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An RDoC-inspired examination of pharmacological, sex-specific, and hormonal modulators of Positive Valence Systems

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List of abbreviations

5-HT	Serotonin
5-HTT	Serotonin transporter
DSM	Diagnostic and Statistical Manual of Mental Disorders
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
ICD	International Classification of Diseases
NAcc	Nucleus accumbens
OC	Oral contraceptive
PVS	Positive Valence Systems
RDoC	Research Domain Criteria framework
SSRI	Selective serotonin reuptake inhibitor
VTA	Ventral tegmental area

1. Introduction

1.1. Research Domain Criteria framework – Positive Valence Systems

The current diagnostic systems *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases* (ICD) provide a common language in mental health based on clinical consensus about categories and behavioral symptoms. However, categories based upon presenting behavioral symptoms do not capture underlying mechanisms of dysfunction. Moreover, there is growing resentment that these symptom-based diagnoses do not yield the kind of specificity that we have in the rest of medicine, e.g., the use of biomarkers to direct treatments for subtypes of cancer (Insel et al., 2010). Clinical neuroscience has made tremendous discoveries in the organization of neural circuits and their associated behaviors over the past two decades, yet those efforts have only slowly been translated into understanding of etiology and developing new treatments (Morris & Cuthbert, 2012). A neuroscience-based approach to classification of mental disorders offers promising advantages for research and clinic, with the common goal of improving treatment outcomes.

To address this endeavor, the US National Institute of Mental Health has initiated the *Research Domain Criteria* framework (RDoC). The aim of RDoC is precision medicine for psychiatry, based on a profound understanding of the psychological and biological basis of several disorders, which share behavioral symptoms (Insel et al., 2010). Currently, RDoC does not serve as a diagnostic system, but rather as a framework for guiding research. As such, the overarching goal is to understand mechanisms in normal and abnormal behavior on different levels. These levels are captured in the two-dimensional RDoC matrix (Morris & Cuthbert, 2012). One dimension represents the six major *domains* of basic human neurobehavioral functioning, (1) Negative Valence Systems, (2) Positive Valence Systems, (3) Cognitive Systems, (4) Social Processes, (5) Arousal and Regulatory Systems, and (6) Sensorimotor Systems. Each domain is further subdivided into three to six psychological/biological constructs, which are recommended to be studied from normal to abnormal functioning. The second

dimension of the matrix represents the *units of analysis* to measure these constructs, i.e., molecules, cells, circuits, physiology, behavior, and self-report (Table 1). The RDoC framework further proposes paradigms, which have been commonly approved by the scientific community to be useful to measure the constructs. The RDoC framework thus emphasizes an integrative approach in studying basic psychological and biological mechanisms of mental health and disease. It further encourages studies to deconstruct any of the proposed domains/constructs in order to identify core features relevant for a group of disorders (e.g., a deficit in working memory and fear processing) (Insel, 2014).

Table 1

Research Domain Criteria Matrix, showing the two dimensions 'domains' and 'units of analysis'.

	Units of Analysis					
Domains	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report
Negative Valence Systems						
Positive Valence Systems						
Cognitive Systems						
Social Processes						
Arousal/Regulatory Systems						
Sensorimotor Systems						

The present project focused on the *Positive Valence Systems* (PVS) domain (Table 2), which describes responses to positive motivational situations and states, such as seeking and consuming rewards (National Advisory Mental Health Council Workgroup on Changes to the RDoC Matrix, 2018). The constructs of PVS are best described by using the example of palatable food, for example cake. The first construct is *reward responsiveness*, which includes the subconstructs reward anticipation, initial response to reward, and reward satiation. Imagine how your mouth already waters when you enter the kitchen and smell freshly baked cake (reward anticipation). Then, the first bite of cake initiates several processes in your body, brain, and subjective experience (initial response to reward). After you have finished one or two pieces of cake, satiation sets in and you stop eating cake (reward satiation). The second PVS domain is *reward learning*, with the subconstructs probabilistic/reinforcement learning, reward prediction error, and habits. Probabilistic and reinforcement learning literally describes 'stick and carrot', i.e., the positive element of trial and error. Staying with our cake example, this means that we have learned that cake tastes good and associate it with a positive state. The reward prediction error is a neuronal process and encodes the difference of the reward from the prediction, e.g., the cake tasted much better or worse than expected. As soon as we have learned something, it may start becoming a habit, for example we always eat a piece of cake after lunch. *Reward valuation* is the third PVS construct and includes reward probability, delay, and effort. Thus, the perceived value of our cake reward depends on how certain it is that we will get a piece of cake (probability, uncertain rewards are usually of lesser value) and how long we must wait for it (delay, later rewards are usually of lesser value). Finally, the perceived value of cake depends on how much effort we have to put in, e.g., if we have to bake the cake first or if it is already baked and served in front of us.

Table 2

The Positive Valence Systems domain, subdivided in constructs and subconstructs. Highlighted cells represent which subconstructs and units of analysis were investigated in the present work, together with the respective paradigms.

Positive Valence Systems		**Units of Analysis**		
		Circuits	Behavior	Paradigms
Constructs	**Subconstructs**			
Reward Responsiveness	Reward Anticipation			
	Initial Response to Reward			Guessing Task
	Reward Satiation			
Reward Learning	Probabilistic and Reinforcement Learning			
	Reward Prediction Error			
	Habit			
Reward Valuation	Probability			Probability Choice
	Delay			Delay Discounting
	Effort			Effort Allocation

Put formally, the PVS domain focuses on reward processing, which is one of the best described neurobehavioral systems in animals and humans (Walter et al., 2021). To date, disruptive PVS constructs are best described for schizophrenia, substance use disorders, and major depressive disorder. In schizophrenia, disrupted reward prediction errors are assumed to cause delusions and psychosis (Corlett et al., 2007; Ermakova et al., 2018). At the onset of substance use disorders, reward responsiveness, and in particular the initial response to drugs, plays a major role; reinforcement learning and difficulties in delaying gratification contribute to the progression of the disorder (Heinz et al., 2019; Schultz, 2011). In major depressive disorder, both impaired reward responsiveness (Hallford & Sharma, 2019; Starr & Hershenberg, 2017) and

reward valuation (Berwian et al., 2020; Treadway et al., 2012) likely explain the main symptom of anhedonia. Thus, disruptions in one or more PVS constructs are shared behavioral symptoms in several mental disorders, a main idea of the RDoC framework.

Fractioning symptoms into PVS constructs offers the possibility to investigate the underlying mechanisms which play a role in different disorders, and which of them may be understood as a transdiagnostic syndrome. Individuals may have difficulties (1) to anticipate rewards (reward responsiveness), (2) to associate values and costs with rewards as well as (3) to determine the effort needed to obtain rewards (both reward valuation), and (4) to integrate this information and learn from outcomes of their actions to guide future behavior (reward learning) (Der-Avakian & Markou, 2012; Husain & Roiser, 2018).

In the following, I examine *reward responsiveness* and *reward valuation* in the context of motivational behavior with a focus on investigating different modulators of these subconstructs. In the first part, I investigated the neurotransmitter serotonin as a modulator of reward responsiveness. Although numerous psychotropic drugs act on serotonergic neurotransmission, the role of serotonin in motivational behavior lacks empirical work (Husain & Roiser, 2018). The second part focused on sex-specific and hormonal modulators of reward valuation. Numerous mental disorders have prominent sex differences. For example, women experience major depressive disorder twice as often as men in their lives (Kuehner, 2017). Substance use disorders are two times more prevalent in men than in women (Grant et al., 2016), but women show more severe illness progression and poorer treatment outcomes than men (Becker, 2016). Current research concerning development of disorders, prevalence and response to treatment suggests a significant role for sex and sex hormones as modulators to account for differences in disorders with reward-related deficits (for review, see Ambrase, Lewis et al., 2021).

1.2. Reward Responsiveness

Reward responsiveness comprises processes that regulate an organism's hedonic response to positive and negative reinforcers (anticipation), the receipt of reinforcers (initial response to reward), and processes following repeated receipt of reinforcers (reward satiation). Reward responsiveness is mainly reflected in neural activity to reward and punishment cues (National Advisory Mental Health Council Workgroup on Changes to the RDoC Matrix, 2018).

1.2.1. Neural networks of reward responsiveness

Responding to rewards begins with recognizing valenced cues which inform an organism about receiving rewards or punishments. Research in this area mostly focused on reward cues in animals and humans, i.e., reward sensitivity and positive reinforcers (for review see O'Doherty et al., 2017). Reward prediction cues are encoded within the reward circuitry, with the ventral tegmental area (VTA) being the source of dopamine projections to the nucleus accumbens (NAcc) in the ventral striatum (the mesolimbic dopamine system), to higher cortical areas (the mesocortical dopamine system), and to the amygdala (Dichter et al., 2012; Krolick et al., 2018; Schultz, 1997). Another dopamine pathway leads from the substantia nigra to the dorsal striatum, i.e., the caudate putamen (Der-Avakian & Markou, 2012). Serotonergic neurons in the dorsal raphe nuclei have also been found to code reward prediction cues (Cohen et al., 2015). Moreover, reward prediction cues are assumed to be encoded by the interaction of the dopaminergic and serotonergic systems, as neurons from the dorsal raphe nuclei project to the VTA and the NAcc (Liu et al., 2014; Zhou et al., 2015).

