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ORIGINAL INVESTIGATION

Dose-dependent effects of estrogen on prediction error related neural activity in the nucleus accumbens of healthy young women

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Abstract

Rationale Whereas the effect of the sex steroid 17-beta-estradiol (E2) on dopaminergic (DA) transmission in the nucleus accumbens (NAc) is well evidenced in female rats, studies in humans are inconsistent. Moreover, linear and inverted u-shaped dose response curves have been observed for E2's effects on hippocampal plasticity, but the shape of dose response curves for E2's effects on the NAc is much less characterized.

Objectives Investigation of dose response curves for E2's effects on DA-related neural activity in the human NAc.

Methods Placebo or E2 valerate in doses of 2, 4, 6 or 12 mg was orally administered to 125 naturally cycling young women during the low-hormone menstruation phase on two consecutive days using a randomized, double-blinded design. The E2 treatment regimen induced a wide range of E2 levels, from physiological (2- and 4-mg groups; equivalent to cycle peak) to supraphysiological levels (6- and 12-mg groups; equivalent to early pregnancy). This made it possible to study different dose response functions for E2's effects on NAc activity. During E2 peak, participants performed a well-established reversal learning paradigm. We used trial-wise prediction errors (PE) estimated via a computational reinforcement learning model as a proxy for dopaminergic activity. Linear and quadratic regression analyses predicting PE-related NAc activity from salivary E2 levels were calculated.

Results There was a positive linear relationship between PE-associated NAc activity and salivary E2 increases.

Conclusions The randomized, placebo-controlled elevation of E2 levels stimulates NAc activity in the human brain, likely mediated by dopaminergic processes.

Keywords Estrogen · Reward · Prediction error · fMRI · Ventral striatum

Introduction

The mesolimbic reward system mediates reward processing, motivation and reinforcement learning (Glimcher 2011). The network is comprised of dopaminergic neurons projecting from the ventral tegmental area to the ventral striatum (Ikemoto and Panksepp 1999). The nucleus accumbens (NAc), as a part of the ventral striatum, is a key region involved in reward processing and reinforcement learning (Haber and Knutson 2009). For instance, the mere stimulation of DA-signaling in the NAc can lead to a quick acquisition of various behaviors in animals (Carr and White 1986; Ikemoto et al. 1997; Cole et al. 2018).

The sex steroid 17-beta-estradiol (E2) exerts various effects on the brain, including the stimulation of synaptogenesis and the facilitation of long-term potentiation (Luine 2014; Vierk et al. 2015). In addition, E2 modulates several neurotransmitter systems such as dopamine (DA), serotonin, glutamate and GABA (Barth et al. 2015). Of these interactions, the stimulation of DA-signaling in the mesolimbic reward system by E2 has been most intensely studied (Yoest et al. 2014, 2018). In the NAc, E2 modulates DA-release, -uptake, -turnover and -receptor binding (Di Paolo et al. 1985; Thompson and Moss 1994; Thompson 1999; Le Saux et al. 2006; Calipari et al.

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2017). However, only few studies describe the effects of different doses of E2 on dopaminergic transmission (Gordon 1980; Renner and Luine 1986; Becker 1990; Pasqualini et al. 1995). In contrast, linear and inverted u-shaped dose response functions have been characterized for E2's effects on synaptic transmission and morphology in the hippocampus (Scharfman et al. 2007; Bakkum et al. 2011; Bayer et al. 2018).

Findings from translational studies in humans on neural responses to reward-related paradigms such as gambling tasks seem to contrast the well-evidenced effects on the dopaminergic processes in the NAc of female rats (Yoest et al. 2018). While some studies speak to variations in NAc activity across the human menstrual cycle (Frank et al. 2010; Ossewaarde et al. 2011; Bayer et al. 2013), others did not observe such effects (Dreher et al. 2007; Alonso-Alonso et al. 2011; Reimers et al. 2014; Diekhof and Ratnayake 2016). Similarly, when hormone levels were manipulated through sequential E2 and progesterone replacement or the administration of a gonadotropin releasing-hormone antagonist, no effects on NAc activity were detected (Thomas et al. 2014; Macoveanu et al. 2016). Potential explanations for conflicting results include the fact that not all reward-related processes are mediated by dopaminergic processes within the NAc (Macoveanu 2014). Moreover, some effects of E2 occur only within a specific range of E2-concentrations (Becker 1990; McLaughlin et al. 2008; Inagaki et al. 2010).

The direct assessment of E2's effects on DA and its metabolites in the human NAc is difficult to realize. However, well-established non-invasive proxy measures have been developed based on the reward prediction error (PE) hypothesis of dopamine (Schultz et al. 1997). Supported by a multitude of observations in several species (Schultz et al. 1997; Fiorillo et al. 2003; O'Doherty et al. 2004; Bayer and Glimcher 2005; Gläscher and O'Doherty 2010; Jocham et al. 2011; Hart et al. 2014), the hypothesis states that DA neurons increase phasic firing rates when better than predicted outcomes occur and pushed down to below base firing rate levels, when worse than predicted outcomes occur. Importantly, the magnitude of these changes in phasic firing rates scales with the size of the deviation from the prediction (Stauffer et al. 2014). The association between DA and PE-related NAc activity in humans, assessed via functional magnetic resonance imaging (fMRI), is supported by pharmacological evidence (Jocham et al. 2014; Diederen et al. 2017) as well as the combination of fMRI with position emission tomography (PET) (Schlagenhauf et al. 2013).

