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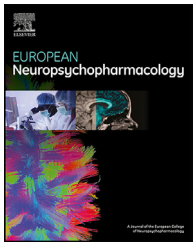

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ORIGINAL RESEARCH PAPER

Sex differences in economic decision-making: Exogenous estradiol has opposing effects on fairness framing in women and men

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Abstract
Burgeoning evidence indicates that women are more sensitive to the context of an offer and show a stronger propensity to adjust their behavior with changing fairness frames. We evaluated whether the sex hormone estradiol and associated stereotypical beliefs contribute to fairness framings by administering topical estradiol (2 mg) to 108 healthy women and 104 heathy men in a randomized, double-blind, placebo-controlled between-subject study design. Participants played the role of the responder in a modified version of the Ultimatum Game (UG), in which identical offers for the division of a given amount of money were framed as either fair

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or unfair. Furthermore, participants completed an unframed UG and a delayed discounting task to probe possible effects of estradiol on altruistic preferences and delay gratification. Our results show that women were more sensitive to fairness frames than men. Intriguingly, however, estradiol had sex-specific effects on fairness sensitivity by increasing the acceptance rate of proposals with a fair frame in men and reducing it in women. Furthermore, the mere belief of receiving estradiol treatment significantly increased the acceptance of unfair-framed offers in both sexes, but estradiol did not significantly alter the response to unframed offers and impulsive decision-making. Collectively, our findings indicate that estradiol has opposing effects on the sensitivity to the perceived fairness of economic offers in women and men. The profound effects of estradiol treatment and stereotypical beliefs provide support for the notion that sex differences in fairness framing are rooted in both biological and environmental factors.
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1. Introduction

Human economic decision-making is not perfectly rational, but highly susceptible to the framing of choices (Ruggeri et al., 2020; Tversky and Kahneman, 1981) and social preferences such as fairness norms (Fehr and Gachter, 2002; Henrich et al., 2006). Depending on the context and the available options, the same monetary offer can be considered fair or unfair. Accumulating evidence indicates that women are more sensitive to the context of an offer than men and show a stronger propensity to adjust their behavior with changing frames (Ellingsen et al., 2013; Espinosa and Kovarik, 2015; Miller and Ubeda, 2012). Surprisingly, however, the mechanisms mediating sex-specific framing effects are still unclear.

Current perspectives on the neurobiological substrates of framing biases in the context of risk decisions emphasize a central role of an affect heuristic, evident for example in the sensitivity of limbic brain regions to risk framing (De Martino et al., 2006). According to a dual system view, different frames evoke distinct emotional responses that require "top-down" mental efforts to resist them (Gosling and Moutier, 2019; Kahneman and Frederick, 2007). Interindividual differences in the susceptibility to framing bias have been linked to genetic variations of serotonergic and dopaminergic pathways (Gao et al., 2017; Roiser et al., 2009). Fairness-related framing effects have been probed with an adapted version of the Ultimatum Game (UG) (Güth et al., 1982), in which a proposer has two options how to split a stake (Falk et al., 2003). If the responder accepts, the deal goes ahead and if the responder rejects, neither player gets anything. Rejection rates for the same offer vary substantially depending on the proposer's alternative because the chosen offer signals either an unfair or fair intentionality. The incorporation of intentionality into decision-making follows a linear developmental trajectory across adolescence, with the relative importance of the proposer's intentions increasing with age (Guroglu et al., 2009; Sutter, 2007). The gradual emergence of intention-consideration is paralleled by enhanced activation in the temporoparietal junction and the dorsolateral prefrontal cortex during rejection of unintentional unfair offers, which may reflect increased perspective taking (Guroglu et al., 2011).

Various lines of research indicate that women are more sensitive to the context of an offer and its associated social cues than men (Ellingsen et al., 2013; Espinosa and Kovarik, 2015; Miller and Ubeda, 2012). For instance, procedural fairness in the UG is more important for determining subsequent behavior in women than men (Hack and Lammers, 2009). It is clear that sex differences in social-cognitive domains may result from interactions of numerous environmental and biological factors including stereotypical beliefs as well as hormonal and genetic variables (Cahill, 2006; Kret and De Gelder, 2012). Gonadal steroids are likely to contribute to sex-specific behaviors. While several previous studies examined the impact of the primary male sex hormone testosterone on human social-emotional behavior (Bos et al., 2012; McCall and Singer, 2012), very little is known about the modulatory role of the female sex hormone estradiol. Studies exploring natural variations of endogenous estradiol in women found menstrual cycle effects on reward-based decision-making. Specifically, higher estradiol levels are positively related to increased risk-taking behavior and reduced loss aversion (Ambrase et al., 2021). In addition, elevations in estradiol levels during the reproductive cycle were associated with a reduced immediate reward selection bias in intertemporal decision-making (Smith et al., 2014), as well as higher proposer demands in the UG, which suggests a reduced willingness to cooperate and an increased disposition to risk a monetary punishment (Eisenbruch and Roney, 2016). Furthermore, the administration of exogeneous estradiol enhanced the ability to recall extinction memory in women (Graham and Milad, 2013) and increased vicarious emotional reactivity in men (Olsson et al., 2016), but as yet no study probed the effects of estradiol administration on decision-making in both women and men. Interestingly, stereotypical beliefs about gonadal steroids seem to be influential beyond the hormonal effects. The folk hypothesis on the effects of testosterone implies an increased antisocial, egoistic and aggressive behavior. The mere belief in receiving testosterone, led to an increased unfair bargaining behavior in healthy women, although against stereotypical beliefs, the actual treatment with testosterone promoted fair bargaining behavior in participants (Eisenegger et al., 2010). By contrast, the folk hypothesis on estradiol predicts that men and women view females as being more affable and empathetic as well as more concerned about others than males (Hentschel et al., 2019).

Consequently, estradiol as a typical female hormone, might be associated with a distinctive prosocial behavior.