Considerably less research has focused on brain signals in response to negative reinforcers, i.e., cues predicting punishment or loss, especially in humans. Thus, neural networks of punishment prediction cues are less well understood. It is assumed that punishment prediction cues suppress VTA dopamine neuron activity while concurrently exciting γ-aminobutyric acid (GABA)

neurons in this region (Cohen et al., 2012). Animal and human studies further suggest that punishment prediction cues are encoded in the central area of the ventral striatum (Palminteri et al., 2015) (for review see Delgado et al., 2008).

1.2.2. Serotonergic neurotransmission in reward responsiveness

The reward circuitry is governed by complex neurochemical signaling. The main monoamine neurotransmitters specifically involved in reward responsiveness are dopamine and serotonin.

Preclinical and neuroimaging studies mainly focused on dopamine as main monoaminergic neurotransmitter involved in the reward system. The phasic firing response pattern of midbrain dopamine neurons signaling the anticipation of rewards is a fundamental hypothesis in the field (Schultz, 1997). Efforts towards understanding the impact of serotonin firing patterns on the reward system as well as the synergistic interaction between dopamine and serotonin pathways led to two main hypotheses within the framework of reward responsiveness. The first model suggests that serotonin modulates signals predicting punishment or loss, as opposed to dopamine predicting reward (Daw et al., 2002; Deakin & Graeff, 1991). For example, a reduction in central serotonin levels after acute tryptophan depletion led to enhanced responsiveness to punishment or loss but not to reward (Cools et al., 2008; Crockett et al., 2009). The second model proposes an overall inhibitory influence of serotonin on the reward system (Cools et al., 2011; Soubrie, 1986), which is assumed to arise from interactions with the mesolimbic dopamine system (Liu et al., 2014; Zhou et al., 2015). For instance, empirical evidence demonstrated reduced neural responses in the reward system after raising serotonin levels (Browne et al., 2019; Browne & Fletcher, 2016; McCabe et al., 2010).

An effective method to investigate the consequences of acutely enhanced serotonergic transmission in the human brain *in vivo* is administering an acute dose of selective serotonin reuptake inhibitors (SSRIs; Bruhl et al., 2010; Loubinoux et al., 2002). The main target of action for SSRIs is the serotonin

transporter (5-HTT), which is essential for maintaining adequate brain serotonin homeostasis (Krishnan & Nestler, 2008; Mercado & Kilic, 2010). The primary action of SSRIs is to prolong serotonin (5-HT) action by blocking the 5-HT transporter from transporting 5-HT from synaptic cleft back into the presynaptic neurons (Nutt et al., 1999). Acute administration of SSRIs has been shown to raise extracellular serotonin levels in several projection regions of the forebrain (El Mansari et al., 2005; Garcia-Garcia et al., 2014). As SSRIs are the most widely prescribed class of antidepressants worldwide (Bauer et al., 2017), another advantage in using this pharmacological intervention is the possibility to draw conclusions about refining treatment strategies for mental disorders with serotonergic dysfunction, e.g., major depressive disorder.

1.2.3. Reward Responsiveness: Aims of the study

Study 1 focused on reward responsiveness, and more specifically on the initial response to reward or punishment cues during acutely increased serotonergic transmission. In this pharmacological functional resonance imaging (fMRI) study, healthy participants received a single dose of 20 mg escitalopram in a double-blind, placebo-controlled, crossover design. Participants performed a well-established card guessing task with both reward and punishment cues, which is a RDoC-approved paradigm to measure initial responses to reward and punishment.

The goal of this study was two-fold. Firstly, we aimed at understanding basic mechanisms of reward responsiveness on a neurobehavioral level, i.e., to identify relevant brain regions. A second objective was to elucidate serotonin's role in reward responsiveness, i.e., if serotonin modulates primarily punishment prediction cues or if serotonin has an overall inhibitory effect on the reward system. Although empirical evidence exists for both approaches, most studies did not use tasks which reflect on brain responses to both reward and punishment. Ultimately, we expected this extended knowledge of acute

neurotransmitter action to be beneficial for refining treatments targets for motivational deficits.

1.3. Reward Valuation

The PVS construct of *reward valuation* describes processes by which the benefits of a future outcome are computed depending on external information and/or prior experience. This process is influenced by several factors, e.g., biases, learning, and stimulus characteristics. Based on these computations, a subjective value is assigned to a reinforcer. Reward valuation comprises the subconstructs *reward probability*, *delay*, and *effort*, and RDoC proposes experimental paradigms for assessing each subconstruct in human subjects. *Reward probability* describes how the subjective value of a reinforcer is computed by reference to its magnitude, valence, and predictability, and is typically assessed with probability choice tasks. In these tasks, participants are faced with a decision between a sooner, small certain reward and a later, less certain but larger reward, and thus also captures risk behavior. *Delay* refers to processes by which the magnitude of a reinforcer and the time interval until it is received define the subjective value of a reinforcer. Delay discounting tasks are typical paradigms for assessing this computation, in which participants decide between a smaller, sooner reward and a larger, later reward. Finally, *effort* describes subjective value computations depending on the magnitude of the reinforcer and the perceived costs of cognitive or physical effort required to earn it. Effort allocation tasks are the standard in the field, in which participants must earn rewards of variable magnitude by hand grip force or button presses.

1.3.1. Sex-specific effects on reward valuation

Women and men have different trade-offs in cost-benefit computations which may contribute to differences in reward valuation (Ambrase, Lewis et al., 2021). Sex differences are well described for decision costs such as probability

and delay. For example, women prefer frequent and safer yet smaller rewards in gambling tasks as well as safe options when they lost a reward in a previous decision (Byrne & Worthy, 2015; Cornwall et al., 2018; Lee et al., 2009). Men, in turn, tend to maximize rewards even if this strategy is not optimal and are overall more likely to take a risk (Byrne & Worthy, 2015; Byrnes et al., 1999; Cornwall et al., 2018). In instrumental physical effort, women prefer easy trials with smaller rewards, whereas men prefer difficult trials with higher rewards (Treadway et al., 2009). However, the basic mechanisms of this sex-specific behavioral variability in different aspects of reward valuation are still elusive.

Various hypotheses have been proposed to explain these sexual dimorphisms, e.g., on a neural level from sex differences in functional activation of brain areas involved in reward-related circuits (Sutterer et al., 2015), and dissimilar involvement of neurotransmitter systems which are relevant for reward processing, such as dopamine and serotonin (Georgiou et al., 2018). Moreover, sex differences in the behavioral inhibition and activation systems (BIS/BAS; Strobel et al., 2001) likely contribute to a different valuation of rewards (Li et al., 2014). Furthermore, current research concerning development of disorders, prevalence, and treatment response suggests a significant role for sex hormones as modulators to account for sex differences in reward valuation (for review, see Ambrase, Lewis et al., 2021).

1.3.2. Effects of sex hormones on reward valuation

Sex differences in reward valuation may occur due to the interaction between neurotransmitter systems and sex hormones, which have been shown for both women and men in reward-related circuits (for review, see Barth et al., 2015). For women in particular, systemic variation of ovarian hormones, i.e., estradiol and progesterone, likely affect reward valuation processes.

The menstrual cycle provides a natural model of investigating influences of ovarian hormones on reward valuation in women. Over the course of 28 days on average, ovarian hormones show characteristic variation (Bull et al., 2019). In the

follicular phase, estradiol levels increase and surge before ovulation, while progesterone levels are low. In the luteal phase, after ovulation, progesterone levels rise gradually to a mid-luteal peak, together with another blunted peak of estradiol. Before menses initiates, both estradiol and progesterone levels rapidly decrease (Sundström & Gingnell, 2014). During the early follicular phase, women have been found to prefer sooner, smaller rewards (Diekhof, 2015), whereas rising estradiol levels made women less sensitive for immediate rewards (Smith et al., 2014). During ovulation, i.e., with high estradiol levels, women preferred risky over safe options to maximize rewards and were less loss averse compared with women in other cycle phases and men (Lazzaro et al., 2016). Typically, testosterone is hypothesized to affect risk behavior in women and men, however, one has to keep in mind that testosterone is aromatized to estradiol in women (Azcoitia et al., 2011).

Investigating oral contraceptive (OC) use provides another experimental model to examine ovarian hormone effects on female behavior. The most widely used OCs contain a synthetic estrogen (ethinyl estradiol) and a synthetic progesterone (progestin) (United Nations, 2015), and thereby suppress endogenous estradiol and progesterone fluctuations. Results from studies investigating the influence of OC-use on reward valuation were mixed so far, showing both more or less sensitivity for immediate rewards compared to naturally cycling women (for review, see Lewis et al., 2019).