Reversal learning paradigms, in combination with computational modelling, have proven to be a successful approach to evoke reliable PE-related signals in the human NAc (O'Doherty et al. 2004; Gläscher and O'Doherty 2010; Jocham et al. 2011). During reversal learning paradigms, participants have to learn via trial and error which of two stimuli has a greater probability of winning a monetary reward (Yaple and Yu 2019). From time to time, reward contingencies reverse so that participants have to overcome the former and learn the new contingencies. Here, the PE quantifies the differences between received and predicted monetary rewards and is updated with every new trial (Schultz et al. 1997; Abler et al. 2006; Sutton and Barto 2011; Hart et al. 2014). Reinforcement learning models are used to estimate trial-wise PE's (Cools 2006; Gläscher et al. 2009), which are then included as parametric regressors in fMRI analyses to assess PE-related brain activity (Gläscher and O'Doherty 2010).

In the current study, we used PE-related activity in the NAc as a proxy for DA-signaling to provide evidence for the effects of E2 on DA-related NAc activity in humans. To connect to the findings gained from the well-controlled studies in rodents, we employed a randomized, double-blind and placebo-controlled design to elevate E2 pharmacologically within physiological and supraphysiological ranges. This induction of a wide range of E2 levels enabled us to detect linear and inverted u-shaped dose response functions within the human hippocampus in a previous study (Bayer et al. 2018).

In detail, we administered E2 valerate in doses of 0, 2, 4, 6 or 12 mg orally to 125 naturally cycling women during the low-hormone menstruation phase on two consecutive days. The E2 treatment regimen induced a wide range of E2 levels, from physiological (within 2- and 4-mg groups; equivalent to cycle peak) to supraphysiological levels (within 6- and 12-mg groups; equivalent to early pregnancy) (Bayer et al. 2018). Therefore, different dose response functions for E2's effects on PE-associated NAc activity using a sensitive model-based region-of-interest (ROI) approach could be studied. In accordance with animal studies, we expected that higher E2 concentrations would be associated to higher PE-related activity in the NAc, at least within certain concentration ranges. Importantly, this strictly data-driven approach does not make any a priori assumptions about the inflection point of a potential U-shaped relationship (Sommer et al. 2018).

Materials and methods

Participants

One hundred and twenty-five healthy, naturally cycling female participants aged 18 to 35 years (M = 26, SD = 4) took part in the current study. All subjects were right-handed and reported to be free of psychiatric illnesses and to be neither users of illicit drugs, central nervous medications nor smoke on a regular basis. None of the participants had contraindications for taking E2 (e.g. obese, at risk for cardiovascular problems) or for MR examinations. Only women who had not taken any oral contraceptives or were pregnant in the 6 months prior to the study were included. Menstrual cycle lengths (M =

30, *SD* = 5), based on the reported dates of last menstruation, were used to determine adequate time points for testing.

Participants were randomly assigned to receive either placebo (PL; mannitol and highly dispersed silicon dioxide) or E2 valerate in doses of 2, 4, 6 or 12 mg (from Progynova 21 UTA, Schering, Germany). Placebo or E2 was administered in the form of two identical capsules taken orally (see Table 1 for group sizes). E2 valerate is the synthetic esther of natural E2, with an average t_{max} of approximately 3 to 6 h and a half-life of 14 h (Kuhl 2005; Ndefo and Mosely 2010). Two days of E2 intake were chosen in order to maintain E2 at elevated levels for a time period of several hours.

All participants visited the institute on three consecutive days. The first day was matched to menstruation onset estimated from previous cycle history (*M* = 1 day, *SD* = 4 days after confirmed menstruation onset). The first dose of E2 was administered double-blind by the experimenter in the evening of day 1 (*M* = 15.45 hours before second dose on Day 2, *SD* = 1.37 h). Participants took the second dose on their own the next morning of Day 2 (*M* = 5.71 h before testing on Day 2, *SD* = 0.90 h). On all testing days, participants rated their mood and side effects attributed to pill intake on a standardized questionnaire (for details, please refer to Bayer et al. 2018). Saliva samples were collected on every testing day (Supplementary Methods). Please refer to our previous paper for E2 levels from a subsample of the participants, which enabled us to verify that saliva and serum E2 levels were highly correlated (Bayer et al. 2018). On the last testing day, participants were asked to guess whether having received placebo or E2.

The reversal learning task was performed on Day 2 after 2 p.m. inside the scanner when E2 levels peaked (Kuhl 2005). Please note that data from an emotional memory paradigm performed before the reversal learning tasks by the same participants are published elsewhere (Bayer et al. 2018). All experimenters were female to avoid gender stereotype effects (Levine and De Simone 1991).