Previous research on estradiol mostly focused on women's risk behavior during the different menstrual cycle phases. However, natural hormonal fluctuations in the menstrual cycle hinder a hormone-specific interpretation of these results (e.g. behavioral changes may result from changes in estradiol levels but could also be related to changes in progesterone levels). The goal of our study is to specifically investigate the modulatory role of the sex hormone estradiol on sex differences in fairness framing via a selective exogenous hormone administration.

We hypothesized that if women are more sensitive to fairness frames than men, estradiol may contribute to these sex differences and administration of the hormone would increase the fairness sensitivity of women and men (Ambrase et al., 2021; Eisenbruch and Roney, 2016; Smith et al., 2014). In accordance with the folk hypothesis on estradiol we expected that stereotypical beliefs about estradiol would be associated with increased acceptance of unfair-framed offers (Eisenegger et al., 2010; Hentschel et al., 2019).

2. Experimental procedures

2.1. Participants

A total of 212 healthy adults (108 females; mean age $\pm$ SD $= 23.55 \pm 3.75$ years; cf. Table S1) participated in the study after giving written, informed consent. The study was part of a larger project (cf. SI) and was approved by the institutional review board of the Medical Faculty of the University of Bonn and carried out in compliance with the latest revision of the Declaration of Helsinki. Screenings of the participants were conducted prior to the test sessions. Subjects were free of current and past physical or psychiatric illness, as assessed by medical history and the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) prior to enrollment. In addition, they were naive to prescription-strength psychoactive medication, and had not taken any over-the-counter psychoactive medication in the past 4 weeks. The participants were asked to maintain their regular bed and waking times and to abstain from caffeine and alcohol intake on the day of the experiment. None of the women used hormonal contraceptives or were pregnant during the study. All women were tested in their early follicular phase of their menstrual cycle (days 1–6) as validated by blood assays obtained on the testing day (see Table S2).

2.2. Experimental design and procedures

We conducted a randomized, double-blind, placebo-controlled, parallel-group design study. The estradiol gel (Estramon 2 mg estradiol, Hexal AG, Holzkirchen, Germany) or the placebo gel (ultrasonic gel) was transdermally applied to the participants' back prior to the experiment. The dose was chosen in accordance with a recent pharmacokinetic study (Eisenegger et al., 2013) to minimize side effects and negative feedback loops in the neuroendocrine system. The estradiol treatment was balanced within the male subsample (estradiol $n = 53$, placebo $n = 51$) and the female subsample (estradiol $n = 54$, placebo $n = 54$). In accordance with our pharmacokinetic pre-study (cf. SI), the decision-making tasks commenced 2.5 h after the gel administration. Blood samples were collected before and 3.5 h after the gel administration. At the end of the experiment, participants were asked to estimate their received treatment. Out of the 105 participants in the estradiol group with available treatment estimates (two data points missing), 34 (32.4%; 22 men) believed that they had received estradiol, while 28 subject (26.9%; 16 men) in the placebo group (with $n = 104$) believed that they had received the verum treatment ($X_{(1)} = 0.75$, $p = 0.39$).

2.3. Tasks

2.3.1. Ultimatum game

In the UG, a proposer suggests a way to divide a fixed sum of money and if the responder accepts, the deal goes ahead. If the responder rejects, neither player gets anything. Each trial started with the presentation of a fixation cross for a random time interval between 1 and 2 s. Then a picture of the proposer was displayed for 1 s, after which the proposer's offer was shown. Subjects could accept or reject an offer by pressing one of two buttons. They were instructed to decide as fast as possible.

Participants played three different versions of the UG (framed, unframed and computer). In the framed version, the proposer had to decide between two given options of monetary splits. Thus, the chosen offer could be framed as fair or unfair depending on the alternative offer. For instance, an offer of 3€ can be perceived as fair, if the alternative option is 2€, but as unfair if the other option is 4€. In the framed version of the UG, there were 36 trials, half with a fair framing (4€ vs. 3€, 3€ vs. 2€, 2€ vs. 1€ and 1€ vs. 0€) and half with an unfair framing (4€ vs. 5€, 3€ vs. 4€, 2€ vs. 3€ and 1€ vs. 2€). The two potential offers were displayed for 6 s and the selected option was marked with a black box (cf. Figure S2).

In the unframed UG, the proposer could freely decide how to split 10€. There were 24 trials in the unframed UG, each with a different proposer. The offers systematically varied between 0 and 5€, each proposal was repeated 4 times. In addition, participants completed 24 trials of a computer version of the unframed UG, in which the word "computer" was shown instead of a picture of the proposer. The orders of the UG version and the proposers' offers were randomized across participants.

As a cover story, participants were told that they would play against real partners, who had taken part in previous experiments. However, the proposals and stimuli were predetermined and equally divided into offers made by female and male proposers with common names in Germany. Pictures of the proposers were selected from the Center for Vital Longevity (Park Aging Lab, PAL) database (Minear and Park, 2004). Subjects were told that they were randomly assigned to either the responder or proposer group, although it was predetermined that all subjects acted as responders. It was emphasized that there are no repeated interactions (i.e. they encountered every player only once; "one-shot" trials).

The UG was implemented in Presentation 20 (Neurobehavioral Systems, Albany, CA). After completing the experiment, one decision was randomly selected and participants were paid according to their choice (i.e. they either received no payment if they rejected the offer or obtained the amount they accepted).

2.3.2. Delayed discounting task

We used a delayed discounting task to assess the ability to control impulsive preferences (i.e. to suppress the impulsive choice of smaller, but sooner incentives over long-term greater benefits). In 36 trials participants had to choose between rewards, which were either smaller and paid sooner or larger and paid later. The amounts were pseudo-randomly drawn from a normal distribution with a mean of 45€ and a standard deviation of 12€. The larger-later rewards were 0.5–75% larger than the smaller-sooner rewards. The order of the trials was randomized with half of the trials including an immediate reward as the smaller-sooner option and the larger-later reward being delayed for two or four weeks. In the other half of the trials, the smaller-sooner option was paid in two weeks and

the larger-later alternative in four or six weeks. The proportion of patient choices (i.e. larger-later rewards) was used as dependent variable.

