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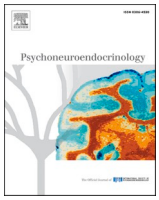

The effect of short-term increase of estradiol levels on sexual desire and orgasm frequency in women and men: A double-blind, randomized, placebo-controlled trial

Matthias K. Auer [a,1], Gina Joue [b,1], Sarah V. Biedermann [c], Tobias Sommer [b], Johannes Fuss [a,*]

[a] Institute of Forensic Psychiatry and Sex Research, Center for Translational Neuro, and Behavioral Sciences, University of Duisburg-Essen, Essen, Germany
[b] Institute of Systems Neuroscience, Center of Experimental Medicine, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany
[c] Social and Emotional Neuroscience, Department of Psychiatry and Psychotherapy, Center of Psychosocial Medicine, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany

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ABSTRACT

Estradiol (E2) has been implicated in sexual functioning in both sexes. E2 levels change distinctively over the menstrual cycle, peaking around ovulation. Data on short-term effects of fluctuating E2 levels on sexual desire are however sparse and mostly based on observational studies. To fill this gap, we ran a double-blind, randomized, placebo-controlled study (N = 126) to investigate the effects of a short-term increase in E2 on sexual desire and orgasm frequency in healthy, young men and women. Circulating E2 levels were elevated through estradiol valerate (E2V) administered over two consecutive days to simulate the rise in E2 levels around ovulation. E2V had no effect on orgasm frequency and only minor effects on sexual desire. On average, the administered E2V dampened change in sexual desire compared to untreated participants with comparable baseline sexual desire in such a way that sexual desire was slightly reduced even in those with higher baseline sexual desire. These findings suggest that short-term increases in E2 have little effect on sexual function and are unlikely to explain the increase in sexual desire around ovulation.

1. Introduction

Regulation of sexual desire is complex as it involves hormonal, psychosocial and cultural influences (Carvalho and Nobre, 2010; Nimbi, 2018). Sexual interaction has gained relevance as a social component in the course of evolution (Thornhill and Gangestad, 1996; Thornhill and Gangestad, 2008). If sexual desire was motivated only for reproductive reasons, an increase in sexual desire in women should be observable in the ovulation phase of the menstrual cycle when successful conception is most likely. As conception is, however, a necessary but not sufficient requirement for the successful raising of a child, sexuality serves additional functions, such as forming pair bonds and maintaining relationships (Thornhill and Gangestad, 2008).

Despite the fact that desire and frequency of sexual intercourse are highest during the reproductive years in women and might decline with age (Avis, 2000; Beutel et al., 2008), a significant amount of sexual desire remains, pointing to the social role of sexuality (Thornhill and Gangestad, 2008). The decline in sexual desire with age is also rather gradual and not immediately associated with the onset of menopause and therefore also not directly paralleled by the rather sudden changes in sex hormones (Avis, 2000).

Nonetheless, in line with the argument that a climax in desire should coincide with the most likely period of the menstrual cycle to conceive, it has been reported that sexual desire and motivation is highest at mid-cycle and associated with the corresponding hormonal milieu that is characterized by high estradiol (E2) and low progesterone (P4) levels (Roney and Simmons, 2013). During the luteal phase, when the likelihood of conception steadily decreases, desire is negatively associated with increasing P4 levels (Roney and Simmons, 2013).

While pharmacologically induced hypogonadism results in a decrease in sexual desire in men and women equally, and hormonal replacement can restore sexual desire in men, E2 and P4 replacement does not necessarily have the same effect in women (Schmidt, 2009). The role of testosterone (TST) in sexual motivation in women is even less

* Corresponding author.
E-mail address: johannes.fuss@uni-due.de (J. Fuss).
[1] Contributed equally and share first authorship

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clear. Despite the fact that TST peaks in women around ovulation and evidence of an associated increase in libido (Bancroft, 1983), it is unclear if this association is independent of the aforementioned changes in E2 and P4 (Roney and Simmons, 2013). While low-dose TST therapy during post-menopause can restore pre-menopausal TST levels and be beneficial in terms of treating hyposexual desire disorder (Davis, 2019), epidemiological studies have repeatedly failed to show a clear relationship between androgen levels and sexual desire in women (Davis, 2005; Zheng, 2020).

Although the association of sexual functioning and desire with TST in men has always been clearer than in women (Schmidt, 2009), the role of TST-derived E2 in this context has long been ignored. An elegant study that shed light on this neglected aspect demonstrated that restoration of eugonadal TST levels following pharmacologically induced hypogonadism is not sufficient to restore sexual functioning in men when aromatase, the enzyme required in the biosynthesis of E2 from its precursor TST, is blocked (Finkelstein, 2013). In line with this, it has been reported that libido is highest in men receiving TST replacement therapy and with the highest degree of aromatization (Pastor et al., 2013). This emphasizes the importance of both major sex steroids for sexual functioning in men and is in line with anecdotal reports that TST replacement alone is insufficient in increasing libido in men with aromatase deficiency (Carani, 2005).

Most studies on the effects of E2 on sexual desire in women only report associations of varying sex steroid levels over the course of the menstrual cycle (Roney and Simmons, 2013; Roney and Simmons, 2016), therefore not allowing to draw causal conclusions, or investigate long-term effects of hormonal contraceptive (Pastor et al., 2013) or replacement therapies (Lobo, 2003). The literature on the effects of isolated E2 treatment in men is even more limited. While complete androgen withdrawal and E2 replacement therapy as part of gender-affirming hormone therapy (GAHT) in transgender women does result in an increase in long-term sexual desire (Defreyne, 2020), this effect cannot be directly translated to cisgender people as hormonal therapy in trans people is associated with numerous desired physical changes that may interact with sexual desire (Laube, 2020) as well as sexual orientation (Auer, 2014).

To understand the influence of a short-term increase in E2 levels on sexual desire and the interaction with TST levels, we investigated the effects of administering either E2V over two consecutive days, mimicking the periovulatory E2 peak, or placebo in healthy premenopausal women in their low-hormone early follicular phase as well as healthy men.