1.3.3. Reward valuation: Aims of the studies

Studies 2 and 3 examined sex-specific and hormonal modulators of reward valuation and, thus, aimed at elucidating potential mechanisms underlying sex differences in the integration of benefits and costs. In study 2, we investigated sex differences in reward valuation, specifically in instrumental physical *effort*. We tested whether healthy women and men would differ in the motivational phases of an effort allocation task and if this difference would depend on reward magnitude, reward type, and/or task difficulty. Study 3 focused on influences of

ovarian hormones on reward valuation, in particular on *probability* and *delay* as computational costs. Here, we tested naturally cycling and OC-using women in probability and delay discounting tasks and hypothesized that endogenous and exogenous hormonal milieus would influence reward valuation differently.

2. Results and discussion

2.1. A single dose of escitalopram blunts the neural response in the thalamus and caudate during monetary loss

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Research Paper

A single dose of escitalopram blunts the neural response in the thalamus and caudate during monetary loss

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Background: Selective serotonin reuptake inhibitors (SSRIs) show acute effects on the neural processes associated with negative affective bias in healthy people and people with depression. However, whether and how SSRIs also affect reward and punishment processing on a similarly rapid time scale remains unclear. **Methods:** We investigated the effects of an acute and clinically relevant dose (20 mg) of the SSRI escitalopram on brain response during reward and punishment processing in 19 healthy participants. In a double-blind, placebo-controlled study using functional MRI, participants performed a well-established monetary reward task at 3 time points: at baseline; after receiving placebo or escitalopram; and after receiving placebo or escitalopram following an 8-week washout period. **Results:** Acute escitalopram administration reduced blood-oxygen-level-dependent (BOLD) response during punishment feedback in the right thalamus (family-wise error corrected [FWE] p = 0.013 at peak level) and the right caudate head (p_{FWE} = 0.011 at peak level) compared to placebo. We did not detect any significant BOLD changes during reward feedback. **Limitations:** We included only healthy participants, so interpretation of findings are limited to the healthy human brain and require future testing in patient populations. The paradigm we used was based on monetary stimuli, and results may not be generalizable to other forms of reward. **Conclusion:** Our findings extend theories of rapid SSRI action on the neural processing of rewarding and aversive stimuli and suggest a specific and acute effect of escitalopram in the punishment neurocircuitry.

Introduction

How our brain responds to reward and loss is a critical aspect of mood regulation. A blunted hedonic response to rewards or an enhanced sensitivity to loss can underlie negative bias in reward processing, which has been shown in patients with major depressive disorder (MDD)[1] and anxiety disorders.[2] Evidence from human and animal studies that manipulate serotonin levels provides robust support for the role of serotonin in modulating the neural circuit that underlies rewarding and aversive processing.[3] This association between serotonin and neural processing of reward and loss may explain why selective serotonin reuptake inhibitors (SSRIs), which manipulate serotonergic activity, can help improve the processing capabilities of patients with MDD and anxiety disorders in the context of reward and/or punishment. However, the direction of association and specificity of this neural signal during positive and negative feedback remains to be clarified.

We know that SSRIs modulate serotonergic activity[4] by blocking the serotonin transporter within a single dose of oral administration,[5] and this leads to increased levels of extracellular serotonin. It has long been recognized that the acute administration of SSRIs reduces raphe neuron firing rates mediated by serotonin-1A autoreceptors, which become activated by increased extracellular serotonin levels, particularly in regions such as the dorsal raphe nucleus.[6] This decrease in firing rates seems to be dose-dependent[7] and region-specific;[8] some studies have reported no change in serotonin levels at low SSRI doses.[9] Although this negative feedback mechanism effectively controls serotonergic neuron firing rates and (partly) serotonin release, evidence from microdialysis studies[10] indicates that the acute administration of SSRIs can increase extracellular serotonin levels in several projection regions, such as certain regions of the forebrain, with noteworthy variability likely based on region-specific differences in serotonin-1A receptors.[8,11,12]

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Two main models have been put forward for the role of serotonin in modulating the neural circuitry that underlies reward and punishment. The first centres on serotonin in an opponent role to dopamine, suggesting that while dopamine modulates reward processing, serotonin modulates aversive signals such as punishment and loss.[13,14] Daw and colleagues[13] proposed that phasic serotonin firing underlies prediction error for future punishment but not future reward. This theoretical framework[15,16] is supported by empirical evidence from interventional studies that demonstrate potentiated responsiveness to loss or punishment but not to reward after a reduction in central serotonin levels. By using a novel fast-scan cyclic voltammetry procedure to identify serotonin signals in vivo while participants completed an investment task, Moran and colleagues[17] provided further direct evidence that serotonin encodes loss-related prediction errors.

A second main theoretical approach suggests that serotonin has an overall inhibitory role in the reward system.[18,19] Neuronal activity in the raphe nuclei in single-unit recordings correlates with both expected and received reward values (see Nakamura[20] for a review). Raising extracellular serotonin levels reduces neural responses in the reward system.[21,22] The inhibitory role of serotonin may arise from interactions with the dopamine system, given that parts of the mesolimbic dopamine system receive extensive serotonergic innervation.[23,24] By using optogenetic stimulation of dorsal raphe nucleus serotonin input to the ventral tegmental area combined with the administration of an SSRI, Browne and colleagues[25] found reduced reward-related response in rats. Thus, several lines of evidence suggest that enhanced serotonergic signalling may exert an overall inhibitory influence on the neural reward system.

By assessing the brain responses to reward and punishment stimuli following a serotonergic intervention, pharmacological functional MRI (fMRI) studies have begun to provide evidence for the role of serotonin in reward and loss processing in humans in vivo. Lowering serotonin levels via acute tryptophan depletion increases the blood-oxygen-level-dependent (BOLD) response to errors during negative feedback in fMRI in the prefrontal cortex (PFC).[26] A single dose of citalopram decreased the neural response to negative outcomes in the dorsomedial PFC and increased the neural response to negative outcomes in the left amygdala during a card gambling task.[27] Using a loss/no-loss paradigm, Del-Ben and colleagues[28] reported increased BOLD signals in the insula and decreased BOLD signals in the orbitofrontal cortex during loss avoidance after citalopram intake. The suggestion that serotonin mediates overall reward processing has also received empirical support. Marutani and colleagues[29] found decreased BOLD signals in the insula, putamen and dorsolateral PFC in anticipation of rewards during a monetary incentive delay task after a single dose of the SSRI paroxetine.

Acute serotonergic modulation affects reward and punishment processing, but the net effect of an impairment or a facilitation is not entirely consistent across studies. Underlying reasons for this include the fact that not all of the studies investigated the influence of serotonergic manipulation on responses to reward and punishment in the same experiment. We lack a clear understanding of whether acutely enhanced serotonergic transmission specifically attenuates the brain response to loss or punishment in healthy humans, or if this attenuation centres on reward processing. Taking this next step is important not only for a better understanding of how serotonergic agents generate their antidepressant effect, but also to increase our knowledge of the role of serotonin for processing reward and punishment or loss in the human brain.

In this pharmacological fMRI study, we used a validated and simple monetary reward task in a double-blind, placebo-controlled, crossover design in healthy participants. We administered a single dose of 20 mg escitalopram, a clinically relevant dose of one of the most widely prescribed SSRIs.[30] The goal of the present study was to investigate whether an acute serotonergic challenge modulated BOLD responses in the main areas of the neural circuit implicated in monetary reward (ventral striatum and medial PFC[31]) and monetary loss (anterior insula, caudate, putamen, thalamus, anterior cingulate cortex[32]) and whether any changes in the neural response would be specific to the loss or punishment contrast, or extend to reward-specific feedback. Given the putative specificity of acute serotonergic depletion effects on the loss or punishment condition, we hypothesized that we would find decreased brain responsiveness to monetary loss or punishment but not to reward during acutely increased serotonergic transmission.

Methods

Study design

We used a double-blind, placebo-controlled, crossover design to investigate neural responses to a single oral dose of 20 mg escitalopram (to reliably block 80% of serotonin transporters[5]) and placebo (mannitol and aerosol) in identical capsules provided by the pharmacy of Leipzig University Clinic in 19 healthy participants (9 women, 10 men), with a washout period between sessions of 8 weeks (see Figure 1A for an overview of the study design). On the first test day, participants underwent a baseline fMRI scan before initial drug administration. For the drug fMRI scans, we measured participants 3 to 4 hours after drug administration, during peak blood concentration of escitalopram.[33] The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of the University of Leipzig. All participants provided written informed consent before participating, and were compensated for participation at €8 per hour.