2.4. Hormonal assessments

In line with the manufacturer's instructions (Siemens Healthineers, Eschborn, Germany) and based on the LOCI™ technology on a Dimension Vista™ System, serum estradiol and serum testosterone were determined by fully automated homogeneous sandwich chemiluminescent immunoassays. For estradiol, the detection limit of the assay was 5 pg/ml and the coefficients of variation for intra-assay and inter-assay precision were 5.5% and 5.9%. Testosterone was tested with a detection limit of 0.025 ng/ml and the intra-assay and inter-assay precision variation coefficients were 4.7% and 6.7%. By applying a fully automated solid-phase competitive chemiluminescent enzyme immunoassay on an Immulite™ 2000xpi System according to the manufacturerś instructions (Siemens Healthineers) the serum progesterone was analyzed with a detection limit of 0.1 ng/ml. For the intra-assay and the inter-assay precision, the coefficients varied between 4.2% and 5.5%. There was a minimal cross-reactivity of all assays with other related compounds.

2.5. Statistical analysis

The behavioral, demographical and neuropsychological data were processed using standard procedures in SPSS 24 (IBM, New York, NY, USA). The quantitative behavioral data were analyzed with mixed-design analysis of variance (ANOVA) and for correlation analyses Pearson's product-moment correlations (r) were used. The acceptance rates in percent and the response time of these decisions served as dependent variables. Independent factors were framing (fair vs. unfair), proposal magnitude (1,2,3 and 4 €), sex (female vs. male) and treatment (estradiol vs. placebo). Furthermore, the effects of the believed treatment were assessed in ANOVAs with the additional independent factor believed treatment (believed estradiol vs. believed placebo). To control for the varying increases in estradiol levels, we computed an analysis of covariance (ANCOVA). The difference score of the baseline and post-treatment estradiol levels for each participant served as a covariate in our main analysis. We used the acceptance rate of fair framed offers as our dependent variable and treatment (placebo vs. estradiol) and sex (male vs. female) as between-subject factors. The assumption of sphericity was assessed with Mauchly's test, and Greenhouse-Geisser's correction was applied for significant violations. The *P*-values are two tailed and considered as significant at a level of $P < 0.05$. Post-hoc *t*-tests were Bonferroni-corrected (P_{cor}) to account for multiple comparisons.

3. Results

3.1. Effects of proposal magnitude, fairness frames and estradiol treatment

The acceptance rate in the framed version of the UG significantly increased with the magnitude of the proposal ($F_{(1,206)} = 356.73$, $p < 0.01$, $\eta_p^2 = 0.63$) and was higher for fair-framed than unfair-framed offers ($F_{(1,206)} = 214.81$, $p < 0.01$, $\eta_p^2 = 0.51$). Importantly, the treatment effect differed significantly between the sexes and framings (treatment x framing x sex interaction: $F_{(1,206)} = 10.34$, $p < 0.01$, $\eta_p^2 = 0.05$; cf. Figure 1). Under placebo, the framing effect in the framed UG was more pronounced in women than men ($F_{(1,101)} = 16.10$, $p < 0.001$, $\eta_p^2 = 0.14$), with women accepting significantly more fair-framed offers than men ($t_{(82.84)} = 2.65$, $p_{cor} = 0.02$, $d = 0.53$). After estradiol treatment, the pattern was reversed ($t_{(105)} = -2.50$, $p_{cor} = 0.03$, $d = 0.49$). Thus, estradiol selectively decreased the acceptance rate of fair-framed offers in women ($t_{(97.63)} = -2.79$, $p_{cor} = 0.01$, $d = -0.54$) and had the opposite effect in men ($t_{(91.86)} = 2.43$, $p_{cor} = 0.03$, $d = 0.48$). The treatment effect was not moderated by the magnitude of the offer (all *p*s > 0.05). Furthermore, women accepted significantly fewer unfair-framed offers than men ($F_{(1,206)} = 4.68$, $p = 0.03$, $\eta_p^2 = 0.02$), but there was no significant main or interaction effect of treatment for unfair-framed offers (all *p*s > 0.05).

In general, participants needed more time for their decisions in the framed UG if the offer was framed unfair (mean ± SD = 1.87 ± 0.70 s) compared to a fair framing (1.77 ± 0.63 s; $F_{(1,206)} = 13.80$, $p < 0.001$, $\eta_p^2 = 0.06$). Additionally, they were faster in responding to smaller (1.75 ± 0.64 s) than larger offers (1.88 ± 0.73 s; $F_{(2.86,588.41)} = 7.63$, $p < 0.001$, $\eta_p^2 = 0.04$). After the estradiol treatment women had a faster reaction time (1.70 ± 0.47 s) compared to the placebo group (1.90 ± 0.67 s), in contrast to men, who decided more slowly after receiving estradiol (placebo: 1.75 ± 0.46 s; estradiol: 1.94 ± 0.84 s; interaction between sex and treatment, $F_{(1,206)} = 5.20$, $p = 0.02$, $\eta_p^2 = 0.03$). However, post-hoc comparisons showed no significant treatment effects on the reaction times in the male and female subsample (all *p*s > 0.05).