2. Methods

2.1. Participants

Participants (N = 126, women n = 62) were randomly assigned in a double-blind manner to receive either placebo (PBO) (n = 64; women: n = 33, men: n = 31) or estradiol valerate (E2V; Progynova® 21, Schering, Germany) (n = 62; women: n = 29, men: n = 33). Both substances were administered orally in the form of two identical capsules. All participants were healthy (see criteria below), young (mean age in years ± standard deviation: F.PBO 26.4 ± 3.80, F.E2V 25.9 ± 4.20, M.PBO 26.4 ± 3.77, M.E2V 25.8 ± 3.63), and had normal BMI (mean BMI in kg/m^2 ± standard deviation: F.PBO 22.4 ± 2.63, F.E2V 21.8 ± 2.38, M.PBO 23.6 ± 2.33, M.E2V 23.2 ± 2.92). All women were in their early follicular phase (mean|median days that menses onset was after testing day, i.e. Day 2: F.PBO 0.57|1, F.E2V 1.9|2) when estrogen levels are expected to be the lowest and comparable to levels in men. Menstrual cycle length was based on self-reported dates of last menstruation to determine adequate time points for testing. All participants received two capsules over two consecutive days. Dosages differed between men (12 mg per day) and women (8 mg per day) to induce comparable elevated E2 levels based on previous research (Bayer, 2018; Bayer, 2020; Sommer, 2018). This study was part of a larger project also including an fMRI task as well as two behavioral studies reported elsewhere (Joue, 2022; Nouri, 2022).

Participants were recruited via a local chapter of stellenwerk.de, a popular local website used for biomedical research recruitment. All participants reported to be free of psychiatric illnesses, to not be users of illicit drugs or central nervous medication, and to not smoke on a regular basis. None of the participants had contraindications for taking E2V (e.g., obesity or at risk for cardiovascular problems). On all testing days, participants rated side effects potentially elicited by the drug as well as any mood changes using standardized questionnaires (Multidimensional Mood Questionnaire (Steyer, 1997). Only naturally cycling women who had not taken any oral contraceptives or were pregnant in the 6 months prior to the study were included. Ethics approval was obtained from the local Ethics Committee (Ärztekammer Hamburg; PV4738). All volunteers gave written, informed consent for this study and received a base monetary reimbursement of €140 for their complete participation in the overall 3-day pharmacological study.

2.2. Assessment of hormone concentrations

Three saliva samples were collected from all participants over about an hour on Day 1 and on Day 2 and pooled for analysis (~3 mL in total) in order to achieve stable hormone level measurements. When the participant consented and medical staff was available, blood was also drawn (~1 mL) on Days 1 and 2. For financial reasons and given the known high correlation of serum and saliva hormone levels (Bayer, 2018), serum samples were not analyzed in the PBO groups. Hence, only saliva hormone concentrations are reported and analyzed here. Saliva samples were stored at − 18 °C until analysis by IBL (Hamburg, GER) using highly sensitive luminescence assays for salivary E2 (sensitivity 0.3 pg/mL), P4 (2.6 pg/mL) and TST (0.06 ng/mL).

2.3. Measures

2.3.1. Total sexual outlet

To assess total sexual outlet (TSO), participants indicated the total number of orgasms within the previous 48 h, regardless of the way the orgasm was achieved (partnered sex or masturbation). TSO was assessed twice, before E2V/PBO intake and 48 h after the first dose of E2V/PBO.

2.3.2. Sexual desire and change in desire post treatment

Sexual desire was assessed before E2V/PBO intake (Day 1) using the SDI-2 developed by Spector, Carey, and Steinberg (Spector et al., 1996), which also has subscales to measure dyadic and solitary aspects of sexual desire. It is a brief 14-item questionnaire where participants report the frequency of their sexual thoughts and sexual desire over the prior month on an 8-point Likert scale. The total score ranges from 0 to 112. Dyadic sexual desire is based on 2 items addressing the frequency (0 −7 points each) and 6 items addressing the strength of dyadic sexual desire (0 −8 points each). Solitary sexual desire is based on one item addressing the frequency (0 −7 points each) and 2 items addressing the strength of solitary sexual desire (0 −8 points each). The maximum score for dyadic sexual desire is thus 62, and the maximum score for solitary desire is 23. Cronbach's alpha was calculated to assess the internal consistency of the total sexual desire score as well as the subscales for solitary and dyadic sexual desire. The internal consistency of the questionnaire was satisfactory, with Cronbach's alpha for total sexual desire = 0.91, for solitary sexual desire = 0.76, and for dyadic sexual desire = 0.87.

Additionally, 48 h after the first dose (Day 3), change in sexual desire was assessed using 4 modified items from the SDI-2. In this modified SDI-2, participants were asked to indicate, on a scale from –4 (strongly reduced) to 4 (strongly increased), the change in 1) frequency of sexual thoughts and fantasies, 2) intensity of sexual desire, 3) desire for sex with a partner, and 4) desire to masturbate since taking the capsules as

part of the study. Therefore, the total score of the modified SDI-2 on Day 3 ranged from –16 to + 16 with solitary and dyadic sexual desires each gauged by one question (single point scores in the range [−4,4]). The internal consistency of the sum score was excellent, with Cronbach's alpha for total sexual desire change = 0.93.

2.4. Statistical analyses

One participant (F.PBO) was excluded from all analyses as her high E2 (Day 1: 14.38 pg/mL; Day 2: 12.47 pg/mL; see Table 1 for IBL-reported range during follicular phase; IBL reported range during mid-cycle 3.79–16.05 pg/mL), P4 (Day 1: 247.16 pg/mL; Day 2: 111.55 pg/mL; IBL reference values during luteal phase 87.3–544.30 pg/mL), and TST (Day 1: 149.56 pg/mL, Day 2: 117.28 pg/mL) levels on both days indicated a problem with her sample assessment, that she was tested in the wrong phase of her menstrual cycle, or her group assignment was incorrect. An additional 2 participants (both M.PBO) had hormone levels indicating hormone assay error for one sex hormone but otherwise plausible hormone levels and no indications of group assignment error (one M.PBO with Day 1 E2: 24.12 pg/mL, Day 2 E2: 5.02 pg/mL; another M.PBO with Day 1 P4: 494.38 pg/mL, Day 2 P4: 20.37 pg/mL but Day 2 E2 of 3.16 pg/mL indicating correct PBO group label). These participants were therefore included in analyses as actual hormone level values were not considered here. The following number of participants could not be included due to missing data for at least one of the two time points: 23 for TSO (2 F.PBO, 6 F.E2V, 3 F.PBO, and 12 M.E2V) and 5 for SDI (2 M.PBO and 3 M.E2V).