Participants

Twenty-four healthy participants (12 men, 12 women; age 25 ± 2 years [mean ± standard deviation], range 21–29 years; body mass index 23 ± 2 kg/m^2) were recruited from the Max Planck Institute of Human Cognitive and Brain Sciences

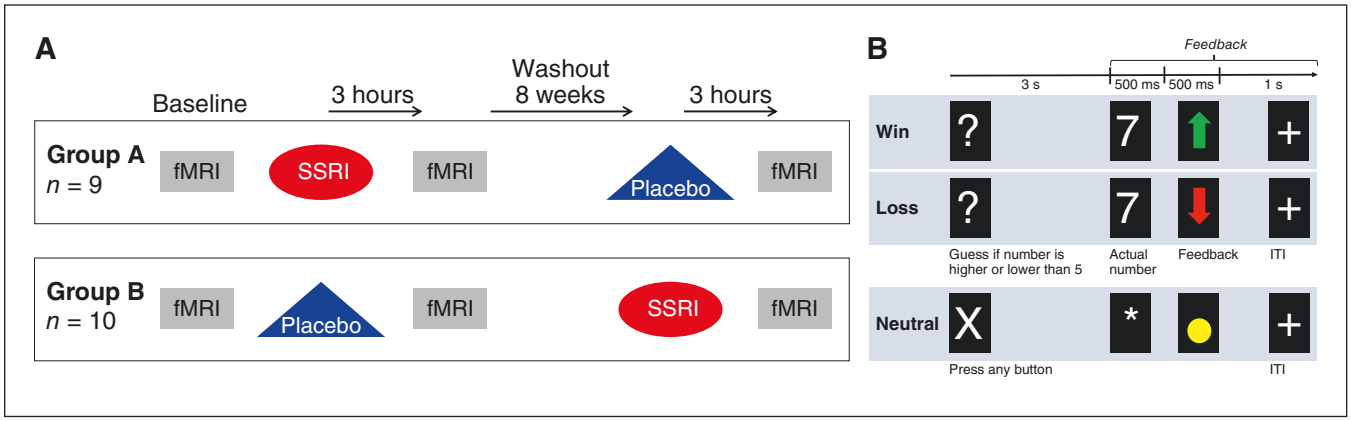

Fig. 1: (A) Study design. Nineteen participants underwent 3 fMRI scanning sessions. After a baseline fMRI scan (grey square), participants received a single oral dose of the SSRI escitalopram (20 mg; red circle) or placebo (blue triangle) in a randomized design. We determined serum levels of escitalopram after 3 hours (T_{max}) and then conducted a second fMRI scan. After a washout period of 8 weeks, the protocol was repeated with the alternate study drug (escitalopram or placebo) to adhere to a double-blind intraindividual design. (B) Monetary reward task. The task consisted of 3 different block types (win, loss and neutral), with 45 trials in total. In win and loss trials, participants had 3 s to guess via button press whether the hidden number (between 1 and 9) on a visually presented card would be higher or lower than 5. Then, the actual number was displayed for 500 ms and participants received outcome feedback for 500 ms (a green up-arrow for win outcomes or a red down-arrow for loss outcomes). Each trial ended with a crosshair symbol presented in the middle of the screen for 1 s (intertrial interval). In neutral trials, participants were asked to press a button when an X was displayed (3 s), followed by an asterisk (500 ms) and a yellow circle for neutral outcomes (500 ms). fMRI = functional MRI; ITI = intertrial interval; SSRI = selective serotonin reuptake inhibitor; T_{max} = time to peak concentration.

and the University of Leipzig. Exclusion criteria were pregnancy (urine pregnancy test at screening and before each test session); current or previous major psychiatric disorders (assessed using the Semi-structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Axis I disorders,[34] by a trained psychiatrist); the use of medications that might interfere with the study medication (e.g., antidepressants, antipsychotics, sedatives); chronic or acute physical illness (abnormal physical examination, electrocardiogram, or hematological and chemical blood analyses); tobacco smoking; lifetime illicit drug use more than 10 times (except for Δ^9-tetrahydrocannabinol); illicit drug use within the last 2 months; and illicit drug use during the study (determined by urine drug tests). Subclinical depressive, hypomanic or anxiety symptoms were assessed using the 17-item Hamilton Depression Rating Scale[35] by a trained psychiatrist, the self-report version of the Structured Clinical Interview for Mood Spectrum (MOODS-SR)[36] and the State-Trait Anxiety Inventory.[37] All participants were naive to antidepressants and free of medications except for the contraceptive pill.

Of the 24 enrolled participants, 1 was excluded because of a preanalytical error in acquisition of the serum sample, and 4 were excluded because of missing or corrupted log files from the presentation software. We analyzed the data from 19 right-handed participants with a normal weight (10 men, 9 women; age 24 ± 2 years, range 21–29 years; body mass index 23 ± 2 kg/m^2). Serum values of escitalopram (ng/mL) were acquired at peak concentration (T_{max})[33] in blood and determined using liquid chromatography with UV detection. The quantification limit for escitalopram was 1 ng/mL.

fMRI paradigm

We used a well-established monetary reward task, which elicits reliable activation in the neural reward circuitry and was designed to index the neural response to feedback about wins (rewards) and losses (punishment).[38,39] The task consisted of 3 block types (win, loss and neutral), with 45 trials in total. Participants were told that their performance would determine a post-scan monetary reward: €1 for each win and €0.50 deducted for each loss. The blocks were presented in fixed pseudorandomized order with identical predetermined outcomes across participants (Figure 1B). Participants were unaware of the fixed outcome probabilities (80/20; i.e., 80% win outcomes and 20% loss outcomes in a win block and vice versa in a loss block).

In win and loss trials, participants had 3 s to guess via button press whether a hidden number (between 1 and 9) on a visually presented card would be higher or lower than 5. Then, the actual number was displayed for 500 ms and participants received outcome feedback for 500 ms. For win outcomes, feedback was a green up-arrow, and for loss outcomes, feedback was a red down-arrow. A trial ended with a crosshair symbol presented in the middle of the screen for 1 s (intertrial interval). In neutral trials, participants were asked to press a button when an "X" was displayed (3 s), followed by an asterisk (500 ms) and a yellow circle for neutral outcomes (500 ms). The total length of a trial was 5 s. Before each block started, participants viewed instructions for the win, loss or neutral condition for 3 s; this was not analyzed further.

Based on our hypotheses, the contrasts of interest derived from the task were win–neutral and loss–neutral.

The feedback phase was defined as the intervals that included the number presentation and the feedback arrow. Similarly, the feedback phase in the control condition was defined as the interval between the display of an asterisk and a yellow circle. If the durations of the events of interest are the same and are less than 2 s, it is common practice to model those events with a length of 2 s in further analyses.[40]

Neuroimaging data collection and preprocessing

We acquired MRI data using a 3 T Verio 3 scanner (Siemens), equipped with a 32-channel head coil, at the Day Clinic for Cognitive Neurology, University of Leipzig Medical Center. We acquired functional T_2*-weighted images using a gradient echo echo-planar imaging sequence with the following parameters: repetition time 2000 ms; echo time 30 ms; flip angle 90°; field of view 256 × 256; 30 axial slices; slice acquisition matrix 64 × 64; slice thickness 4 mm; voxel resolution 3 × 3 × 4 mm^3. Functional images were coregistered to T_1-weighted images, obtained using a magnetization-prepared rapid gradient echo sequence with the following parameters: repetition time 2300 ms; inversion time 90 ms; echo time 2.98 ms; flip angle 9°; voxels 1 × 1 × 1 mm^3. We scanned every participant 3 times: at baseline (without medication), with placebo and with escitalopram (randomized treatment order; for study design overview, see Figure 1A).

We preprocessed and analyzed data sets using SPM12 (Wellcome Trust Centre for Neuroimaging) and Matlab (The MathWorks Inc.). Preprocessing comprised head motion correction using realignment, including unwarping to correct for echo-planar imaging distortions using voxel displacement maps from the Fieldmap toolbox in SPM. We also checked if the degree of motion varied between scanning sessions by computing frame-wise displacement (FD).[41] As an input, we used the translational and rotational motion parameters obtained by motion correction in SPM. For the full series of 150 functional images, motion between volumes was characterized using 149 FD values for each participant and both sessions. Finally, all FD time courses were characterized by the mean FD, the maximum FD, the maximum FD after eliminating the largest 5% of the FD values and the number of FD values that exceeded 0.5 mm. We then analyzed mean and maximum FD to detect systematic motion differences between the SSRI and placebo scans across participants using paired-sample *t* tests (2-tailed). For all participants and both sessions, the mean FD was less than 0.5 mm, and we found no significant differences in FD parameters between the SSRI and placebo sessions. No participants were excluded for excessive motion. Further preprocessing steps included slice-time correction, coregistration with the mean anatomic image, and normalization to the Montreal Neurological Institute (MNI) space based on the unified segmentation approach.[42] We resampled functional images in the MNI space with a resolution of 2 × 2 × 2 mm^3. Finally, we performed spatial filtering using a Gaussian kernel with 8 mm full width at half maximum.