Participants received financial compensation of €120 for their time plus the amount of money won in the reversal learning task. All participants gave written informed consent according to the Declaration of Helsinki. Ethics approval was obtained from the Ethics Committee of the Hamburg Medical Association (PV3612).

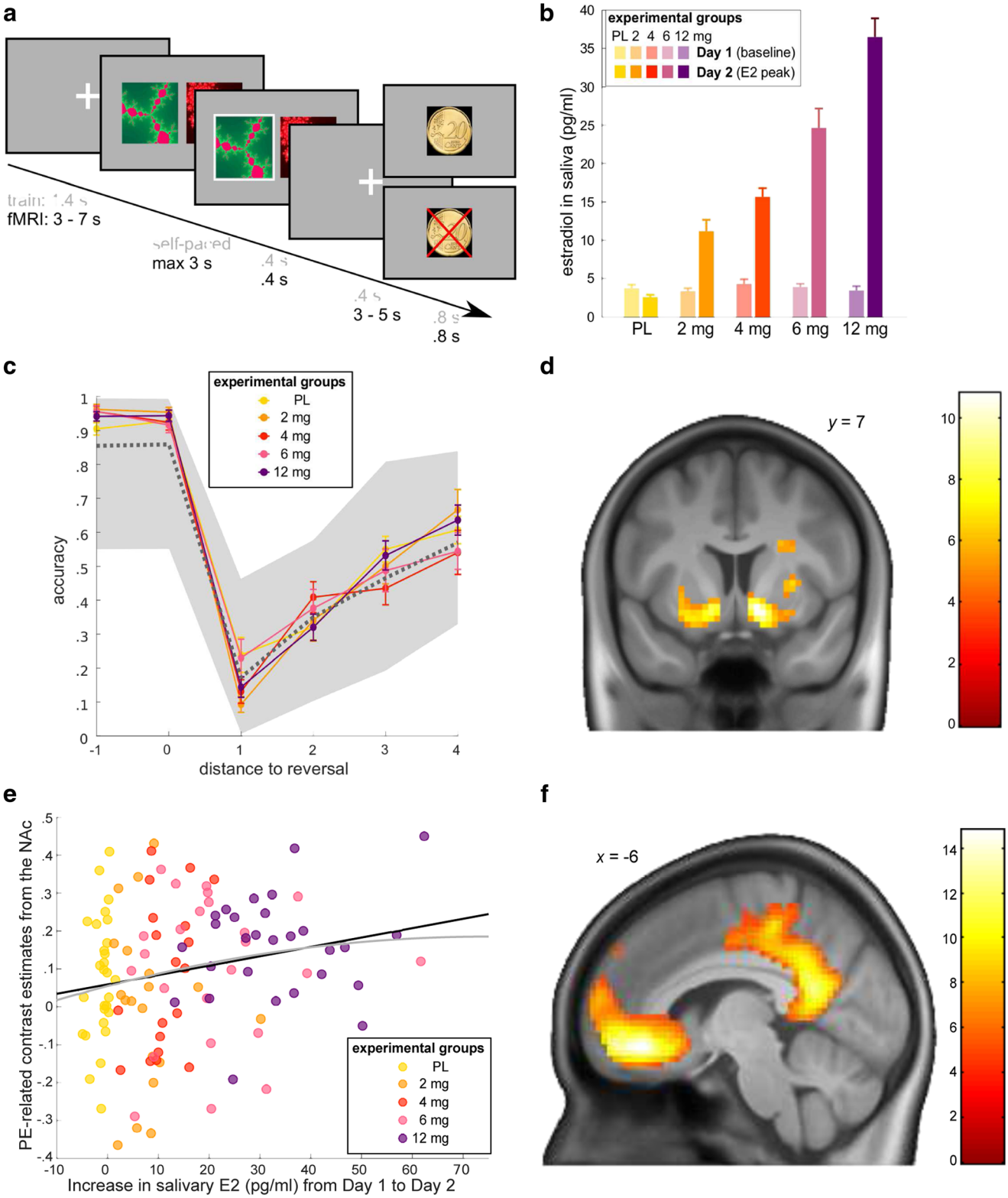
Reversal learning task

Each trial began with the presentation of two fractals side by side on the horizontal midline of the computer screen (Fig. 1a). Participants were told that one of the fractals had a higher probability to be rewarded than the other. They were also instructed that stimulus-reward contingencies can be only acquired via trial and error. They were not informed about the exact reward probabilities (.3 and .7). The assignment of fractals to the left or right side in every trial changed randomly with a probability of .5. Participants chose between the two fractals by pressing a button, with the chosen fractal being highlighted by a white rectangle. Participants received visual feedback about the trial's outcome, with wins indicated by a 20-cent coin and losses indicated by a crossed out 20-cent coin.