Table 1
Saliva concentrations (mean ± standard deviation) of estradiol (E2), progesterone (P4) and testosterone (TST) in groups under estradiol valerate treatment (E2V grp) and placebo (PBO grp). Baseline hormone levels (Day 1) showed comparable hormone concentrations across groups. E2V administration in E2V groups increased E2 levels in both men (M) and women (F). Reference ranges (ref. range) shows the 90% normal ranges for the age group of our sample (and follicular phase for women) as published by the manufacturer of the assays used. T-statistic, associated degrees of freedom (df), standard error (std.err.) and p values (p) were 2-sample t-tests between treatment and placebo groups within each sex.

hormone	PBO grp	E2V grp	ref. range	PBO – E2V			
	(pg/mL)	(pg/mL)	(pg/mL)	t	df	std. err.	p
Day 1							
F							
E2	3.38 ± 1.80	3.31 ± 2.29	1.29 – 7.76	0.64	63.36	0.15	0.53
P4	70.84 ± 54.68	66.20 ± 41.31	30.3 – 51.30	–0.04	63.11	0.17	0.97
TST	17.96 ± 15.62	20.75 ± 15.20	7.35 – 42.50	–0.90	65.00	0.17	0.37
M							
E2	3.19 ± 1.96	2.76 ± 1.41	2.71 – 4.75	0.64	59.20	0.13	0.53
P4	52.71 ± 23.50	58.89 ± 26.97	0 – 58.00	–1.00	64.21	0.11	0.32
TST	96.30 ± 45.58	96.69 ± 46.47	36.32 – 117.91	0.04	65.00	0.12	0.97
Day 2							
F							
E2	2.74 ± 1.65	24.23 ± 10.66		–16.18	54.31	0.14	0.00
P4	59.99 ± 41.86	45.93 ± 32.07		1.42	61.33	0.15	0.16
TST	16.55 ± 13.58	14.36 ± 7.95		0.47	64.94	0.17	0.64
M							
E2	2.81 ± 1.68	34.54 ± 15.24		–18.85	64.97	0.13	0.00
P4	43.14 ± 16.75	47.94 ± 19.19		–0.91	64.99	0.10	0.36
TST	86.35 ± 33.46	41.98 ± 31.30		6.53	55.67	0.13	0.00

2.4.1. Total sexual outlet

Differences between groups in reported TSO on each day were checked with Fisher's exact test. The change in TSO was tested using the Wilcoxon rank sum test. Data was zero-inflated (19.5% zeros reported on Day 1 and 28.8% on Day 3, over-dispersion parameter k = 1.49), so we fitted a Conway-Maxell-Poisson regression model to test the predictive power of E2V/PBO group and sex of TSO, with Day 1 TSO as a covariate and each individual as a random effects term (R package glmmTMB; Brooks, 2017). Residuals were normally distributed. The contribution of model predictors was assessed with likelihood ratio tests on pairwise comparisons of nested models.

2.4.2. Sexual desire

To investigate whether sex and treatment could predict sexual desire, the changes in total, solitary, and dyadic sexual desire reported following treatment (Day 3 modified SDI-2 questionnaire score) were each regressed against sex and treatment group assignment with the respective Day 1 SDI-2 scores, standardized across all participants, as a covariate in three separate models. Model parameters were estimated using ordinary least squares (maximum likelihood) and effect (sum) contrast coding (R base function lm). Although Day 3 SDI-2 questions were framed in terms of change in sexual desire since E2V administration and arguably subsumes "baseline" sexual desire (prior to treatment), Day 1 SDI scores were included as we cannot assume the change in sexual desire for those scoring lower on SDI-2 to be the same as change for those scoring higher. Robust standard errors were calculated using the sandwich estimator function (HC3) to deal with heteroscedastic standard errors (JA, 2020) (R package jtools).

The total score model respected assumptions of homogeneity of variance (studentized Breusch-Pagan test BP(7) = 9.90, p = 0.19), but residual plots were not ideal. The model respected assumptions of linearity, normality of distributed residuals, and low collinearity of model terms (all low variance inflation factors VIFs < 5, with the three-way interaction of Day 1 SDI scores, sex and group having the highest VIF = 4.75). Predictors were assessed via likelihood ratio tests of pairwise fits of nested models as well as through a best subset regression approach (R packages olsrr). Wald test statistics on individual model parameters were also performed for comparison but were not used for final model selection given the better reliability of the likelihood ratio test. Several other model-fit metrics were also considered in order to evaluate model performance on different dimensions (detailed in Suppl. Info Sec. S1.1).

As the dyadic and solitary SDI scores post-treatment (Day 3) were each based on a single 9-point scale question, the predictive power of elevated estrogen and sex, covarying with standardized pre-treatment (Day 1) SDI scores, was tested using ordinal logistic regression. Specifically, a proportional odds cumulative logit model, which calculates cumulative probabilities as log odds, was fitted using the polr function from the R package MASS (Venables and Ripley, 2002). The Brant test (Brant, 1990) verified the proportional odds assumption of ordinal logistic regression was met, indicating that one set of coefficients would be sufficient in describing the relationship between predictors and the range of post-test SDI subscale scores. As the variance of the subscale was high, all estimates for all non-Bayesian models are reported based on robust standard errors to minimize influence of outliers (variance--covariance matrix recalculated with the R package lmtest (Zeileis and Hothorn, 2002) using the HC3 estimator from the R package sandwich (Zeileis et al., 2020). Assessment of each predictor was done via F-tests, which are special cases of the likelihood ratio test in that they treat noise as Gaussian.

These maximum likelihood estimates were verified using Bayesian estimations via MCMC (R package rstanarm (Villanueva et al., 2016). A conservative informative prior on R2 at location 0.5 was specified.