Neuroimaging data analysis

We analyzed preprocessed functional images using an event-related design in a general linear model to analyze the hemodynamic response to reward and punishment feedback at peak escitalopram plasma concentration. For each participant and scan, we performed parameter estimation and generated contrast images for the contrasts of interest (win–neutral and loss–neutral, trial by trial). We then included these first-level contrast images in a second-level analysis using a paired design. Thereafter, we computed statistical analyses using each contrast of interest (win–neutral and loss–neutral) to investigate potential differences between SSRI and placebo administration. After using an initial voxel threshold of $p < 0.001$, we obtained significant results with family-wise error (FWE) correction at peak level at $p < 0.05$, given previous work[43] showing that the cluster inference is prone to producing false-positive results but the voxel inference shows FWE rates in the expected order of magnitude. We performed all analyses at the whole-brain level.

Results

Sample characteristics, mood questionnaires and drug levels

Table 1 summarizes the demographic characteristics of the 19 healthy participants who completed the study protocol. We found no significant changes in depression and mood scores after the single dose of escitalopram compared to placebo.

Mean (± standard deviation) plasma levels of escitalopram were in the expected range (23 ± 6 ng/mL) when fMRI scans took place (3–4 hours after drug administration).

Neuroimaging results

Investigating the loss–neutral contrast, we found a diminished BOLD response after a single 20 mg dose of escitalopram in the right posterior thalamus (cluster-size k = 197 voxels; $T_{max} = 7.7$; $p_{FWE} = 0.013$ at peak level; $p_{FWE} = 0.086$ at cluster level; MNI coordinates x, y, z = 10, −26, 4) and the right caudate head (k = 424 voxels; $T_{max} = 7.9$; $p_{FWE} = 0.011$ at peak level; $p_{FWE} = 0.005$ at cluster level; MNI coordinates

Table 1. Sample demographics and depression and mood scores

Characteristic	Finding*	*t* value; *p* value
Demographics		
Age, yr	24 ± 2	—
Body mass index, kg/m^2	23 ± 2	—
State-Trait Anxiety Inventory, trait anxiety	33 ± 8	—
Rating scales		
Hamilton Depression Rating Scale	SSRI: 2 ± 2 Placebo: 2 ± 1	$t_{1,17} = 0$, $p = 1$
Mood Spectrum Self-Report	SSRI: 42 ± 25 Placebo: 37 ± 22	$t_{1,17} = 1.2$, $p = 0.25$

SSRI = selective serotonin reuptake inhibitor.
*Values are mean ± standard deviation; n = 19, within-subjects.

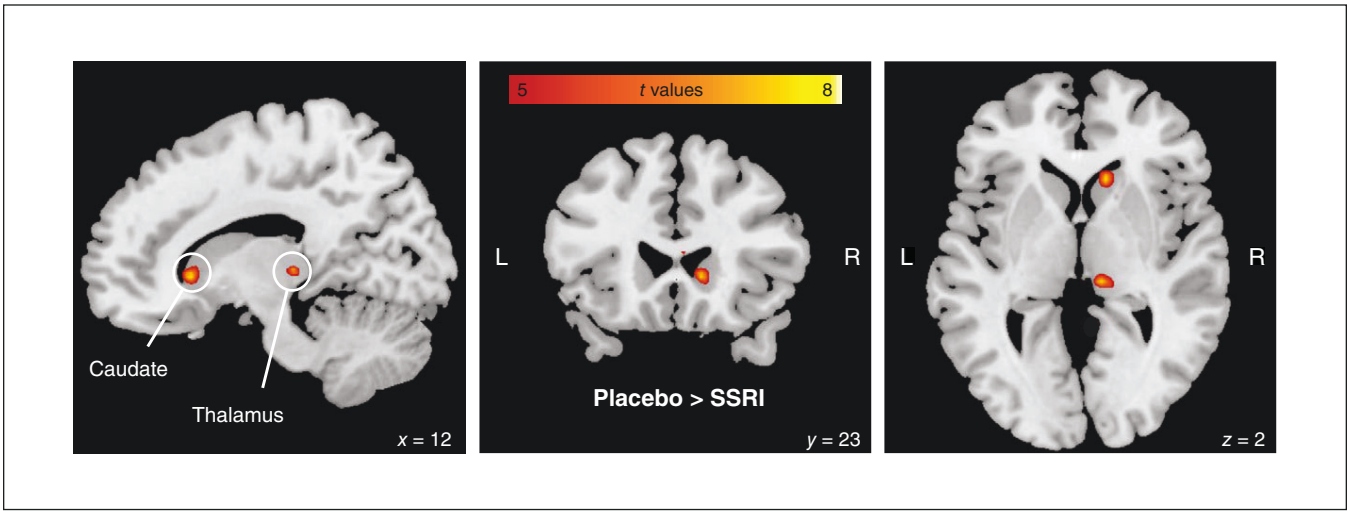

Fig. 2: Brain response to punishment feedback. Orthogonal brain sections showed reduced blood-oxygen-level-dependent signal difference between the monetary loss and neutral conditions after a single oral dose of escitalopram (20 mg) compared with placebo. Significant effects were obtained in the right posterior thalamus (*x*, *y*, *z* = 10, –26, 4) and the right caudate head (*x*, *y*, *z* = 12, 22, 0) using family-wise error correction at peak level with $p < 0.05$. Cluster-defining threshold $p < 0.001$ (uncorrected). SSRI = selective serotonin reuptake inhibitor.

x, *y*, *z* = 12, 22, 0) compared with placebo at the whole-brain level (Figure 2). We found no significant voxels that showed a BOLD increase with escitalopram, even without correction for multiple comparisons.

Investigating the win–neutral contrast revealed no significant medication effects, even without correction for multiple comparisons.

Discussion

In this placebo-controlled, crossover, double-blind pharmacofMRI study, we report the effects of an acute single dose of the SSRI escitalopram on neural response to reward and punishment feedback in healthy human participants. The main findings of this study were that acutely administered escitalopram reduced BOLD response in the right caudate nucleus and the right thalamus during monetary loss, and it did not induce changes in BOLD response to feedback on monetary wins. These results were consistent with previous work on the effects of SSRIs on the emotional processing of aversive stimuli,[44] and they provide additional support for the neuropsychological theory that acute administration of SSRI reduces negativity bias.

Furthermore, our data extend this theory by suggesting a specific role for acute serotonin transporter occupancy in the modulation of healthy neural response to punishment feedback. Given that SSRIs are used as a first line of treatment for depression and anxiety disorders, a clinical response is typically expected after several weeks.[45] This delayed onset of symptom relief in response to SSRI treatment is in contrast to the time it takes for the majority of SSRI target sites (the serotonin transporters) to be blocked to up to approximately 80%. This percentage is within the occupancy range established to be required for a therapeutic effect[46] and can already occur 3 hours after intake of the first clinical dose.[5] The discrepancy in time of onset between the acute occupancy of the serotonin transporter and a clinical response has been explained by the time required for presynaptic serotonin 1A autoreceptors to desensitize: it is postulated that the acute blockage of serotonin reuptake triggers a negative feedback mechanism via attenuated serotonergic firing, mediated by presynaptic serotonin 1A autoreceptors.[47] The resulting serotonin 1A receptor-desensitization theory is supported by indirect evidence demonstrating decreases in the functional sensitivity of serotonin 1A autoreceptors following chronic SSRI treatment in rodents.[48] It is also supported by preliminary findings from positron emission tomography studies in people with MDD demonstrating a decrease in serotonin 1A receptor binding in the dorsal raphe nuclei (albeit unrelated to the antidepressant response)[49] and decreased serotonin 1A receptor binding limited to a significant effect in the hippocampus in people with anxiety disorders.[50]

However, at a cognitive psychological level it has been argued[51] that acute effects can be detected after a single SSRI dose. Pioneering work by Harmer and colleagues[52,53] has shown that acute SSRI administration modulates implicit negative attention bias. Additional work in humans has shown that acute tryptophan depletion (i.e., acute decreases in serotonin levels) results in enhanced brain responses to threat-related stimuli, punishment predictive learning and interference from sad distractors (reviewed in Cools and colleagues[54]). Further evidence for this specific effect on negative bias is provided by a study in rats,[55] which demonstrated that acute citalopram administration influenced negative feedback sensitivity, and subchronic administration influenced reward sensitivity. Moreover, the authors observed that dose level was an essential factor for sensitivity to negative feedback; a low single dose was associated with increased negative feedback sensitivity, and a high single dose was associated with decreased negative feedback sensitivity.[55] This body of work, combined

with our findings, suggests that acute SSRI administration may be specifically related to negative bias modulation, and that a single high SSRI dose (as used in our study) may already cause phasic increases in serotonergic signalling.