Table 1 Descriptive and inferential statistics of sample characteristics

	Experimental group					Statistical analyses	
	PL	2 mg	4 mg	6 mg	12 mg		
	(*n* = 28)	(*n* = 19)	(*n* = 19)	(*n* = 24)	(*n* = 28)	*F*	*p*
Age (years)	25.36 ± 3.43	26.42 ± 4.00	26.50 ± 4.03	26.68 ± 4.14	25.61 ± 3.58	.49	.741
Weight (kg)	61.36 ± 6.79	63.53 ± 8.85	64.85 ± 10.72	65.63 ± 9.01	65.79 ± 10.31	1.61	.176
BMI	21.68 ± 2.35	22.27 ± 2.18	23.48 ± 3.68	23.80 ± 2.97	22.63 ± 3.38	1.72	.134
						X^2	*p*
Education (n cases)						.15	.478
~10 y	0	0	2	0	1		
~11 y	1	0	0	0	0		
~12 y	2	1	0	1	1		
~13–16.5 y	18	11	7	15	15		
> 16.5 y	7	7	10	8	11		
Nulliparity (n cases)	27	17	18	22	27	.15	.819
Guessed E2 (n cases)	11	6	10	17	15	.44	.351
Side effects (n cases)	4	2	2	4	2		.853

BMI body-mass-index, *PL* placebo group. Women were considered as 'nulliparous' when they have never been pregnant for longer than 8 weeks. Welch's Robust Test for Equality of Means was calculated for the variable BMI because of inhomogeneous variances across groups



All participants performed two practice runs outside the scanner. The first round was performed until participants reached a criterion of 5 consecutive correct responses. Before starting the second round, participants were told that reward contingencies will change (reversal) in this run. Participants were not informed that reversals occur with a probability of .4 after 5 correct consecutive responses. Again, the second training round ended when participants achieved 5 consecutive correct responses after at least one reversal has occurred. Prior to scanning, participants were told

◀ **Fig. 1** **a** Timing of the reversal learning task. **b** Absolute salivary 17-beta-estradiol (E2) levels for each experimental group on the two testing days. The pills of the placebo group (PL) contained mannitol and highly dispersed silicon dioxide. Salivary E2 levels showed a robust, dose-dependent increase. Error bars represent standard errors of the means. **c** Colored lines represent observed averaged accuracy rates relative to time points of reversals. The dotted line indicates the mean over all simulated subjects obtained from the winning model (posterior predictive check), shaded areas 95% highest density interval (HDI) across subjects. **d** Statistical t-map for the main effect of prediction error (PE) estimates illustrating robust PE-related activity in the nucleus accumbens (NAc) [NAc, $p_{FWE} < .05$]. **e** Regression analyses yielded a positive linear association (black line) between E2 increases and prediction error (PE)-related contrast estimates extracted from the anatomical NAc mask. There was no statistical evidence for a quadratic relationship (grey line) between the two measures. **f** Statistical t-map for the main effect of the expected value estimates [$p_{FWE} < .05$]. Expected values correlated with activity in the ventromedial prefrontal cortex and the posterior cingulate

that they would be rewarded with 10 € +/− the cumulated outcome of the $n = 100$ trials performed in the scanner. Fig. 1a depicts the timing of the reversal learning task.

To formalize subjects' learning processes in the reinforcement learning task, we considered 5 variants of the standard Rescorla–Wagner model (Rescorla and Wagner 1972). All models were fit to the subjects' trial-by-trial choices. To evaluate which model performed best, Leave-One-Out Information Criterion scores (LOOIC) (Vehtari and Gelman 2014) scores and model weights were used. Please refer to Supplementary Methods for further details on computational modeling. Based on the best fitting model and the posterior mode of individual subjects' parameters, we computed trial-wise prediction errors (PEs), expected values, learning rates and temperatures (reflecting the randomness of choice; see Supplementary Methods for details) for all subjects.

Acquisition and preprocessing of neuroimaging data

Event-related functional MRI was performed on a 3 Tesla scanner (Siemens Trio) with an echo planar imaging T2*-weighted sequence in 38 contiguous axial slices (2-mm thickness with 1-mm gap; TR 2.27 s; TE 25 ms; flip angle 80°; field of view 216 × 216; matrix 108 × 108). For spatial normalization, a high-resolution T1-weighted structural MR image was acquired by using a 3D-MPRAGE sequence (1-mm slices, TR 2300 ms, TE 2.89 ms, flip angle 9°, field of view 256 × 192; 240 slices).

Event-related fMRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) in Matlab R2014b. To prevent biases due to spin saturation, the first five functional images were discarded. All functional images were slice-time corrected. To correct for susceptibility-by-movement artifacts, all functional images were realigned and unwarped (as implemented in SPM12). Individual structural T1 images were then coregistered to functional images. Coregistered T1 images were segmented into gray and white matter, which were subsequently used within the "diffeomorphic anatomic registration through an exponentiated lie algebra algorithm" (DARTEL) toolbox to create structural templates and individual flow fields. The latter was used for normalizing structural and functional images to Montreal Neurological Institute (MNI) space. Finally, images were smoothed with a full-width half maximum Gaussian kernel of 8 mm in all spatial directions.