Bayesian models were run with 4 chains, each with 2000 iterations of which 1000 iterations were discarded as warm-up. Model convergence was verified by R-hat values (all less than 1.1), visually (all chains converging to the same distribution), by MCSEs (ranging from 0.1 −0.2 except for the intercept where MCSE = 0.4), and the number of effective samples (all more than half the draws except for the intercept). All plots were generated with the R package ggplot2 (Villanueva et al., 2016), occasionally with the help of R package ggeffects (Lüdecke, 2018).

3. Results

3.1. Overview of hormone levels

Baseline E2 and P4 levels (i.e., on Day 1, prior to E2V/PBO treatment) were similar between sexes and those randomly assigned to the control/PBO or test/E2 group (Table 1; Fig. 1). Baseline TST levels were naturally lower in women than in men. E2V intake lowered TST levels in men but did not have a significant effect on TST levels in women or P4 levels in either sex.

3.2. Effect of E2 on TSO

Baseline TSO levels were comparable across all the four groups (mean | median ± standard deviation: M.PBO 1.63 | 2.00 ± 1.13; M.E2V 2.03 | 1.50 ± 1.69; F.PBO 0.94 | 0.00 ± 1.27; F.E2V 0.57 | 0.00 ± 1.03). There was no difference in the change of reported orgasms from Day 1 to Day 3 between any of the groups (all p's > 0.1; M.PBO 1.03| 0.00 ± 1.40; M.E2V 1.24 | 1.00 ± 1.45; F.PBO 0.44 | 0.00 ± 0.80; F.E2V 0.31 | 0.00 ± 0.74). Only baseline TSO was predictive of Day 3 TSO. E2V intake did not predict TSO, though sex weakly did, corrected for Day 1 reports (estimated 0.51, 95% CI [0.0815, 1.09]). Men tended to report higher TSO than women on Day 3 (Fisher's exact test for Day 1 p < 0.0001, Day 3 p = 0.016), although overall, all groups reported lower TSO on Day 3 than on Day 1.

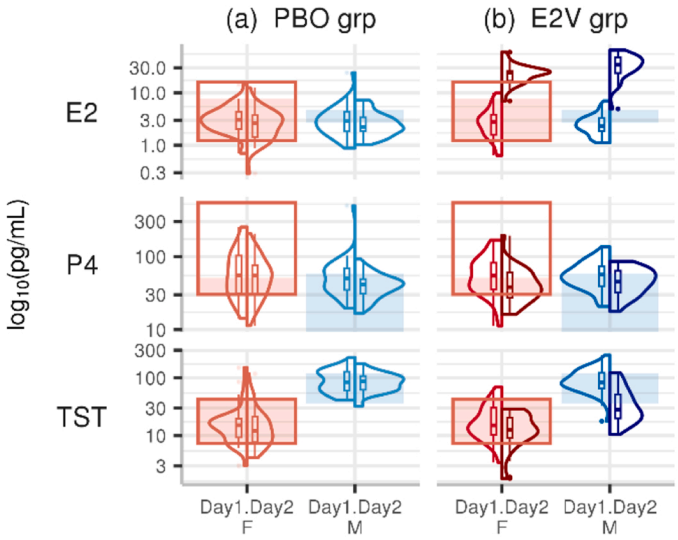

Fig. 1. Saliva levels of sex hormones estradiol (E2), progesterone (P4), and testosterone (TST) across groups before (Day1) and after (Day2) treatment. Day 1 shows hormone levels before treatment of either placebo (PBO, panel a) or estradiol valerate (E2V, panel b), dosed at 12 mg per day for men (M) and 8 mg for women (F) over two days. Day2 levels were measured about 7 h after the second dose. Levels verified that women were tested in the low E2/P4 phase of their cycle when levels are comparable to men and that E2V intake (b, darker colors) increased E2 levels. E2V intake lowered TST levels in men. Levels are shown on a log scale. Shaded areas delimit the normal physiological range of the respective hormone for each sex (in the follicular phase of women) and in the age group of our participants, as reported by the manufacturer of our assays. Red box outlines delimit the normal physiological range across the entire menstrual cycle in women for the age group of our female participants. Also see Table 1 for untransformed values.

3.3. Effect of E2V intake on sexual desire

SDI scores were generally higher in men (Fig. 2).

Adjusted R2 indicated that only 4% of the variation in Day 3 SDI scores was explained by the linear regression model containing elevated E2, sex, and their interactions, adjusted for Day 1 SDI reports (Fig. 3). Bidirectional step regression and regression subset selection based on several model comparison criteria supported the predictive power of the additive effects of E2V intake and sex, and each of their multiplicative effects with baseline SDI.D1 (see Suppl. Info Sec. S1.1), that is, zSDI.D1 + Grp + Sex + zSDI.D1:Grp + zSDI.D1:Sex, where the colon indicates interaction. This is further supported by the combined performance averaged over all normalized metrics (Suppl. Info Sec. S1.1). However, we retained the weak predictors given our a-priori hypotheses that acute elevation of E2 would affect the sexes differently (resulting in an overall model with F(7112) = 1.69, p = 0.12) and indicate the parameters of the best-fitting model in Table 2 in bold. Parameter estimates from the best-fitting model, the model without the baseline SDI covariate SDI.D1, and the fully specified model, which is reported here, were all similar (Suppl. Info Fig. S1), corroborating VIFs of the independence of the contributions from Grp, Sex, and zSDI.D1 to accounting for change in sexual desire post-treatment.

Models indicate there is no overall, dominant average effect of E2V on sexual desire across both sexes or systematically different effects in either of the sexes (no reliable Grp or Grp:Sex effects, respectively; Table 2), but that women with higher baseline SDI will have increased sexual desire over the course of the study while those with lower baseline SDI will have decreased sexual desire, whereas men have a slight decrease in sexual desire on average. There is, however, much variability, and many reported no change in sexual desire regardless of baseline SDI (zSDI.D1:Sex; Fig. 4a). Although there is no reliable Grp by Sex effect covarying with baseline SDI (zSDI.D1:Grp:Sex), this relationship is depicted in Fig. 4c for purely exploratory reasons and to show that the pattern of change in sexual desire over the course of the study in women might be driven mostly by the stronger relationship between change in sexual desire depending on baseline sexual desire in women on placebo (PBO) compared to the weaker overall effect of decrease in sexual desire in women on estradiol valerate (E2V; Fig. 4c, rather constant line around zero for F.PBO, dark line). However, caution must be taken given the considerable variability of sexual desire responses and high number of reports of no change, i.e. zero SDI Day 3 (SDI.D3) scores, in particular among men in both treatment groups (Table 2, Fig. 4c, right panel). Elevated E2 levels has an overall effect of flattening changes in sexual desire. That is, models predict that the low baseline sexual desire in the PBO group on average across the sexes will have reduced sexual desire and higher baseline sexual desire increased sexual desire over the course of the study (Fig. 4b, light gray line).