Our findings demonstrate additional support for this acute timeline and show that a single oral dose of escitalopram modulates the functional response to negative feedback in brain areas typically implicated in processing loss, a cognitive process highly relevant to implicit negative bias. In an exploratory fashion, we performed a loss > reward follow-up analysis to the significant loss > neutral findings, because this may provide further insight into whether escitalopram-induced dampening to loss is greater than to reward, compared with placebo. We did not find a significant result, although this could have been influenced by our sample size. As well, because we had observed a right lateralization in our original results, we re-ran this analysis using a less conservative statistical threshold. We observed a bilateral response in the thalamus and the caudate at $p < 0.001$ (uncorrected), with the caudate clusters extending to the ventral striatum. However, given that this was not within our a priori criteria, these findings must be discussed with caution, and future studies with larger samples may be required for further clarification. Regardless, our current findings extend the observation that a single oral SSRI dose can affect emotional processing and may reduce implicit negative bias,[52,53] showing that this acute intervention has a localized effect in the neural reward circuit, namely during punishment feedback.

Serotonergic neurotransmission has long been considered a crucial substrate for aversive processing and negative motivation, based on evidence from pharmacological depletion and challenge paradigms in humans.[16,56,57] A blunted hedonic response to rewards, as well as enhanced sensitivity to punishment, describes a negative bias in reward processing that is common in depression.[1] Recent models in computational psychiatry propose that negative mood reflects the cumulative effect of differences between reward outcomes and expectations.[58,59] These models suggest a bidirectional interaction between mood and reward processing that may play an important adaptive role in healthy behaviour, and whose dysfunction might contribute to depressive disorders.[60] However, the effect of SSRIs on the negative bias in processing rewards is less well understood than for processing emotions. By specifically investigating the modulation of the hemodynamic response to reward and punishment feedback, we found that an acute dose of SSRI attenuated the BOLD response to punishment feedback in the caudate head (which is part of the striatum) and the thalamus. This was in line with previous findings, which demonstrated blunted BOLD responses to both positive and negative feedback in the medial caudate[61] and the caudate and nucleus accumbens[62] in (unmedicated) patients with MDD compared to healthy controls. A recent meta-analysis summarized these findings by reporting the caudate as the only significant region that differed between people with MDD and healthy controls during feedback processing, with decreased caudate activity in people with MDD.[63] These findings are interpreted as evidence for reduced reinforcement of actions in people with MDD. More specifically, McCabe and colleagues[64] found enhanced responses in the caudate and blunted responses in the lateral orbitofrontal cortex to primary aversive stimuli (e.g., mouldy strawberries) in patients with remitted MDD. The authors suggested that the caudate might play a role in automatic negative bias, and that blunted cortical responses represented the inability to integrate potential aversive information into appropriate actions. Although studies investigating unmedicated or remitted patients with MDD provide examples of how serotonergic neurotransmission may affect feedback processing in patient populations, we still lack a comprehensive basic understanding of how changes in acute serotonergic signalling affect reward and punishment feedback processing in healthy individuals.

Kumar and colleagues[65] administered SSRIs to healthy participants for 3 consecutive days and found blunted responses related to reward prediction error in a similar network to that observed in medicated patients with MDD. In response to the SSRI, healthy participants showed a neural BOLD pattern that seemed to display an intermediate state between drug-naive healthy participants and patients with MDD taking SSRIs. This suggests that a "normal" processing of feedback might require a narrow window of serotonergic tone, and any imbalance would cause potential disruptions in feedback processing. Dayan and colleagues[66] proposed that people with normal serotonin levels should reflexively inhibit ("prune") choices with poor expected outcomes. Any rapid drop in serotonin levels would compromise this adaptive mechanism of underexploring negative environments and would lead instead to the subjective experience of more negative events. Our results support this hypothesis by demonstrating that acute serotonergic manipulation alters the neural response to negative feedback. These data complement a recent study reporting that a single dose of escitalopram increased lose-shift behaviour after negative feedback, while win-shift behaviour remained unchanged in healthy participants.[67] At a more general level, our results were in accordance with the role of serotonin in aversive processing, more specifically in inhibiting behaviours associated with adverse consequences[13,14] and possibly linked to promoting patience.[68]

Limitations

One limitation of the study was that the BOLD signal is a nonquantitative measure that integrates both blood volume and oxygen extraction, and it does not allow distinction between the 2 measures. We acknowledge that part of the signal we observed may have been due to SSRI effects on global cerebral blood flow (e.g., via a change in blood-vessel tone).[69] However, it is unlikely that the signal change we observed during punishment feedback was entirely driven by a global change in cerebral blood flow, given the previous work of our group and others demonstrating differentiated regional effects[70,71] and no evidence that the same pharmacological challenge altered resting-state measures, such as the amplitude of low-frequency fluctuations,[70] which would have been highly sensitive to such effects. Finally, even if part of the signal were driven by underlying early changes in

neurovascular coupling in the thalamus and caudate, this was still a finding worth describing and reporting, because it may still be relevant for understanding the initial brain response to the first dose of escitalopram.

Second, we chose to study healthy young participants, and acknowledge that any interpretation of our results is limited to a healthy population and may not apply to middle-aged or older populations, or to patients. Several groups have demonstrated that acute or short-term treatment reduces negative biases in information processing, paralleled by changes of the brain response in the amygdala, thalamus, cingulate and insula in healthy participants.[22,72,73] As well, similar acute BOLD response patterns in the amygdala, thalamus, cingulate and insula during affective processing were predictive of a clinical response to escitalopram after 6 weeks of treatment in patients with MDD. Still, the effects of SSRIs on serotonergic neurotransmission might differ between healthy individuals and clinical populations.[65]

Third, we chose a task that allowed assessment of the brain response but did not include a behavioural assessment or measures of potential arousing or sedating effects of SSRI intake. Consequently, our results are limited to the interpretation of the healthy brain response to punishment feedback during maximum SSRI levels in the periphery and a 75% to 80% block of the central serotonin transporter state. Changes at a neural level can occur without concurrent behavioural change, specifically when assessed on an acute timescale. Given the multilayered concepts of reward and punishment learning, the wide variety of relatively complex paradigms currently applied to tease those layers apart, and the subsequent heterogeneous findings,[74] we opted for a well-established, simple and straightforward task.[38,39] The task, combined with a longitudinal within-subject design, allowed for a robust assessment of the acute effects of a single dose of escitalopram during punishment feedback in a neural circuit relevant to punishment processing and at a considerable effect size and a relatively conservative statistical threshold at the whole-brain level. However, we acknowledge that the thalamus finding did not survive FWE correction at the cluster level. We chose to focus on FWE correction at the voxel level, but as previous work[43] has shown, cluster inference is prone to producing false-positive results, and the voxel inference shows FWE rates in the expected order of magnitude.

Finally, we acknowledge that the activity of SSRIs on the regulation of neural excitation and inhibition is multifactorial and complex, and that serotonin transporter blockade can affect several neurotransmitter systems beyond serotonin, such as dopamine and noradrenaline. Future studies implementing multiple and specific tracer applications for quantitative neuroimaging tools (such as positron emission tomography or magnetic resonance spectroscopy) are needed to shed light on the complex interplay of synergistic neurotransmitters in different aspects of reward and punishment interaction.

Conclusion

Our study provides an important and novel contribution to the understanding of how acute SSRI administration affects the human brain, and specifically the reward system, by demonstrating that a single dose of escitalopram alters the brain response to punishment but not reward feedback in healthy individuals. Our results complement recent theories of antidepressant action by showing an acute blunting effect of SSRI administration on negative feedback processing and demonstrate a role for a single dose of escitalopram in affecting the neural response to punishment. These findings are in accordance with the role of serotonin in aversive processing, and more specifically provide support for the hypothesis of the protective action of serotonin for the healthy brain in the face of negative events. Furthermore, they provide a crucial next step toward testing clinical translation for such paradigms of punishment feedback, particularly in patients with increased punishment sensitivity, such as those with obsessive–compulsive disorder,[75] eating disorders[76] or depression.[1]

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Contributors: E. Forbes, A. Villringer and J. Sacher designed the study. R. Regenthal and J. Sacher acquired the data, which C. Lewis, K. Mueller, R. Zsido, J. Reinelt, H. Okon-Singer and J. Sacher analyzed. C. Lewis, R. Zsido, R. Regenthal and J. Sacher wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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2.2. Women compared with men work harder for small rewards

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Women compared with men work harder for small rewards

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Abstract

In cost-benefit decision-making, women and men often show different trade-offs. However, surprisingly little is known about sex differences in instrumental tasks, where physical effort is exerted to gain rewards. To this end, we tested 81 individuals (47 women) with an effort allocation task, where participants had to repeatedly press a button to collect food and money tokens. We analyzed the motivational phases of invigoration and effort maintenance with varying reward magnitude, difficulty, and reward type. Whereas women and men did not differ in invigoration, we found that women showed higher effort maintenance as well as higher subjective wanting and exertion ratings for small rewards compared with men. Notably, men increased their effort more than women for higher rewards to match women's levels of performance. Crucially, we found no sex differences depending on reward type or difficulty, indicating that sex differences were specific to the encoding of the magnitude of benefits, not costs. To summarize, women exerted higher physical effort for small rewards, which corresponded with an elevated subjective value in women compared with men. Therefore, sex differences in perceived reward magnitude may contribute to differential behavioral preferences highlighting the potential of cost-benefit decision-making to provide insights about potential mechanisms.