Analysis of neuroimaging data

After preprocessing, event-related BOLD responses were analyzed in a general linear model as implemented in SPM using a mass univariate approach. Subject-level models included two regressors for the onsets of fractals and outcomes. An additional regressor of no interest was added to explain additional variance related to missing responses. All regressors were convolved with the canonical hemodynamic response function. The cue onset regressor was parametrically modulated by trial-wise estimates of expected values and reaction times (Yarkoni et al. 2009). To investigate PE-related activity, trial-wise estimates of PE's were used as parametric modulator of the outcome regressor. Additionally, binary coded outcomes (i.e. wins vs. losses) were used as a second parametric modulator of the outcome regressor.

To assess the relationship between E2 and PE-related NAc activity, a contrast weight of 1 was applied to the parametric modulator containing PE estimates. A one sample t test on individual contrast images was employed to confirm that PE estimates were associated to robust activity in the NAc. PE-related individual contrast estimates (c_{pe}) were then extracted using an anatomic, bilateral NAc mask, which was created using the Harvard–Oxford cortical and subcortical structural atlases as distributed with FSL (www.fmrib.ox.ac.uk/fsl). The central research question, how E2-levels are related to PE-related NAc activity, was investigated outside of SPM using a hierarchical robust regression approach run in MATLAB 2014b (Mathworks, Inc, Natick, MA, USA; fitlm function, robust fitting option). This approach automatically down weights potential outliers and is more robust to violations of the normality assumption (Holland and Welsch 1977). Two regression models were calculated using the extracted contrast estimates as the dependent variable and Day 1 to Day 2 E2-increases as independent variable(s):

1. $c_{pe} = a + b * E2_{Day2\text{-}Day1}$
2. $c_{pe} = a + b_1 * E2_{Day2\text{-}Day1} + b_2 * E2_{Day2\text{-}Day1}^2$.

All variables were z-transformed before entering into the regression models so that standardized beta coefficients are reported (β_{std}).

To additionally investigate whether E2 modulates DA-mediated activity in other regions of the brain, exploratory linear and quadratic regression models were implemented for PE-related contrast images on the group level inside SPM. As we were interested in the inverted U-shaped dose-response function, only the negative contrast of the quadratic term has been applied.

All results were considered significant at $p < .05$. A family-wise error correction for multiple comparisons was used on the entire scan volume (denoted by p_{FWE}) when necessary.

Statistical analyses of behavioral data

To investigate relationships between changes in E2 levels and changes in other hormones, mood or behavioral performance in the reversal learning task, linear and quadratic regression analyses were conducted as described above. Regression analyses for data from the mood questionnaire were based on four factors derived from a principal component analysis (for details, see Bayer et al. 2018). All analyses were corrected for multiple comparisons using modification of the alpha criterion according to the Bonferroni method if necessary (denoted by p_{corr}). All results were considered significant at $p < .05$.

Results

We excluded two participants with missing fMRI data due to technical failure (groups: 2 and 12 mg), one participant who missed to respond to 25 % in the reversal learning task (group: 6 mg) and four participants with less than two reversals ($n = 2$ from placebo, $n = 1$ from 2 and 4 mg groups) leaving a sample of $N = 118$ for all analyses.

Sample characteristics and E2 concentrations

Experimental groups did not differ significantly with respect to weight, body-mass index, age, education or lifetime pregnancy (Table 1; all ps > .134). Importantly, there were no significant group differences in self-reported side-effects or guesses of whether having received placebo or E2 (Table 1; all ps > .351).

Increases in saliva E2 concentrations from baseline (Day 1) to expected peak (Day 2) differed highly significantly between experimental groups [$F(4,113) = 56.28$, $p < .001$; Fig. 1b] confirming the effectiveness of E2 manipulation. E2 levels on Day 2 in the 2- and 4-mg groups roughly matched E2 levels during menstrual cycle peaks in late follicular and luteal phase (Stricker et al. 2006). E2 levels in the 6- and 12-mg groups were comparable to E2 levels in early pregnancy (O'Leary et al. 1991; Ghalayani et al. 2013).

Please note that E2 concentrations overlapped between groups so that increases in saliva E2 concentrations from Day 1 to Day 2 were used in all further regression analyses examining linear and quadratic relationships for the effects of E2.

E2 effects on changes in other hormones and mood

Day 1 to Day 2 changes neither in progesterone nor cortisol showed a significant linear [progesterone: $t(116) = 1.24$, $p_{corr} = .554$, $\beta_{std} = .083$; cortisol: $t(116) = .960$, $p_{corr} = .678$, $\beta_{std} = .055$] or quadratic [progesterone: $t(115) = 1.01$, $p_{corr} = .624$, $\beta_{std} = .042$; cortisol: $t(115) = -1.10$, $p_{corr} = .548$, $\beta_{std} = .274$] relationship with E2 increases (Supplementary Fig. 1). Similarly, none of the factors derived from the mood questionnaire showed a linear or quadratic relationship with increases in E2 levels (all p_{corr}'s ≥ 100).