3.2. Hormonal assessments

At baseline, women had significantly higher estradiol concentrations than men ($t_{(187.4)} = 2.44$, $p_{cor} = 0.03$, $d = 0.34$), but lower progesterone ($t_{(102.74)} = -5.85$, $p_{cor} < 0.001$, $d = -0.82$) and testosterone ($t_{(102.36)} = -27.28$, $p_{cor} < 0.001$, $d = -3.82$). Importantly, baseline levels of all three hormones were comparable between treatment groups in women (all *p*s > 0.05) and men (all *p*s > 0.05). Estradiol administration significantly increased blood estradiol levels in women (time x treatment: $F_{(1,105)} = 187.20$, $p < 0.001$, $\eta_p^2 = 0.64$) and men (time x treatment: $F_{(1,100)} = 111.55$, $p < 0.001$, $\eta_p^2 = 0.53$), but had no significant effect on testosterone and progesterone concentrations (cf. Table S2). However, the treatment-induced increase in estradiol was significantly higher in women than men ($F_{(1,207)} = 26.84$, $p < 0.001$, $\eta_p^2 = 0.12$). Importantly, the treatment x sex interaction for fair framed offers remained significant in an ANCOVA after including the increase in blood estradiol levels as a covariate ($F_{(1,202)} = 7.402$, $p < 0.01$, $\eta_p^2 = 0.035$). Furthermore, the increase in estradiol was not significantly related to the acceptance rate of fair framed offers ($F_{(1,202)} = 0.97$, $p = 0.326$, $\eta_p^2 = 0.05$). Likewise, controlling for individual baseline estradiol levels did not change the significant treatment x sex interaction for fair-framed offers ($F_{(1,203)} = 14.65$, $p < 0.01$, $\eta_p^2 = 0.067$).

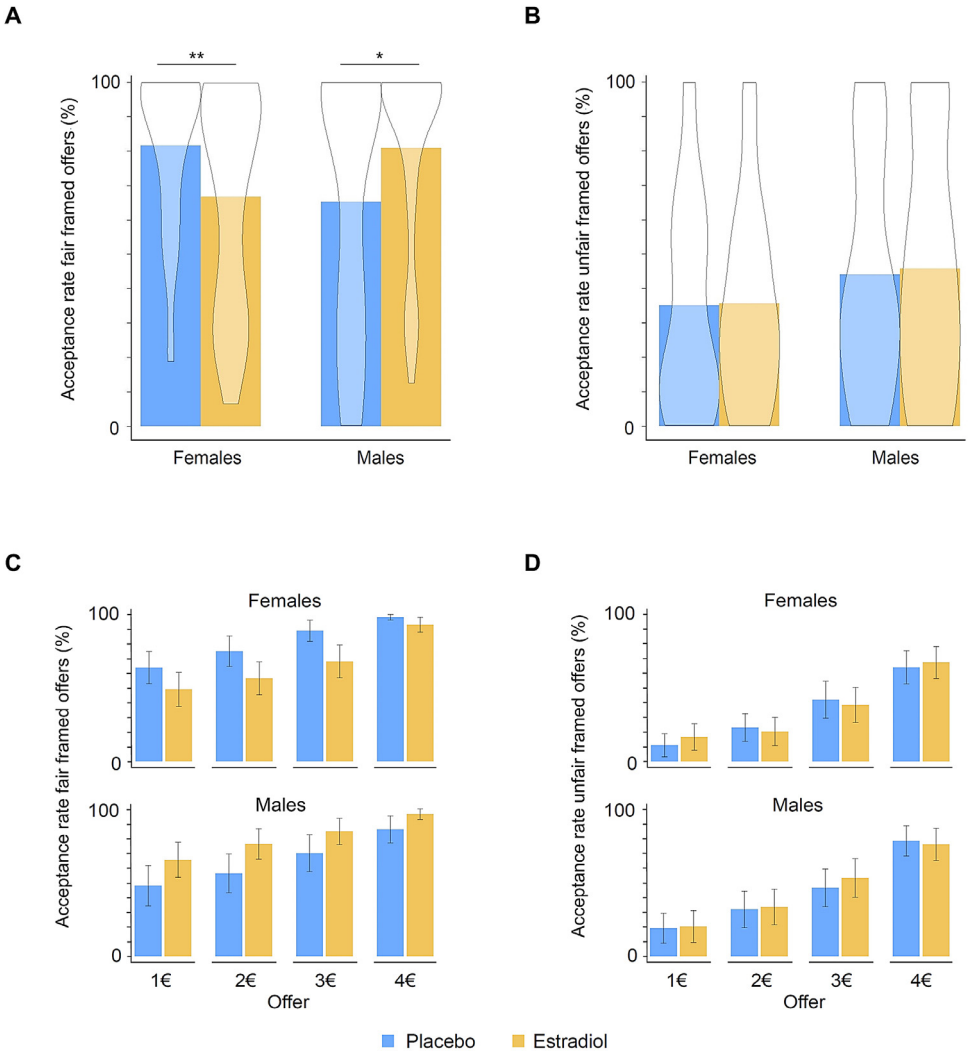

Figure 1 The acceptance rate was significantly lower for unfair-framed offers and women accepted significantly more fair-framed offers than men. Estradiol significantly increased the acceptance rate of fair-framed offers in men and had the opposite effect in women (**A**). The treatment had no significant effect on unfair-framed offers (**B**). The estradiol effect was independent of the offer size (1-4€) (**C, D**). Violin plots are kernel density plots which are comparable to histograms with infinitely small bin sizes. Error bars indicate the 95%-confidence intervals. $^{*}p < 0.05$; $^{**}p < 0.01$.

3.3. Estradiol does not affect sensitivity to offer magnitude or delayed discounting

As expected from the literature, acceptance rates increased with the magnitude of the offer in both, the unframed ($F_{(3.21,663.44)} = 507.74$, $p < 0.001$, $\eta_p{}^2 = 0.71$) and the computer versions of the UG ($F_{(2.85,586.25)} = 370.28$, $p < 0.001$, $\eta_p{}^2 = 0.64$). However, there were no significant main or interaction effects of the estradiol treatment in the unframed version of the UG or the computer UG. A significant sex x offer size interaction in the unframed UG ($F_{(3.21,663.44)} = 4.05$, $p < 0.01$, $\eta_p{}^2 = 0.02$) and computer UG ($F_{(2.85,586.25)} = 7.95$, $p < 0.01$, $\eta_p{}^2 = 0.04$) showed that men accepted more lower offers than women, while this effect was reversed for higher offers.