Introduction

No bees, no honey – no work, no money. The willingness to expend effort is critical in human behavior. The amount of effort we spend depends on the goals we pursue: we study more to get good grades or exercise harder for a bikini body. Put formally, we determine whether an action is worth pursuing by integrating potential benefits with the cost of an action, which is reflected in a cost-benefit trade-off [1, 2].

Cost-benefit valuations are extensively researched in the decision-making literature (e.g., [3, 4]), in particular how decision costs such as delay or uncertainty decrease the subjective value of a reward (i.e., value-based decision-making). So far, it has been shown that women and men differ in important aspects of value-based decision-making (for review, see [5]): For example, men show biases towards maximizing rewards even if this strategy is not optimal, while women seek frequent but smaller rewards. Compared with men, women are more concerned about suboptimal choices in their decision-making strategy [6, 7], and prefer safe options when they lost a reward in a previous decision [8]. Concurrently, men were overall more likely to take risks than women [9]. During reinforcement learning, women outperformed men in learning from positive feedback, while men had enhanced inhibitory control under interference than women [10]. Taken together, women and men show specific preferences to resolve common trade-offs in cost-benefit decision-making that may contribute to differences in reward-related behavior.

Another operationalization of value-based decisions is the allocation of effort, where effort refers to the intensity of mental and/or physical work that individuals apply to obtain some reward [11]. Individuals are considered to exert effort by estimating the expected benefit and the perceived costs to receive a reward [12-14]. The perceived reward value may inform the expected benefit of the effort [15], which is usually reflected in an effort boost for higher rewards [14]. Sex differences in instrumental physical effort have been reported, with women preferring easy trials with smaller rewards and men preferring difficult trials with higher rewards [16]. However, the nature of this sex-specific behavioral variability in instrumental physical effort is still elusive, e.g., if this sex difference depends on reward magnitude, task difficulty or an interaction of both.

We recently developed and validated a frequency-based version of the effort allocation task (adapted from [13]). Similar to lever pressing in preclinical research [17],

participants collect food and money tokens by repeatedly pressing a button [14]. The task captures two motivational phases: invigoration and effort maintenance. Invigoration describes how quickly a participant ramps up effort; it is associated with subjective wanting and mostly insensitive to effort costs. In contrast, effort maintenance relates to how durably a participant keeps this level of effort [18]. Consequently, effort maintenance is associated with both subjective wanting as well as exertion and it is highly sensitive to the costs of effort. Moreover, we previously reported associations of invigoration and effort maintenance with Carver and White's [19] behavioral inhibition system (BIS) and behavioral activation system (BAS), with average effort correlating positively with BIS scores [20]. Taken together, the effort allocation task and its associations with subjective wanting, exertion as well as the BIS/BAS scales provide a good opportunity to elaborate sex differences in instrumental physical effort.

To this end, we re-analyzed a previously collected data set ([14], see Methods) and tested whether women and men would differ in the motivational phases of invigoration and effort maintenance as measured via the effort allocation task. We predicted invigoration and effort maintenance using reward magnitude (low vs. high), difficulty (easy vs. hard), and reward type (food vs. money) as predictors. We further assessed associations of sex with the subjective ratings of wanting, which relates to the benefits of an action, and exertion, which relates to the costs of an action, as well as sex-specific differences on the BIS/BAS scales.

Results

Women have higher BIS and BAS Drive scores than men

We previously reported associations of invigoration and effort maintenance with the BIS/BAS scales in the same sample. We found that average effort correlated positively with BIS scores [20], but did not examine sex differences. Here, we aimed to describe the sample more precisely for our re-analysis and tested for previously described sex differences on the BIS/BAS scales [21]. Similar to Strobel et al. [21], women had significantly higher BIS scores than men, $t(79) = 2.14$, $p = .035$, but BAS overall scores did not differ between sexes, $t(79) = 1.66$, $p = .101$. Women also had significantly higher scores on the subscale BAS Drive than men, $t(79) = 2.41$, $p = .018$. The subscales BAS Fun Seeking, $t(79) = -0.13$, $p = .894$, and BAS Reward

Responsiveness, $t(79) = 1.55$, $p = .126$, did not differ significantly between women and men (Table 1).

Table 1. Means (standard deviations) and statistics of behavioral inhibition system (BIS) and behavioral activation system (BAS) scales.

	Mean (SD)		*t*-value	*p*-value
	female	**male**		
BIS	21.28 (3.51)	19.59 (3.48)	2.14	.035 *
BAS	42.17 (4.15)	40.53 (4.72)	1.66	.101
BAS Drive	12.70 (1.85)	11.68 (1.95)	2.41	.018 *
BAS Fun Seeking	12.38 (1.88)	12.44 (2.00)	-0.13	.894
BAS Reward Responsiveness	17.09 (1.77)	16.41 (2.15)	1.55	.126

Note. P-values with an asterisk indicate significance.

Women and men differ in effort maintenance, but not invigoration

To estimate sex differences, we used mixed-effects models predicting either invigoration slopes or effort maintenance (operationalized as average relative frequency of button presses), using the factors reward magnitude (low vs. high), difficulty (easy vs. hard), reward type (food vs. money), and the interaction between reward magnitude x difficulty (Table 2). Women and men did not differ in invigoration, $b = -0.05$, $t(76) = -0.01$, $p = .989$. However, we found a main effect of sex for effort maintenance, with women having overall higher effort maintenance than men, $b = -9.92$, $t(76) = -3.02$, $p = .003$. A significant Sex × Reward Magnitude interaction showed that women generally outperformed men for small rewards; when more reward was at stake, men adjusted their effort more than women to match their performance $b = 6.01$, $t(76) = 2.33$, $p = .022$ (Figure 1). We found no sex differences depending on reward type or difficulty, nor a significant interaction of reward type x difficulty (all $p > .05$).

In a follow-up analysis, we also examined the total wins of the effort allocation task to see if women or men were overall more successful in earning rewards.

Regarding the total points won (i.e., pooled over money and food wins), women were more successful than men (b = -3.44, t(76) = -2.43, p = .018).