Model comparisons

Table 2 gives an overview of model fits (i.e. LOOIC scores and weights). Three models performed similarly well at predicting subjects' responses: the simple RL, the Win-Loss-, and the Loss-Underweighting model. For all three models LOOIC scores were low and weights high. In all of these models, only the value of the chosen action is updated. The two models including fictive updates performed worst. Overall, LOOIC scores suggested that the simple RL model fitted best ($LOOIC_{simple} = 10{,}252.5$), whereas model weights were in favor of the Loss-Underweighting model ($weight_{Loss\text{-}Underweight} = 0.435$). Given the small difference in LOOIC scores between the standard and the underweighting model ($LOOIC_{simple} = 10{,}252.5$, $LOOIC_{Loss\text{-}Underweight} = 10{,}293.7$), we based the decision about the best fitting model on model weights and selected the Loss-Underweighting model as best fitting model. Posterior model predictions for the best fitting model in comparison to subjects' observed average choice behavior are shown in Fig. 1c.

Table 2 Model fits

Model	LOOIC	Weight
Standard Rescorla-Wagner	10,252.5	.300
Win-Loss	10,833.7	.255
Loss-Underweighting	10,293.7	.435
Fictive Learning	10,907.9	.000
Response-Response and Fictive Learning	13,217.6	.010

LOOIC Leave-One-Out Information Criterion scores

Behavioral performance in the reversal learning task

The rate of missing responses was very low (M = .593, SD = 3.65 trials) indicating that all remaining participants performed the task attentively. Participants required on average 787.03 ms (SD = 147.38 ms) to make their choice. There was neither a significant linear [$t(116) = 1.41$, p_{corr} = .483, β_{std} = .131] nor quadratic relationship [$t(115) = -.99$, p_{corr} = .978, $\beta_{std} = -.095$] between the inverse of reaction times and salivary E2 increases.

Figure 1c illustrates empirical accuracy rates together with accuracy predictions made by the best fitting hierarchical reinforcement learning model. The average estimated learning rate was .72 (SD = .116) and average temperature was 2.23 (SD = 1.24) across all groups. With respect to the effects of E2 on model parameters, neither learning rate [linear: $t(116) = -.32$, $p_{corr} > .999$, $\beta_{std} = -.028$; quadratic: $t(115) = -.77$, $p_{corr} > .999$, $\beta_{std} = -.070$] nor temperature [linear: $t(116) = -.40$, $p_{corr} > .999$, $\beta_{std} = -.040$; quadratic: $t(115) = 2.00$, p_{corr} = .143, β_{std} = .200] was significantly related to salivary E2-increases.

E2's effects on neural responses associated to the PE in the NAc

As expected, PE estimates were associated to robust activity in the NAc [$t(117) = 5.42$; $p < .001$; Fig. 1d]. We tested our central hypothesis by calculating a linear robust regression analysis using salivary E2 increase as the predictor and contrast estimates associated to PE's extracted from the anatomical NAc mask as the dependent variable. Analysis revealed a significant positive linear relationship between E2 increases and PE-associated NAc activity [$t(116) = 2.17$; $\beta_{std} = .209$, $p = .032$; Fig. 1e]. The association between E2 and PE-associated NAc activity also remained significant when absolute E2 levels from Day 2 were used as a regressor [$t(116) = 2.36$; $\beta_{std} = .226$, $p = .020$]. A quadratic robust regression provided no evidence for an inverted u-shaped relationship between E2 increases and PE-related NAc activity [$t(115) = -.38$; $\beta_{std} = -.096$, $p = .703$; Fig. 1e]. Adding the body-mass-index (BMI) as a regressor of no interest did not change the significance levels for the linear or quadratic terms (see Supplementary Results). Exploratory analyses did not reveal any significant associations between progesterone or cortisol levels and PE-related NAc activity (all $p_{corr} > .141$; see Supplementary Results).

E2's effects on neural responses associated to the PE across the whole scan volume

PE estimates were associated with BOLD activity across the entire reward system. Specifically, PE's were associated with activity in the putamen [left: $x = -30$, $y = -9$, $z = -6$; $Z = 7.37$, $p_{FWE} < .001$; right: $x = 15$, $y = 6$, $z = -9$; $Z = 7.88$, $p_{FWE} < .001$], the caudate [left: $x = -15$, $y = -12$, $z = 21$; $Z = 4.98$, p_{FWE} = .012; right: $x = 9$, $y = 12$, $z = -3$; $Z = 5.05$, p_{FWE} = .009], the ventromedial prefrontal cortex [$x = 0$, $y = 45$, $z = 0$; $Z = 4.78$, p_{FWE} = .029] and the orbitofrontal cortex [left: $x = -24$, $y = 33$, $z = -18$; $Z = 6.99$, $p_{FWE} < .001$; right: $x = 24$, $y = 30$, $z = -18$; $Z = 6.79$, $p_{FWE} < .001$; see Supplementary Results for corresponding t-maps].

With respect to the effects of E2, considering the whole scan volume, neither linear [smallest $p_{FWE} > .710$ with $Z = 3.79$ at $x = 21$, $y = -30$, $z = -39$] nor quadratic regression [smallest p_{FWE} of .692 with $Z = 3.81$ at $x = -12$, $y = -54$, $z = 39$] analyses yielded significant relationships between salivary E2 increases and brain activity associated to PE's. Similarly, none of the relationships between salivary E2 increases and PE-related contrast estimates extracted from anatomical masks of regions showing PE main effects (i.e. the putamen, the caudate, the ventromedial prefrontal cortex and the orbitofrontal cortex) turned out significant [all $p_{corr} > .355$; see Supplementary Results for scatter plots].