In the delayed discounting task, participants chose the later-larger option more often when there was a greater relative difference in sooner-smaller/later-larger magnitudes (i.e. main effect of relative difference; $F_{(3.43,710.82)} = 384.16$, $p < 0.01$, $\eta_p{}^2 = 0.65$), but there were no significant sex or treatment effects (all ps > 0.05). Thus, the treatment effect in the framed version of the UG is probably driven by framing sensitivity rather than global changes in economic decision-making or altered intertemporal decision making.

3.4. Effects of the believed treatment

An independent sample of 133 subjects (85 women) described estradiol with the attributes caring, empathetic, loving and friendly, but also weak and anxious (cf. SI). Thus, the mere belief of receiving a treatment could alter the acceptance rate of fair and unfair offers. In line with this prediction, the believed treatment had a significant effect that varied as a function of the actual treatment and fram-

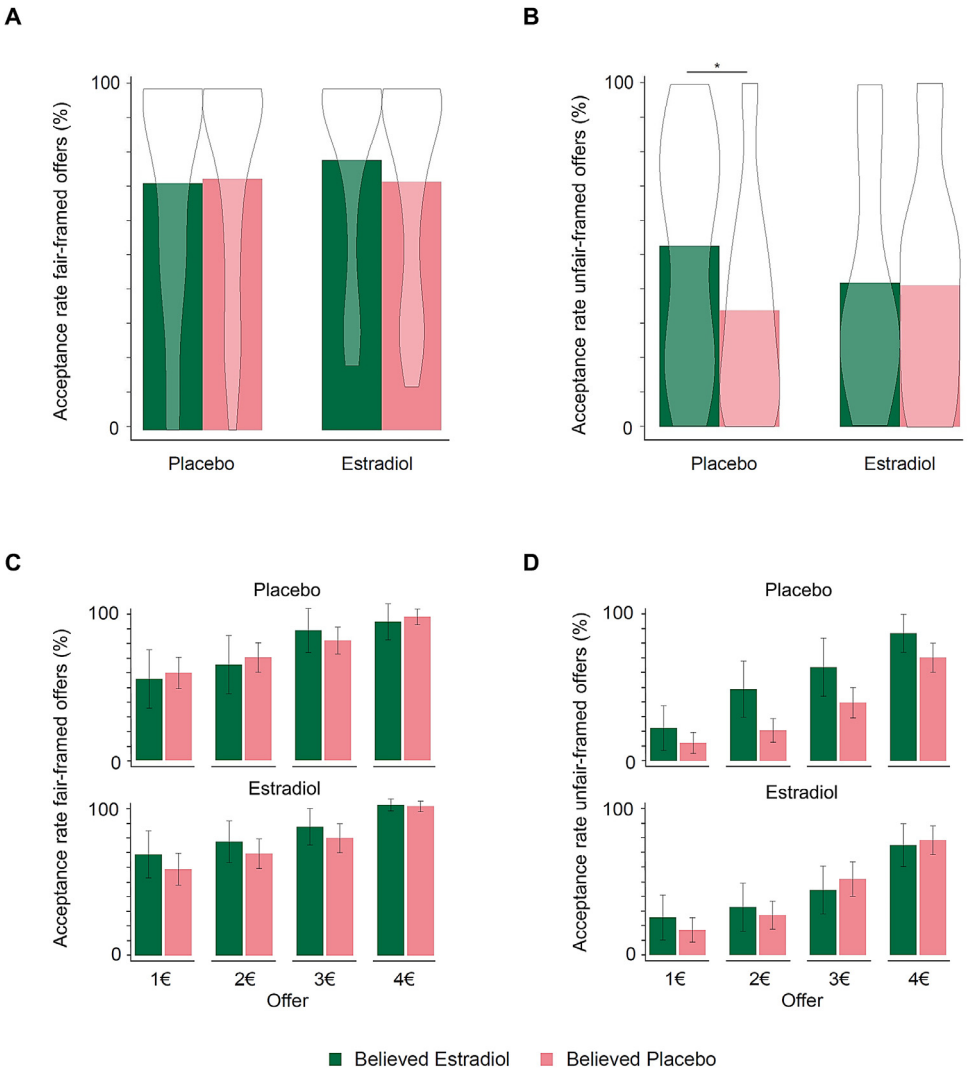

Figure 2 There were no significant belief effects for mean fair-framed offers (**A**). However, participants in the placebo group who believed that they had received estradiol accepted significantly more unfair offers compared to those who believed they had received a placebo treatment (**B**). This effect was not evident in the estradiol group **.** The belief effect was independent of the offer size (1–4€) (**C, D**). Violin plots are the kernel density plots which are comparable to histograms with infinitely small bin sizes. Error bars indicate the 95%-confidence intervals. $^{*}p < 0.05$.

ing ($F_{(1,199)} = 4.89$, $p = 0.03$, $\eta_p{}^2 = 0.02$, cf. Figure 2). In the placebo group, subjects who believed that they had received estradiol accepted significantly more unfair-framed offers than subjects who believed that they had received placebo ($t_{(100)} = 2.68$, $p_{cor} = 0.02$, $d = 0.61$). This belief effect was not evident for fair-framed offers or estradiol-treated subjects (all $ps > 0.05$). Notably, the believed treatment was not significantly associated with the actual treatment in women and men (all $ps > 0.05$).

Furthermore, the believed treatment had significant effects on acceptance rates in the unframed UG and the computer UG. In the unframed UG, there was a significant three-way interaction of the offer size, the treatment and the believed treatment ($F_{(3.27,653.03)} = 2.68$, $p < 0.05$, $\eta_p{}^2 = 0.013$). Likewise, in the computer UG, participants with believed estradiol treatment accepted more lower offers and this effect was significantly stronger in men than in women (i.e. significant three-way-interaction of sex, offer size and believed treatment; $F_{(2.86,568.38)} = 2.76$, $p < 0.05$, $\eta_p{}^2 = 0.014$). No significant belief effects were evident in the delayed discounting task.

