and while comparing different menstrual cycle phases (Gamsakhurdashvili et al., 2021). Moreover, we pre-selected the emotional scenes such that they were rated to be equally arousing by women and men (cf. **SI**) and better emotion-specific recognition memory in women was evident for emotional pictures that were also rated to be more arousing by women (Canli et al., 2002). Furthermore, OXT_{int} administered before the encoding has been found to improve the recognition memory for happy faces (Guastella et al., 2008) and the free recall of negative scenes (Striepens et al., 2012). We did not observe significant interactions between valence and treatments or between sociality and treatments on the behavioral level. This could be related to the use of scenes with a human person as social items instead of faces and may reflect differences between recognition and recall memory. Similarly, OXT_{int} has been shown to enhance emotion recognition of faces overall, while emotion-specific effects (i.e. happy or fearful faces) varied as a function of exposure time (Shahrestani et al., 2013). Our finding of an OXT_{int} effect on both social and non-social stimuli is in accordance with recent theoretical accounts describing OXT as an allostatic hormone that modulates both social and non-social behavior by maintaining stability through changing environments (Quintana and Guastella, 2020). On the neural level, OXT_{in} had no social-specific effects on hippocampus activity, but we observed a significant interaction of sex and OXT_{int} for amygdala responses to social memory (i.e. Social $_{Remembered>Forgotten}$ > Non-social $_{Remembered>Forgotten}$), suggesting that the moderation of OXT effects by sociality differs between brain regions.

The findings of the present study need to be considered in the context of the following limitations. Treatment-induced EST levels were higher in women than in men and although we included the treatment-induced hormone concentrations as control variables, this difference may have contributed to the observed sex-specific treatment effects. In addition, in both sexes, supraphysiological estradiol levels were induced due to the exogenous administration. It is conceivable that interactions between OXT_{int} and EST_{tra} in women would be evident at physiological EST levels occurring during the menstrual cycle. Along these lines, we tested women during the early follicular phase to control for changes in endogenous hormone levels, but this also means that we cannot extrapolate our findings to other cycle phases which are associated altered hippocampal gene expressions (Iqbal et al., 2020). Future studies should employ different doses in women and men and postlearning administration protocols to further delineate the sex-specific memory effects of EST_{tra} and OXT_{int}. Furthermore, we observed strong evidence for an interaction between sex, EST and OXT, but the hippocampal sex differences within the treatment groups did not survive correction for multiple comparisons and thus should be interpreted cautiously. Of note, millions of women around the world use steroid-based hormonal con-

traception as an effective way of birth control (Alkema et al., 2013). Some studies have shown an increased emotional memory recall in hormonal contraceptive users (Spalek et al., 2019), whereas other studies reported that neither pill phase (on and off) nor oral contraceptive use in general affected emotional memory (Kuhlmann and Wolf, 2005; Mordecai et al., 2017). Nevertheless, one has to keep in mind that different estrogen types and dosages are used for the preparation of oral contraceptives (Mawet et al., 2021), which may explain these conflicting findings. Thus, additional clinical trials using long-term applications are needed to further disentangle the hormones' impact on (emotional) episodic memory.

Collectively, our results provide evidence that EST_{tra} and OXT_{int} modulate episodic memory and hippocampal functioning in men. In contrast to our hypotheses, the treatments did not selectively affect the recognition memory of emotional material but rather the overall memory performance in men. Hence, future studies should consider sex as an important moderator variable and further explore the effects of EST-OXT interactions on (emotional) memory. Antagonistic effects of EST_{tra} and OXT_{int} may contribute to the previously observed sex-specific hormonal effects in hippocampus reactivity. Our findings support the increasingly recognized notion that it is vital to consider sex differences and hormonal interactions in pharmacological clinical trials.

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Data availability statement

A preprint of this article is published at the BioRxiv preprint server (https://doi.org/10.1101/2021.11.22.469500). The data that support the findings of the present study are openly available in the repository of the Open Science Foundation at https://osf.io/hvknp/ (doi:10.17605/OSF.IO/HVKNP). The unthresholded statistical maps of the fMRI results can be accessed at https://neurovault.org/collections/FBHLSKJX/. The code that supports the findings of the present study is openly available in the repository of the Open Science Foundation at https://osf.io/hvknp/ (doi:10.17605/OSF.IO/HVKNP).

Declaration of Competing Interest

The authors declare no competing interests.

Credit authorship contribution statement

Marie Coenjaerts: Conceptualization, Formal analysis, Methodology, Investigation, Visualization, Project administration, Writing – original draft, Writing – review & editing. **Isabelle Trimborn:** Formal analysis, Methodology, Investigation, Writing – review & editing. **Berina Adrovic:** Formal analysis, Methodology, Investigation, Writing – review & editing. **Birgit Stoffel-Wagner:** Resources, Writing – review & editing. **Larry Cahill:** Conceptualization, Writing – review & editing. **Alexandra Philipsen:** Writing – review & editing. **René Hurlemann:** Supervision, Writing – review & editing, Funding acquisition. **Dirk Scheele:** Conceptualization, Formal analysis, Methodology, Supervision, Funding acquisition, Writing – original draft, Writing – review & editing.

Data availability

The data is freely available on an online repository. The link has been included in the manuscript..

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Study approval statement

This study protocol was reviewed and approved by the institutional review board of the medical faculty of the University of Bonn [Approval number: 213/16]. Written informed consent was obtained from all participants included in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119689.

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