4. Discussion

In the present study, we found that E2V intake had only subordinate effects on sexual desire in men and women in addition to the stronger influence of baseline sexual desire level. It was associated with a levelling out in the changes in sexual desire, averaging to a slight reduction that is estimated in the PBO group with lower than average baseline sexual desire. In contrast, orgasm frequency was not affected by E2 intake and decreased in the course of the study in both sexes.

Contrary to our hypothesis, administering E2V to women during the early stages of their menstrual cycle did not increase their sexual desire. Initial sexual desire appears to play a more substantial role: in the placebo group, women who reported higher baseline sexual desire maintained this elevated desire three days into the study, whereas those who reported a low initial desire experienced a decrease in desire on the third

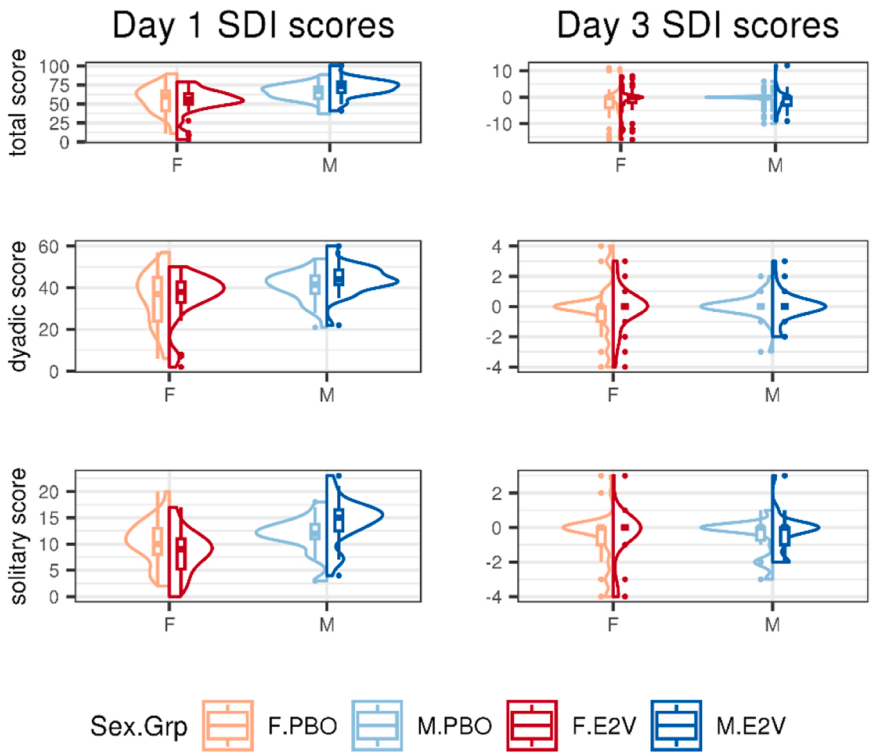

Fig. 2. Distribution of SDI total scores and subscales before E2V intake (Day 1) and 48 h after (Day 3) by sex (F = female, M = male) and treatment group (Grp; administered with E2V = estradiol valerate or PBO = placebo). Men generally scored higher than women on overall Day 1 SDI scores and its subscales.

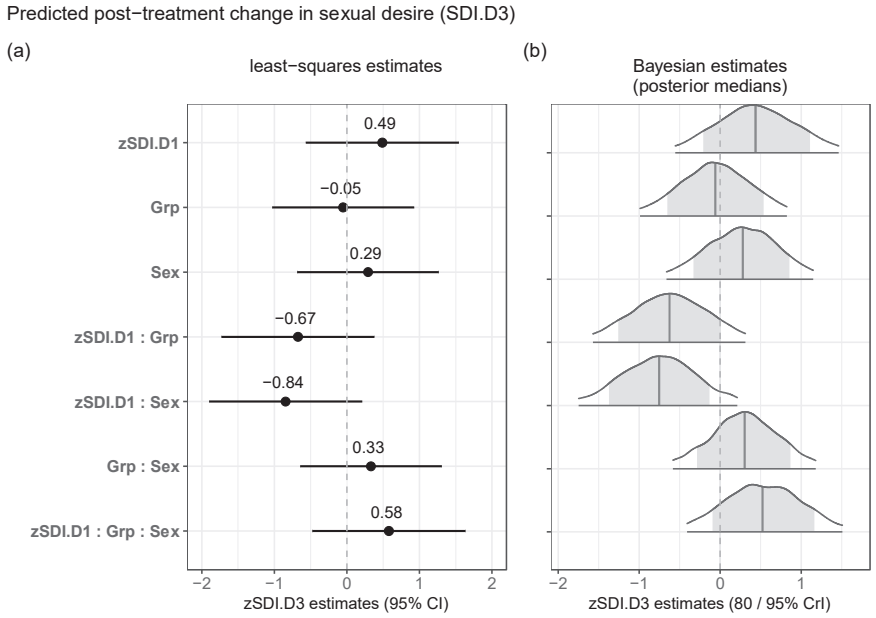

Fig. 3. Linear regression models of post-treatment sexual desire estimates based on (a) classic least−squares (maximum likelihood) estimates and (b) Bayesian estimates using Markov Chain Monte Carlo (MCMC). Likelihood ratio model selection shows that overall total scores on Day 3 SDI (shown standardized, zSDI.D3, for illustration purposes) are best described by Day 1, i.e. baseline/pre-treatment, sexual desire reports (standardized in analyses, zSDI.D1), as well as by E2V intake when both are adjusted for Day 1 SDI total scores (zSDI.D1:Grp) and with sex when adjusted for Day 1 SDI (zSDI.D1:Sex). The pattern for the cross-over effects of E2V intake and sex differences, taking in consideration baseline SDI (zSDI.D1: Grp: Sex), cannot be reliably estimated given the heterogeneity of responses. The means of the linear model estimates are shown with line widths reflecting 95% confidence intervals. The shaded areas of posterior medians (post. medians) of the Bayesian estimates correspond to an MCMC 80% credible interval (CrI), width of base to an MCMC 95% CrI. Also see Table 2.

day. In contrast, regardless of their initial reports, women treated with E2V were predicted to exhibit a slight reduction in sexual desire.