4. Discussion

The aim of the current study was to investigate the impact of exogenous estradiol and the associated stereotypical beliefs on fairness framing in women and men. Our results provide evidence for strong sex differences in the impact of fairness frames on the acceptance of ultimatum offers, with women demonstrating a stronger fairness sensitivity than men. This observation is consistent with previous research indicating a stronger propensity of women to adjust their behavior with changing frames (Espinosa and Kovarik, 2015;

Fehr and Gachter, 2002; Miller and Ubeda, 2012). Importantly, in contrast to our hypothesis, this sex-specific effect was reversed after estradiol treatment, with the sex hormone increasing the acceptance rate of proposals with a fair frame in men and reducing it in women. Furthermore, we found that stereotypical beliefs about estradiol modulated the acceptance rate of unfair-framed offers in both sexes under placebo. Thus, our results support the notion that both biological and environmental factors contribute to framing effects on ultimatum bargaining.

Sex differences in emotion recognition are less pronounced during periods of high estradiol levels in women (Derntl et al., 2008) and estradiol-treated women in our study showed a fairness framing effect comparable to men under placebo. It has been proposed that low estradiol enhances attentional vigilance for emotional information (Albert and Newhouse, 2019) as the memory for emotional content is improved during the menstrual phase when estradiol is low (Ertman et al., 2011). We found a selective effect of exogenous estradiol on the acceptance rate of fair-framed offers, but no significant effect in the unframed UG. Given that the intentionality of the proposer differentiates the two versions of the UG (Radke et al., 2012), our data indicate that the sensitivity for the intentionality of bargaining offers is also increased when exogenous estradiol levels are lower in women. The absence of an estradiol effect in the unframed UG corresponds to a previous study, in which no significant effect of a long-term estradiol treatment on decision-making in the unframed UG was observed in postmenopausal women (Zethraeus et al., 2009). Unfair-framed offers seem to be less volatile than fair-framed offers because a further decrease in the acceptance rate may be hindered by bottom effects and an increase would require the participants to overcome the prepotent preference to reject unfair intentions. Of note, millions of women around the world use steroid-based hormonal contraception as an effective way of birth control (Alkema et al., 2013). While previous studies have yielded inconsistent results about the impact of hormonal contraception on altruistic preferences and financial risk taking (Buser, 2012; Chen et al., 2013; Ranehill et al., 2018; Wozniak et al., 2014), our findings introduce the question whether long-term hormone treatments may influence framing effects in economic decision-making.

In men, exogenous estradiol increased the impact of fairness framing on ultimatum bargaining similarly to what is observed in women under placebo. In contrast to the effect in women, the estradiol administration resulted in supraphysiological levels of the hormone in men, but our control analysis did not indicate a significantly different direction of effects in participants with lower estradiol increase. Studies exploring the effects of estradiol administration in men are scarce, but it was recently found that estradiol treatment made motivational choices (i.e. the preference of cocaine over food reinforcement) in male rats comparable to that of female rats (Bagley et al., 2019). There were no significant a-priori sex differences in the cognitive control of prepotent impulses during delayed discounting and estradiol did not significantly alter choice preferences. Thus, it would appear that estradiol-induced changes in the susceptibility to fairness framing effects are unlikely to result from altered intertemporal decision making. Instead, estradiol may enable men to more strongly incorporate the proposer's intentionality into their decision-making by facilitating perspective taking (Guroglu et al., 2011). Sex-specific effects of estradiol were also evident in response times, with men making slower decisions in the framed UG after estradiol treatment and women becoming faster. It has been suggested that the acceleration of the deterioration of processing speed following menopause is associated with a lack of gonadal hormones, indicating that estradiol may have pro-cognitive functions in women (Halbreich et al., 1995). Effects of endogenous estradiol on working memory function crucially depend on baseline fluctuations in cortical dopamine indexed by the catechol-O-methyltransferase (COMT) Val(158)Met-genotype (Jacobs and D'Esposito, 2011). Given sex-specific effects of COMT on inhibitory brain activation (White et al., 2014), it is conceivable that the observed sex-specific effects of estradiol on fairness framing result from dopamine-estradiol interactions. Interestingly, similar sex-specific effects have been observed for testosterone. Importantly, exogenous testosterone administration caused women to make higher offers in the role of UG proposer (Eisenegger et al., 2010), but it produced the opposite effect in men (Zak et al., 2009). However, it is still not clear why testosterone has different behavioral effects in women and men (Stanton, 2017). Sex-specific effects of testosterone are also evident in other domains. A recent study examined genetic determinants of testosterone levels and found that higher testosterone is harmful for metabolic diseases in women but beneficial in men (Ruth et al., 2020). Clearly, the apparently sex-divergent effects of estradiol would have been obfuscated by an aggregated analysis. Our findings thus underscore the importance of including both women and men in the same experimental protocol and conducting sex-specific analyses.

Participants who believed that they received estradiol may have wanted to respond in accordance with their stereotypical beliefs and show concern for the proposer by accepting significantly more unfair-framed offers. Belief effects were also evident in the unframed and computer UG, indicating that stereotypical beliefs can have a broad impact on economic decision-making. In contrast to the stereotypical beliefs, estradiol had no significant effect on unfair-framed offers and it even reduced the acceptance rate of fair-framed offers in women. Importantly, selective belief effects in the placebo group speak against the idea that estradiol mediates these stereotypical behavioral changes.