Neural responses associated to the expected value across the entire brain

Consistent with previous literature (Clithero and Rangel 2014), trial-wise estimates of expected values (i.e. task-evoked activity at cue onset) were positively associated with activity in brain regions such as the ventromedial prefrontal cortex [$x = -6$, $y = 39$, $z = -12$; $Z = 11.04$, $p_{FWE} < .001$, extending into the anterior cingulate cortex], the orbitofrontal cortex [left: $x = -36$, $y = 33$, $z = -15$; $Z = 9.17$, $p_{FWE} < .001$; right: $x = 36$, $y = 33$, $z = -18$; $Z = 6.22$, $p_{FWE} < .001$], the posterior cingulate cortex [$x = -3$, $y = -54$, $z = 21$; $Z = 9.75$, $p_{FWE} < .001$] and the NAc [$x = 6$, $y = 12$, $z = -6$; $Z = 5.66$, $p_{FWE} < .001$]. See Fig. 1f for a t-map of brain activity associated to expected values.

To investigate whether E2's effects on the NAc is specific to PE-related activity, contrast estimates associated with expected values were also extracted from the anatomical NAc mask. In support of the specificity of E2's effects, robust regression analyses did not indicate a linear [$t(116) = .07$; $\beta_{std} = -.006$, $p = .944$] or a quadratic relationship [$t(115) = -.43$; $\beta_{std} = -.102$, $p = .667$] between E2 increases and NAc activity related to expected values. Moreover, exploratory regression analyses considering the whole scan volume did not indicate any significant linear [smallest p_{FWE} of .162 with $Z = 4.34$ at $x = -36$, $y = -27$, $z = 45$] or quadratic relationship [smallest p_{FWE} of .464 with $Z = 4.00$ at $x = 15$, $y = -54$, $z = 39$] between E2 increases and brain activity related to expected values.

Discussion

Studies in female rodents deliver convincing evidence that E2 modulates dopaminergic transmission in the NAc, but

translational studies in humans investigating hormonal effects on reward-related activity in gambling tasks are inconsistent. To investigate this matter, we administrated four different doses of E2 to young women using a randomized, double-blind and placebo-controlled design. PE-related activity in the NAc was used as a proxy for DA-signaling (Schultz et al. 1997; O'Doherty et al. 2004; Gläscher and O'Doherty 2010; Jocham et al. 2011). As expected, E2 administration resulted in a wide range of physiological to supraphysiological E2-levels. E2 administration did not induce any perceivable side effects or changes in mood (see also Sommer et al. 2018). Using a highly sensitive model-based ROI approach, E2's effects on DA-mediated NAc activity were studied using robust regression analyses. In these analyses salivary E2-increases were used as predictors for BOLD effects associated with trial-wise estimates of PE's from a reversal learning paradigm. Consistent with our hypothesis, we found a positive linear relationship between PE-associated NAc activity and increases in salivary E2 levels.

DA release in the NAc has been linked to neuronal firing (Suaud-Chagny et al. 1992; Nicola and Deadwyler 2000) and an increase in the BOLD signal mediated by postsynaptic D1 receptors (Knutson and Gibbs 2007). Moreover, PE-related increases in the BOLD signal have been shown to be mediated by dopaminergic signaling in the human brain (Jocham et al. 2011, 2014). In addition, the positive linear relationship between PE-related NAc activity and E2 observed in the current study connects well to the E2-triggered enhancement of dopaminergic transmission observed in animals (Thompson and Moss 1994; Calipari et al. 2017).

Interestingly, our data speak to a linear but not an inverted u-shaped relationship between E2 and NAc activity within the chosen range of E2 concentrations. At first sight, this contrasts inverted u-shaped dose-response curves observed in other striatal and hippocampal regions (Becker 1990; Disshon and Dluzen 1997; Cordellini et al. 2011; Bayer et al. 2018). However, the observation that linear as well as inverted u-shaped dose-response functions can be present in adjacent hippocampal regions demonstrates a high regional specificity for the shape of E2's dose-response curves (Bayer et al. 2018). With respect to E2's hippocampal effects, it has been hypothesized that, while lower ERα/ERβ ratios are related to inverted u-shaped dose-response curves, higher ERα/ERβ are rather related to monotonic or even linear dose-response curves (Foster 2012). However, E2's effects on dopaminergic transmission appear to be mainly mediated by ERβ (Satta et al. 2018; Yoest et al. 2018), and it is unclear whether ERα is present in the NAc at all (Shughrue et al. 1997; but see Almey et al. 2015). One possibility could be that a relatively high expression of the G-protein coupled ER (GPER) at DA neurons in the NAc (Almey et al. 2015), which is likely not present at DA neurons in the dorsal striatum (Almey et al. 2012), plays a role in E2's linear effects. However, dose-response curves for GPER-mediated E2-effects on DA neurotransmission in the NAc have not been characterized yet. Moreover, different subtypes of metabotropic glutamate receptors appear to be involved in E2's effects at hippocampal compared with striatal neurons (Boulware et al. 2005; Grove-Strawser et al. 2010). Again, it is unknown how the differential involvement of these receptors might affect the shape of dose-response curves. Finally, it is possible that E2's effects on PE-related NAc activity are mediated by further brain regions like the medial preoptic or the ventral tegmental areas in which ERα as well as GPER are present (Tobiansky et al. 2016). In summary, although any inferences about underlying mechanisms based on our data are highly speculative, it is well plausible that regional differences in the cellular pathway of E2's actions account for differentially shaped dose-response curves.