Our results contradict the notion that women's self-reported increase in sexual desire around ovulation is due to the sole effect of rising E2 levels while P4 is low. While several studies indicate an increase in sexual desire during the periovulatory mid-cycle phase (Regan, 1996), this effect might not be solely mediated by E2 or, at least, not by E2 alone. It might, instead, depend on other hormonal or non-hormonal

Table 2
Linear regression model estimates of E2V treatment on sexual desire. Likelihood ratio tests indicate that the linear regression model defining post-treatment (Day 3) change in sexual desire as a function of treatment group (Grp) and sex, each with interaction effects with standardized baseline/Day 1 total SDI scores (zSDI.D1), fit the data the best (predictors marked in italics). However, parameter estimates (Est.) are shown for a full model (all interactions based on both maximum likelihood (mL), with 80% and 95% confidence intervals (CI) and p-values of t-tests of each estimate, and Bayesian modeling using Markov Chain Monte Carlo simulation (MCMC), with corresponding 95% credible intervals (CrI). The intercept corresponds to the grand mean of all four groups (M.PBO, F.PBO, M.E2, F.E2).

		least-squares estimates			MCMC estimates	
Predictors	Est.	95% CI	80% CI	p	Est.	95% CrI
(Intercept) [grand mean]	− 0.82	[− 1.80, 0.16]	[− 1.45, − 0.18]	0.10	− 0.84	[− 1.79, 0.12]
zSDI.D1	0.49	[− 0.57, 1.54]	[− 0.20, 1.17]	0.36	0.44	[− 0.55, 1.46]
Grp[E2V]	− 0.05	[− 1.03, 0.93]	[− 0.69, 0.58]	0.92	− 0.06	[− 0.99, 0.82]
Sex[M]	0.29	[− 0.69, 1.27]	[− 0.34, 0.93]	0.56	0.27	[− 0.66, 1.15]
zSDI.D1 * Grp [E2V]	− 0.67	[− 1.73, 0.38]	[− 1.36, 0.01]	0.21	− 0.62	[− 1.57, 0.31]
zSDI.D1 * Sex [M]	− 0.84	[− 1.90, 0.21]	[− 1.53, − 0.16]	0.12	− 0.75	[− 1.75, 0.21]
Grp[E2V] * Sex[M]	0.33	[− 0.65, 1.31]	[− 0.30, 0.97]	0.50	0.30	[− 0.58, 1.18]
zSDI.D1 * Grp [E2V] * Sex [M]	0.58	[− 0.48, 1.63]	[− 0.11, 1.27]	0.28	0.53	[− 0.41, 1.51]
Observations		121	121			
R^2 / R^2 adjusted		0.096 / 0.040	0.12			

signals associated with ovulatory timing (Roney and Simmons, 2013).

It is important to also consider that the effects of E2 on behavior might be delayed (Roney and Simmons, 2013; Blaustein, 2008), partly due to cumulative effects on receptor densities and synaptogenesis (McEwen, 1979). E2 receptor density in the brain is likely to also vary throughout the menstrual cycle (Shughrue et al., 1992; Simerly, 1996) and hence the effects of external sex steroid application would as well (Blaustein, 2008). Roney and Simmons (Roney and Simmons, 2013), for example, found that E2 had a positive effect on sexual desire observable only two days after increased levels. Therefore, had we extended the observation period or conducted the experiment during a different phase of the menstrual cycle, the results of our study might have been different, although conducting the study in a different phase would have made comparisons between men and women more problematic.

Another more straightforward explanation for the lack of increased sexual desire or behavior with E2V treatment in our study could be that women were tested during the early follicular phase of the menstrual cycle when they were menstruating. Menstruation itself might inhibit sexual motivation or at least impede the translation of sexual desire into sexual activity, irrespective of hormonal effects, although it also comes with increased blood flow in the cervix and hence greater sensitivity favoring orgasms along with the lubrication of menstrual blood that arguably should help heighten sexual desire. It is worth noting that orgasm frequency in women does not necessarily correlate with sexual motivation (Gusakova et al., 2020). Furthermore, it is known that women are less likely to experience orgasm during sexual intercourse compared to men (Shaeer, 2020). Finally, it is worth noting that periovulatory hormone levels are also characterized by rising androgen levels (Bancroft, 1983) that might have independent effects on sexual desire (Cappelletti and Wallen, 2016). We could therefore speculate that the periovulatory increase in sexual interest reported elsewhere is mediated by the interplay of rising E2 and androgen levels, although the changes in androgens during the menstrual cycle are much less pronounced than those in E2 and P4 (Skiba, 2019).

While low-dose TST therapy during post-menopause can restore pre-menopausal TST levels and help treat hyposexual desire disorder (Davis, 2019), epidemiological studies have repeatedly failed to show a clear relationship between androgen levels and sexual desire in women (Davis, 2005; Zheng, 2020). There is further evidence that supra-physiological androgen levels must be achieved in postmenopausal women for low-dose estrogen treatment to be effective in increasing sexual desire (Cappelletti and Wallen, 2016).

Interpretation of our results is further complicated by the fact that hormonal control of sexual desire in women for their own partner might differ from their sexual interest in others (Grebe et al., 2016), a distinction that was not accounted for in our study design. Some studies have reported, for example, that E2 increases extra-pair interest (Grebe et al., 2016) while P4 increases sexual interest in one's own partner. However, this is not a consistent finding (Roney and Simmons, 2016), and most studies only report associations of sexual desire and motivation with sex steroid levels over the course of the menstrual cycle (Roney and Simmons, 2013; Roney and Simmons, 2016).