Our study has some limitations that need to be addressed in future research. First, by testing women in their early follicular phase, we ensured low estradiol and progesterone levels and thus comparable baseline conditions to the male sample. The treatment had a specific effect on the estradiol levels, but future studies are warranted to further test possible interactions with other gonadal steroids or neurotransmitters (Ambrase et al., 2021). Second, sex differences in framing effects are moderated by task domain (Huang and Wang, 2010). We observed a significant effect of exogenous estradiol on fairness framing of monetary decisions, but these results cannot directly be extrapolated to other contexts such as risky-choice frames of life-death decisions.

Collectively, our findings provide support for the notion that sex differences in fairness framing are modulated by the sex hormone estradiol. Furthermore, the believed treatment affected the acceptance of unfair-framed offers, illustrating that stereotypical beliefs about hormones can influence decision-making beyond direct hormonal effects. Therefore, integrating sex and gender analysis into research designs (Tannenbaum et al., 2019) may help deciphering the interactions of environmental and neurobiological factors that mediate framing effects in humans.

Data availability

The data that support the findings of the present study are openly available in the repository of the Open Science Foundation at https://www.osf.io/3tmpr/ (doi: 10.17605/OSF.IO/3TMPR).

Contributors

M.C. and D.S. designed the experiment; F.P., V.S. and F.G. conducted the experiments; B.S.-W. contributed new reagents/analytic tools; M.C., F.P. and D.S. analyzed the data. All authors wrote the manuscript. All authors read and approved the manuscript in its current version.

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Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2021.04.006.

References

Albert, K.M., Newhouse, P.A., 2019. Estrogen, stress, and depression: cognitive and biological interactions. Annu. Rev. Clin. Psychol. 15, 399–423.

Alkema, L., Kantorova, V., Menozzi, C., Biddlecom, A., 2013. National, regional, and global rates and trends in contraceptive prevalence and unmet need for family planning between 1990 and 2015: a systematic and comprehensive analysis. Lancet 381, 1642–1652.

Ambrase, A., Lewis, C.A., Barth, C., Derntl, B., 2021. Influence of ovarian hormones on value-based decision-making systems: contribution to sexual dimorphisms in mental disorders. Front. Neuroendocrionl. 60, 100873.

Bagley, J.R., Adams, J., Bozadjian, R.V., Bubalo, L., Ploense, K.L., Kippin, T.E., 2019. Estradiol increases choice of cocaine over food in male rats. Physiol. Behav. 203, 18–24.

Bos, P.A., Panksepp, J., Bluthe, R.M., van Honk, J., 2012. Acute effects of steroid hormones and neuropeptides on human social-emotional behavior: a review of single administration studies. Front. Neuroendocrinol. 33, 17–35.

Buser, T., 2012. Digit ratios, the menstrual cycle and social preferences. Games Econ. Behav. 76, 457–470.

Cahill, L., 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci. 7, 477–484.

Chen, Y., Katuscak, P., Ozdenoren, E., 2013. Why can't a woman bid more like a man? Games Econ. Behav. 77, 181–213.

De Martino, B., Kumaran, D., Seymour, B., Dolan, R.J., 2006. Frames, biases, and rational decision-making in the human brain. Science 313, 684–687.

Derntl, B., Windischberger, C., Robinson, S., Lamplmayr, E., Kryspin-Exner, I., Gur, R.C., Moser, E., Habel, U., 2008. Facial emotion recognition and amygdala activation are associated with menstrual cycle phase. Psychoneuroendocrinology 33, 1031–1040.

Eisenbruch, A.B., Roney, J.R., 2016. Conception risk and the ultimatum game: when fertility is high, women demand more. Pers. Individ. Differ. 98, 272–274.

Eisenegger, C., Naef, M., Snozzi, R., Heinrichs, M., Fehr, E., 2010. Prejudice and truth about the effect of testosterone on human bargaining behaviour. Nature 463 356-U104.

Eisenegger, C., von Eckardstein, A., Fehr, E., von Eckardstein, S., 2013. Pharmacokinetics of testosterone and estradiol gel preparations in healthy young men. Psychoneuroendocrinology 38, 171–178.

Ellingsen, T., Johannesson, M., Mollerstrom, J., Munkhammar, S., 2013. Gender differences in social framing effects. Econ. Lett. 118, 470–472.

Ertman, N., Andreano, J.M., Cahill, L., 2011. Progesterone at encoding predicts subsequent emotional memory. Learn. Mem. 18, 759–763.

Espinosa, M.P., Kovarik, J., 2015. Prosocial behavior and gender. Front. Behav. Neurosci. 9.

Falk, A., Fehr, E., Fischbacher, U., 2003. On the nature of fair behavior. Econ. Inq. 41, 20–26.

Fehr, E., Gachter, S., 2002. Altruistic punishment in humans. Nature 415, 137–140.

Gao, X., Liu, J., Gong, P., Wang, J., Fang, W., Yan, H., Zhu, L., Zhou, X., 2017. Identifying new susceptibility genes on dopaminergic and serotonergic pathways for the framing effect in decision-making. Soc. Cogn. Affect. Neurosci. 12, 1534-1544.

Gosling, C.J., Moutier, S., 2019. Is the framing effect a framing affect? Q. J. Exp. Psychol. 72, 1412-1421.

Graham, B.M., Milad, M.R., 2013. Blockade of estrogen by hormonal contraceptives impairs fear extinction in female rats and women. Biol. Psychiatry 73, 371–378.

Guroglu, B., van den Bos, W., Crone, E.A., 2009. Fairness considerations: increasing understanding of intentionality during adolescence. J. Exp. Child Psychol. 104, 398–409.