In contrast to the effect of E2 on NAc activity, the relationships between E2 and behavioral measures (i.e. reaction time, learning rate and temperature) did not approach statistical significance. This could for instance be explained by a higher sensitivity of the BOLD signal to detect E2's subtle effects on dopaminergic processes in the NAc compared with behavioral variables. Further explanations could be that E2-related behavioral changes either occur with a longer delay after E2 peak or that they require a longer period of elevated E2 levels compared with neuronal changes.

Despite our relatively large sample size, the randomized and placebo-controlled design and the wide range of E2 levels, E2's effects on PE-related activity in the NAc observed in the present study was only moderate. This might explain why previous studies with smaller sample sizes, which rather targeted rather general reward-related functions than explicit dopamine-mediated processes within the NAc, did not consistently find significant relationships between neural activity in this region and E2 (Dreher et al. 2007; Ossewaarde et al. 2011; Bayer et al. 2013; Thomas et al. 2014; Macoveanu et al. 2016). Moreover, E2 concentrations of women in previous menstrual cycle and pharmacological studies had a smaller range and were lower (i.e. comparable with the 0, 2 and 4 mg groups) than those reached in the current study. As higher E2 levels exerted bigger effects on NAc activity in the current study, one would expect that the power of detecting E2's effects at lower E2 concentrations (e.g. during the menstrual cycle) is also much lower. Moreover, not all previous studies used paradigms that depended on dopaminergic signaling within the NAc but rather on other areas such as the putamen or prefrontal areas (Alonso-Alonso et al. 2011; Reimers et al. 2014; Thomas et al. 2014). It is well plausible that the specific processes that mediated reward-related processes in these regions are insensitive to changes in E2 or require deviating administration characteristics (e.g. concomitant increase in progesterone and longer E2 elevation).

Besides methodological issues, concomitant changes in progesterone in the course of the menstrual cycle could influence E2's effects on NAc activity (Floresco et al. 2006; Dreher et al. 2007; Frank et al. 2010; Ossewaarde et al. 2011; Bayer et al. 2013; Barth et al. 2015). Progesterone modulates dopaminergic transmission as well and interacts with E2 in an unpredictable way. In sum, the small size of E2's effect on NAc activity in a well-controlled design helps to understand why previous studies in humans did not always observe this effect.

With respect to the everyday life of naturally cycling women, current data raise the question whether reliable and noticeable variations in the processing of PE's occur in the course of the regular menstrual cycle. In contrast, as hormone levels during pregnancy are much higher than during the menstrual cycle (O'Leary et al. 1991; Ghalayani et al. 2013), changes in the processing of PE's are certainly more likely. However, hormone levels in the current study are only comparable with a limited degree to those during pregnancy, where both E2 as well as progesterone levels rise much slower and remain at a much higher level for a prolonged time period.

While E2's effect on NAc activity in humans is subtle and is not always observable, animal studies reliably report effects of E2 on dopaminergic signaling (Thompson and Moss 1994; Calipari et al. 2017). One explanation for this divergence is likely that animal studies assess alterations in dopaminergic signaling (e.g. by measuring DA release) much more directly than neuroimaging studies. A second explanation could lie in the presence of individual baseline-differences in DA concentrations in humans, which might modulate E2's effects on the NAc. In fact, it has been reported that the direction of naturally fluctuating E2 on working memory during the menstrual cycle depends on genetic predispositions to specific baseline DA levels and an inverted U-shaped relationship between DA and working memory performance (Jacobs and D'Esposito 2011; Cools and D'Esposito 2011).

Some limitations should be considered when drawing inferences from the current study. First, although we demonstrated the validity of salivary E2 levels by a high correlation to E2 serum levels assessed from a subsample (Bayer et al. 2018), the gold standard would be mass spectrometry of E2 in blood samples (Rosner et al. 2013). Second, the sensitivity of the current approach might have been increased using a repeated-measures design. In the same way, we cannot rule out the possibility that ceiling effects for PE-related NAc activity in participants who received the highest E2 dose decreased the strength of the observed relationship.

In summary, using a well-controlled experimental design, we showed that the pharmacological increase of a wide range of physiological and supraphysiological E2 levels stimulates PE-associated neural activity in the NAc. The dose-response curve followed a positive linear function, suggesting that mild supraphysiological E2 levels tend to exert bigger effects on NAc than physiological levels.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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