The interpretation of our results cannot be simply situated in context of studies investigating the effects of hormonal contraceptives (Pastor et al., 2013) or long-term replacement therapies in postmenopausal women (Lobo, 2003) on sexual desire, as they are practically limited in not being blinded or placebo-controlled. Additionally, the varying binding affinity of different progestins on different steroid receptors, including the androgen receptor, and different effects on sex hormone binding globulin (SHBG) secretion and hence free androgen levels, not only make comparisons with these studies difficult, but also perhaps partially explain the inconclusive results of the effects of oral contraceptives on sexual desire (Pastor et al., 2013).

Men generally reported a slight decrease in sexual desire, with the higher the baseline SDI, the slightly greater the decrease. However, responses given by men in all groups were quite variable and E2V seemed to have only minor effects on sexual desire in men, while we would have expected that the concomitantly induced decrease in TST levels resulting from HPG-axis suppression would have more pronounced influence on sexual desire. Moreover, E2 has been suggested to be more relevant for sexual function in men than originally assumed. The literature on this topic is, however, still inconclusive. While some studies from the early 80s (Bagatell, 1994; Gooren, 1985) have questioned the role of E2 in sexual functioning in men, others have indicated that adequate aromatization is essential (Finkelstein, 2013; Luisi and Franchi, 1980).

The results of our study indicate that in men, elevating E2 levels to supraphysiological levels, which concomitantly leads to low TST, has only marginal acute effects on sexual desire. It is possible that there is an optimal balance of these two sex steroids for proper sexual functioning that was not met by our manipulations. There are numerous studies that support this argument. TST alone does not seem to be enough to restoresexual desire when aromatase function is completely absent (Finkelstein, 2013; Carani, 1999). While increasing TST levels can improve sexual functioning to some degree even when aromatase activity is pharmacologically blocked, complete reversal of sexual dysfunction is only achieved when E2 formation is restored (Finkelstein, 2013). In contrast, although mostly anecdotal, reports from men with aromatase deficiency indicate that E2 replacement that brings E2 levels to the female reference range of the late follicular phase and hence almost totally suppressing endogenous TST, is still capable of restoring sexual desire and increasing frequency of sexual intercourse (Carani, 1999). Albeit special cases, studies from men with hypogonadism receiving TST replacement therapy have also shown that aromatization of TST to E2 is an independent predictor for increased libido (Ramasamy, 2014), and patients with high E2 levels have less libido problems than those with normal or low E2 levels (Stephens-Shields, 2022; Tan et al., 2015). E2 might also compensate, at least to some degree, for TST deficiency, as sexual drive has been reported to be significantly higher in men with low TST receiving TST replacement therapy when E2 levels