Guroglu, B., van den Bos, W., van Dijk, E., Rombouts, S.A., Crone, E.A., 2011. Dissociable brain networks involved in devel-

opment of fairness considerations: understanding intentionality behind unfairness. Neuroimage 57, 634–641.
Güth, W., Schmittberger, R., Schwarze, B., 1982. An experimental analysis of ultimatum bargaining. J. Econ. Behav. Organ. 3, 22.
Hack, A., Lammers, F., 2009. Gender as a moderator of the fair process effect. Soc. Psychol. 40, 202–211.
Halbreich, U., Lumley, L.A., Palter, S., Manning, C., Gengo, F., Joe, S.H., 1995. Possible acceleration of age effects on cognition following menopause. J. Psychiatr. Res. 29, 153–163.
Henrich, J., McElreath, R., Barr, A., Ensminger, J., Barrett, C., Bolyanatz, A., Cardenas, J.C., Gurven, M., Gwako, E., Henrich, N., Lesorogol, C., Marlowe, F., Tracer, D., Ziker, J., 2006. Costly punishment across human societies. Science 312, 1767–1770.
Hentschel, T., Heilman, M.E., Peus, C.V., 2019. The multiple dimensions of gender stereotypes: a current look at men's and women's characterizations of others and themselves. Front. Psychol. 10, 11.
Huang, Y.H., Wang, L., 2010. Sex differences in framing effects across task domain. Pers. Individ. Differ. 48, 649–653.
Jacobs, E., D'Esposito, M., 2011. Estrogen shapes dopamine-dependent cognitive processes: implications for women's health. J Neurosci 31, 5286–5293.
Kahneman, D., Frederick, S., 2007. Frames and brains: elicitation and control of response tendencies. Trends Cogn. Sci. 11, 45–46.
Kret, M.E., De Gelder, B., 2012. A review on sex differences in processing emotional signals. Neuropsychologia 50, 1211–1221.
McCall, C., Singer, T., 2012. The animal and human neuroendocrinology of social cognition, motivation and behavior. Nat. Neurosci. 15, 681–688.
Miller, L., Ubeda, P., 2012. Are women more sensitive to the decision-making context? J. Econ. Behav. Organ. 83, 98–104.
Minear, M., Park, D.C., 2004. A lifespan database of adult facial stimuli. Behav. Res. Methods Instrum. Comput. 36, 630–633.
Olsson, A., Kopsida, E., Sorjonen, K., Savic, I., 2016. Testosterone and estrogen impact social evaluations and vicarious emotions: a double-blind placebo-controlled study. Emotion 16, 515–523.
Radke, S., Guroglu, B., de Bruijn, E.R., 2012. There's something about a fair split: intentionality moderates context-based fairness considerations in social decision-making. PLoS ONE 7, e31491.
Ranehill, E., Zethraeus, N., Blomberg, L., von Schoultz, B., Hirschberg, A.L., Johannesson, M., Dreber, A., 2018. Hormonal contraceptives do not impact economic preferences: evidence from a randomized trial. Manag. Sci. 64, 4515–4532.
Roiser, J.P., de Martino, B., Tan, G.C., Kumaran, D., Seymour, B., Wood, N.W., Dolan, R.J., 2009. A genetically mediated bias in decision making driven by failure of amygdala control. J. Neurosci. 29, 5985–5991.
Ruggeri, K., Alí, S., Berge, M.L., Bertoldo, G., Bjørndal, L.D., Cortijos-Bernabeu, A., Davison, C., Demić, E., Esteban-Serna, C., Friedemann, M., 2020. Replicating patterns of prospect theory for decision under risk. Nat. Hum. Behav. 1–12.
Ruth, K.S., Day, F.R., Tyrrell, J., Thompson, D.J., Wood, A.R., Mahajan, A., Beaumont, R.N., Wittemans, L., Martin, S., Busch, A.S., Erzurumluoglu, A.M., Hollis, B., O'Mara, T.A., McCarthy, M.I., Langenberg, C., Easton, D.F., Wareham, N.J., Burgess, S., Murray, A., Ong, K.K., Frayling, T.M., Perry, J.R.B., Consortium, E.C.A., 2020. Using human genetics to understand the disease impacts of testosterone in men and women. Nat. Med. 26, 252–258.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59, 22–33.
Smith, C.T., Sierra, Y., Oppler, S.H., Boettiger, C.A., 2014. Ovarian cycle effects on immediate reward selection bias in humans: a role for estradiol. J. Neurosci. 34, 5468–5476.
Stanton, S.J., 2017. The role of testosterone and estrogen in consumer behavior and social & economic decision making: a review. Horm. Behav. 92, 155–163.
Sutter, M., 2007. Outcomes versus intentions: on the nature of fair behavior and its development with age. J. Econ. Psychol. 28, 69–78.
Tannenbaum, C., Ellis, R.P., Eyssel, F., Zou, J., Schiebinger, L., 2019. Sex and gender analysis improves science and engineering. Nature 575, 137–146.
Tversky, A., Kahneman, D., 1981. The framing of decisions and the psychology of choice. Science 211, 453–458.
White, T.P., Loth, E., Rubia, K., Krabbendam, L., Whelan, R., Banaschewski, T., Barker, G.J., Bokde, A.L.W., Buchel, C., Conrod, P., Fauth-Buhler, M., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Lawrence, C., Mann, K., Paillere, M.L., Nees, F., Paus, T., Pausova, Z., Rietschel, M., Robbins, T., Smolka, M.N., Shergill, S.S., Schumann, G., Consortium, I., 2014. Sex differences in COMT polymorphism effects on prefrontal inhibitory control in adolescence. Neuropsychopharmacol 39, 2560–2569.
Wozniak, D., Harbaugh, W.T., Mayr, U., 2014. The menstrual cycle and performance feedback alter gender differences in competitive choices. J. Labor Econ. 32, 161–198.
Zak, P.J., Kurzban, R., Ahmadi, S., Swerdloff, R.S., Park, J., Efremidze, L., Redwine, K., Morgan, K., Matzner, W., 2009. Testosterone administration decreases generosity in the ultimatum game. PLoS ONE 4.
Zethraeus, N., Kocoska-Maras, L., Ellingsen, T., von Schoultz, B., Hirschberg, A.L., Johannesson, M., 2009. A randomized trial of the effect of estrogen and testosterone on economic behavior. Proc. Natl. Acad. Sci. U.S.A. 106, 6535–6538.