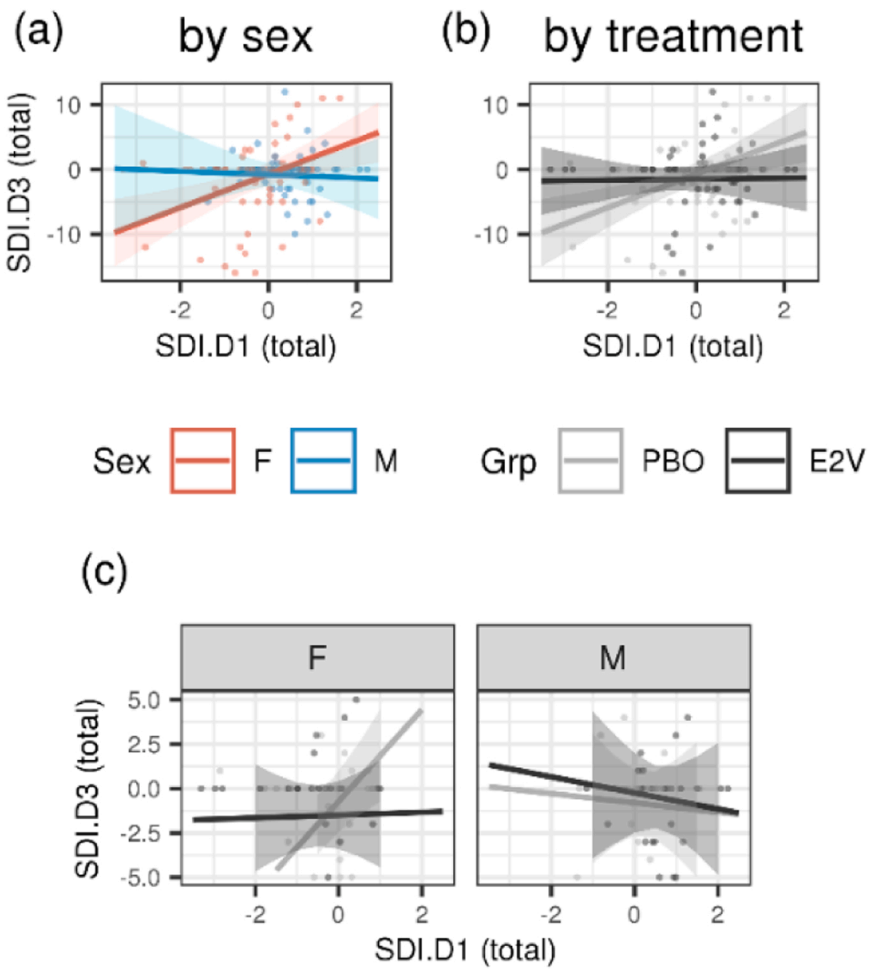

Fig. 4. Linear model predictions of post-treatment/Day 3 sexual desire (SDI.D3 total raw score) given baseline/Day 1 sexual desire (SDI.D1 total score, shown here standardized across all groups). SDI.D3 questions were on a Likert-type scale with negative scores corresponding to reduced sexual desire since treatment, zero to no change, and positive scores to increased sexual desire. A flat/constant slope indicates that post-treatment sexual desire did not depend on baseline sexual desire scores, where the constant value of the slope/intercept with the SDI.D3 is key to knowing what the post-treatment change in sexual desire was: SDI.D3 < 0 for decrease, SDI.D3 $= 0$ for no change, SDI.D3 > 0 for an increase in sexual desire. Likewise, a positive- and negative-sloped relationship between baseline SDI.D1 and post-treatment SDI.D3 has different interpretations depending on whether the relationship is in the positive or negative range of SDI.D3, as detailed specifically below. **(a)** The linear regression model predicts that women (F; red line/points) who had higher than the across-sex average baseline SDI would have increased sexual desire on Day 3 (red line for higher SDI.D1 in the positive range of SDI.D3), whereas women with lower-than-average baseline SDI had decreased sexual desire on Day 3. In contrast, men (M; blue line/points) were estimated to generally have a slight decrease in sexual desire, with the higher the baseline SDI, the slightly greater the decrease (blue line with slightly negative slope with an intercept of 0 at $>$ 2 standard deviations below mean SDI.D1). However, note the wide variability of this relationship**. (b)** Men and women on placebo (PBO; light gray line/points) are generally predicted to have increased sexual desire when their baseline sexual desire was higher than average and decreased sexual desire when their baseline sexual desire was lower than average. Those on estradiol valerate (E2V; dark gray line/points) were estimated to have a more flattened change in sexual desire though change was generally estimated to be a reduction, irrespective of baseline reports (rather horizontal line dark line falling only in the negative SDI.D3 range). **(c)** The 3-way interaction of sex, treatment, and baseline sexual desire are shown only as illustration of the variability of the cross-over effects of treatment in each of the sexes. Shaded bands around mean estimate lines are 95% confidence intervals. Actual data is plotted as points.

are relatively increased (Ramasamy, 2014). In a study by Bagatelle and colleagues (Bagatell, 1994), a reduction in TST levels by 50% for six weeks also did not necessarily result in a significant decline in sexual interest when E2 levels declined by only about 20%.

Studies in men undergoing androgen deprivation due to prostate cancer also point to the essential role of E2. It has been shown that sexual functioning is better in men receiving nonsteroidal androgen receptor blockers compared to those who have undergone castration (Iversen, 1999). This might be explained by the fact that the use of androgen receptor blockers results in high TST levels that, despite being prevented from activating androgen receptors (AR), are significantly aromatized to E2 (Boccardo, 2005). Lastly, a recent study in voluntarily castrated men did not find significant differences between androgen and estradiol supplementation in term of sexual drive (Wibowo, 2021).

The low TST and high E2 combination in our study is rare in non-interventional contexts, with the exception of men with obesity in whom excessive aromatization in fat tissue, among other mechanisms, results in hypogonadotropic hypogonadism characterized by low TST and relatively high E2 levels (Corona, 2013). TST levels might be 50% lower than in their non-obese peers, with free TST levels being even lower (Corona, 2013) and sexual function compromised (Esposito and Giugliano, 2005). However, it is difficult to separate hormonal from the effects of the metabolic syndrome in this context, and sexual dysfunction in these men mainly refers to erectile dysfunction and less commonly to sexual desire problems (Esposito and Giugliano, 2005). A study on the use of clomiphene citrate in obesity, which results in a significant increase in TST and E2 in the treatment group and induces secondary hypogonadism, failed to show differences from placebo in terms of

sexual functioning despite resulting in a significant increase in testosterone and estradiol in the treatment group (Grebe et al., 2016). However, clomiphene is a partial antagonist of E2, therefore hampering interpretation of the results.

A strength of our study is its interventional and blinded design, as most studies on the effects of E2 and P4 on sexual desire in women are either uncontrolled and only report associations of sexual desire and motivation with sex steroid levels in the course of the menstrual cycle (Roney and Simmons, 2013; Roney and Simmons, 2016), or investigated effects of hormonal contraceptives (Pastor et al., 2013) or long-term replacement therapies (Lobo, 2003). Additionally, there are few studies investigating the effects of supraphysiological E2 levels on sexual functioning in men, and our study therefore adds to this limited literature.

5. Limitations

As mentioned, two limitations of our study are we did not control for TST levels in men and the SDI-2 inventory did not differentiate between sexual interest in one's own partner or others. A further limitation is that this study was part of a larger project investigating the effects of estradiol on a variety of behaviors and neurocognitive functions, some of which might have been stressful for participants and therefore have affected sexual functioning. Most notably, participants performed an elevated plus-maze task in a virtual reality environment (Nouri, 2022) designed to assess anxiety and hence increase stress levels in participants. While stress can affect sexual desire, and sex steroids can interact with the physiological stress response (Fuss, 2019), empirical findings on the association between sexual variables and measures of stress (e.g., self-reports, cortisol levels) are mixed, with some studies showing that stress is positively associated with sexual activity (Goldey and van Anders, 2012; López et al., 2009) while others showing that stress is negatively associated with sexual activity or functioning (Bodenmann, 2010; Ein-Dor and Hirschberger, 2012). These mixed findings might stem from differences in how stress is measured, notably that measures of self-reported stress and cortisol diverge (Rosal, 2004). Participants have reported that partnered sexual desire is negatively correlated with stress (Carvalheira et al., 2014). While even fewer studies have investigated how psychological stress affects solitary desire, some research suggests that the desire to masturbate increases when one is stressed or needs to relax. Similarly, lower desire for sexual activity with a partner but greater desire to engage in solitary sexual activity is associated with stressful conditions (Graham, 2004).

We have recently shown in the same cohort that E2V treatment reduced physiological indicators of stress such as increased heart rate and increased cortisol levels during a virtual stress paradigm (Nouri, 2022). In contrast, in another study from our group, androgen withdrawal and E2 treatment in transgender women was associated with an exaggerated stress response to a pharmacological stimulus, while the opposite was true for TST treatment in transgender men (Fuss, 2019).

6. Conclusion

Overall, our study indicates that high E2 levels, irrespective of sex, have only a marginal acute effect on sexual desire, and this slight effect might be influenced by a concomitant decrease in TST in men. Our results make it unlikely that the increase in sexual desire around ovulation is primarily caused by the acute rise in E2 levels in women. However, further studies should investigate how sexual desire is influenced by increasing E2 levels when TST levels are kept stable in order to rule out that suppressed TST levels are responsible for the marginal effects of E2V.

Declaration of Competing Interest

The authors have nothing to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106682.

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