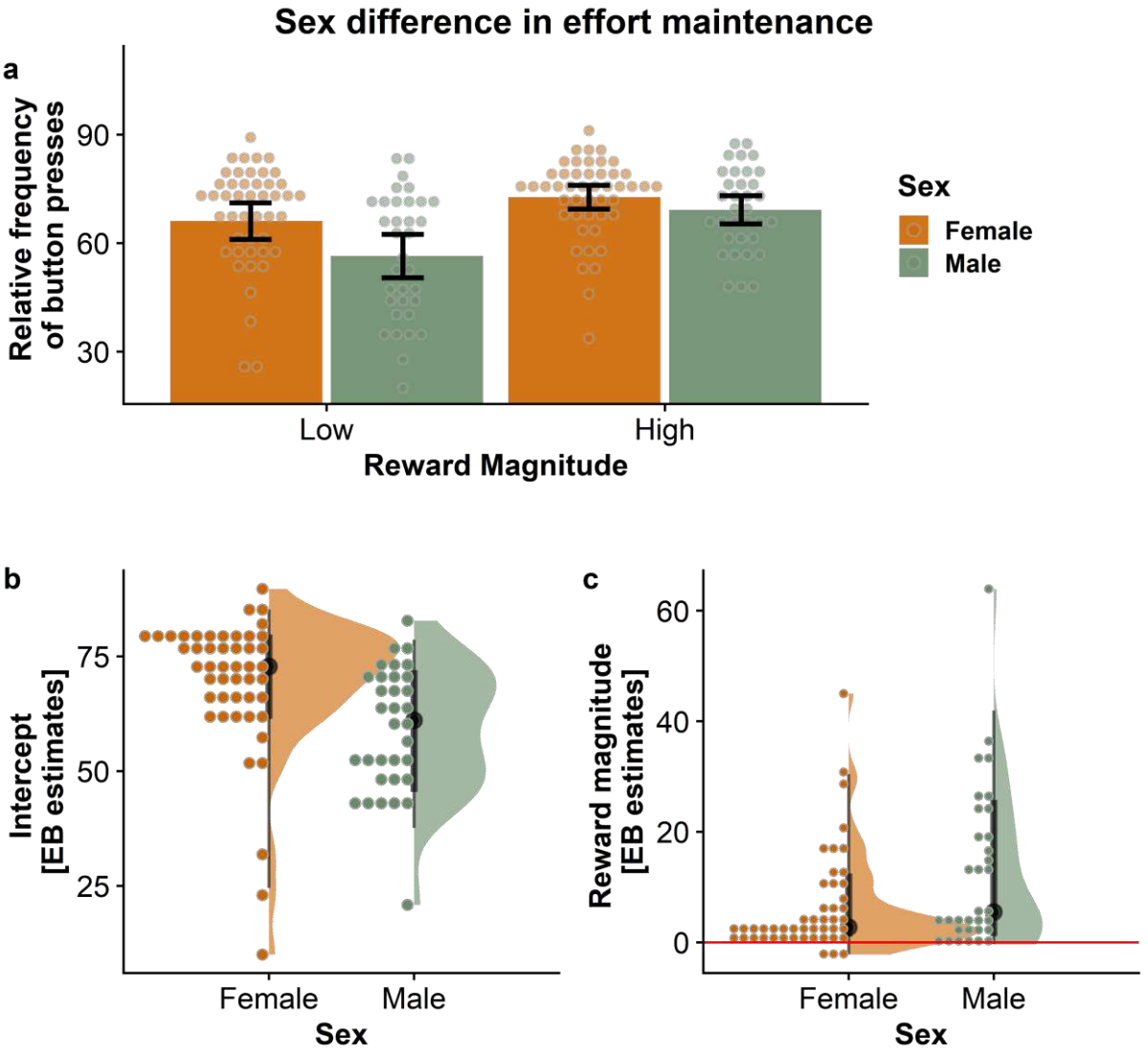

Figure 1. Women and men differ in effort maintenance, depending on reward magnitude. (a) Trial-based data showing that women had overall higher effort maintenance than men (main effect of sex, p = .003). Women generally outperformed men for small rewards, but when more reward was at stake, men adjusted their effort to match women's performance (interaction Sex x Reward magnitude, p = .022). (b) and (c) show empirical Bayes estimates (EB).

Table 2. Estimates of mixed-effects models.

	Coefficient	Standard error	*t*-ratio	*p*-value
Invigoration				
Intercept	55.32	1.71	32.41	<0.001 *
Sex	0.05	3.53	0.01	0.989
Sex x Reward magnitude	0.91	2.55	0.36	0.723
Sex x Difficulty	-0.40	1.54	-0.26	0.798
Sex x Reward type	0.18	1.70	0.11	0.915
Effort maintenance				
Intercept	64.24	1.59	40.43	<0.001 *
Sex	-9.92	3.28	-3.02	0.003 *
Sex x Reward magnitude	6.01	2.58	2.33	0.022 *
Sex x Difficulty	-2.35	2.04	-1.15	0.252
Sex x Reward type	0.65	1.86	0.35	0.727
Wanting				
Intercept	67.43	2.26	29.90	< .001 *
Sex	-9.62	3.65	-2.64	.010 *
Reward magnitude	13.41	1.66	8.06	< .001 *
Sex x Reward magnitude	9.31	3.01	3.10	.003 *
Exertion				
Intercept	64.36	2.67	24.09	< .001 *
Sex	-7.95	4.37	-1.82	.073
Reward magnitude	11.18	1.87	5.98	< .001 *
Sex x Reward magnitude	10.51	3.47	3.03	.004 *

Note. Variables were coded as follows: Sex (male = 0, female = 1), Reward magnitude (low = 0, high = 1), Difficulty (low = 0, high = 1), Reward type (money = 0, food = 1). *P*-values with an asterisk indicate significance.

Women and men differ in subjective ratings of wanting and exertion

For wanting, we found main effects of sex, with women overall having higher wanting ratings than men, b = -9.62, $t(76)$ = -2.64, p = .010, and of reward magnitude, i.e., both women and men wanted higher rewards more than lower rewards, b = 13.41, $t(76)$ = 8.06, p < .001. The interaction of Sex x Reward Magnitude was also significant, meaning that women had higher wanting ratings than men for smaller rewards, b = 9.31, $t(76)$ = 3.10, p = .003 (Figure 2a). For exertion, the main effect of sex was not significant, b = -7.95, $t(76)$ = -1.82, p = .073, only the main effect of reward magnitude, i.e., both women and men reported to put in more effort for higher rewards, b = 11.18, $t(76)$ = 5.98, p < .001. Similar to wanting, we found a significant interaction of Sex x Reward Magnitude for exertion, with women putting in more effort for smaller rewards than men, b = 10.51, $t(76)$ = 3.03, p = .004 (Figure 2b).

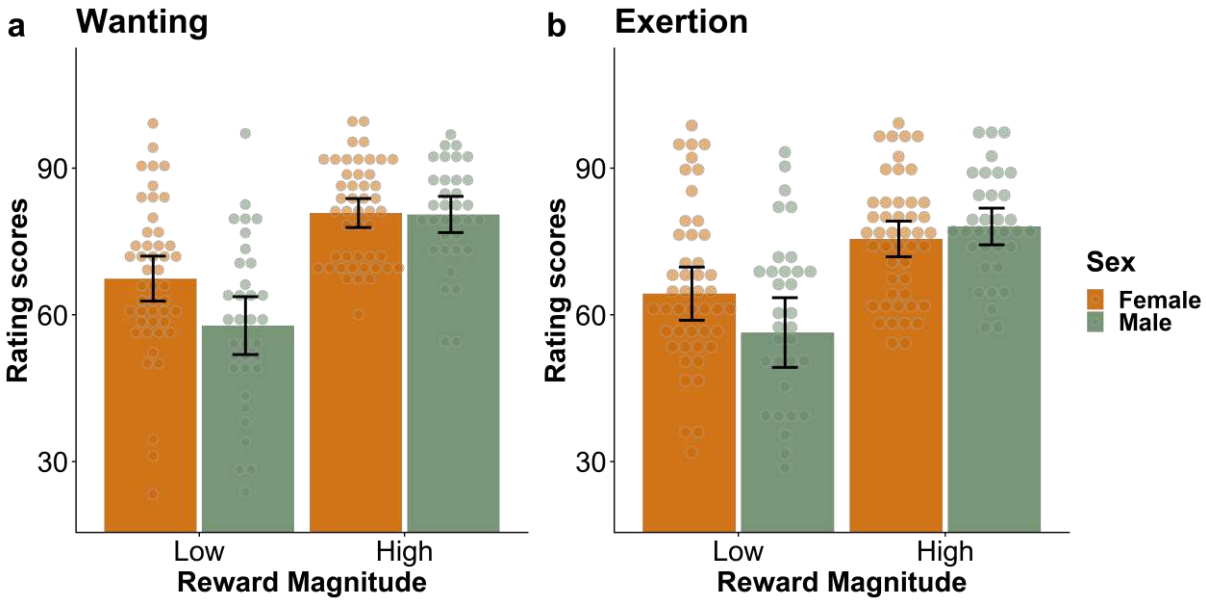

Figure 2. Women and men differed in subjective ratings of wanting and exertion. (a) Both women and men had higher wanting ratings for higher rewards than smaller rewards, p < .001, but women wanted smaller rewards more than men did, p = .003. (b) Both women and men reported to put in more effort for higher rewards than for smaller rewards, p < .001, and women reported more exertion for smaller rewards than men, p = .004.

Discussion

Women and men have specific preferences to resolve common trade-offs in cost-benefit decision-making. However, sex differences in instrumental physical effort are less well understood, especially if sex-specific behavioral variability depends on key factors of the tasks, such as reward magnitude, difficulty, and reward type. To this end, we investigated sex differences in instrumental physical effort in humans using an effort allocation task, which captured the motivational phases invigoration and effort maintenance. Although women and men showed comparable invigoration, women showed overall higher effort maintenance compared with men. More specifically, women outperformed men for small rewards. However, men increased their effort more than women for higher rewards. Notably, women and men showed no behavioral differences when different reward types were at stake or greater difficulty was required to obtain a reward, indicating that sex differences were specific to the encoding of potential benefits, not costs. This interpretation was substantiated by differences in subjective ratings of wanting and exertion because women wanted smaller rewards more and reported higher exertion compared with men, whereas ratings were comparable for large rewards. To summarize, we found sex differences in instrumental physical effort expenditure, which became evident in both objective and subjective measures. By showing that sex-specific behavioral variability depended on reward magnitude, and not on reward type or task difficulty, we contribute to an improved understanding of sex differences in instrumental physical effort that may facilitate differential preferences.

Our results showed that women and men differed in instrumental physical effort, depending on reward magnitude. This difference was mainly driven by the fact that women put in more effort for smaller rewards, while men worked about as hard as women when larger rewards were at stake. We thereby extended results from studies on sex differences in value-based decision-making, e.g., where women seek certain, smaller rewards, while men preferred larger, but less consistent rewards [7]. Effort-based versions of cost-benefit paradigms, like the effort allocation task used in our study, focus on the costs of physical effort to obtain rewards. Here, the perceived reward value is considered to inform the expected benefit of the effort [15], which usually leads to higher effort for larger rewards [14]. Our results show that women and men evaluated the perceived reward value differently and, thus, allocated their effort differently in light of small vs. large rewards. When more reward was at stake, men

increased their effort more than women to match their performance. Consequently, men were more opportunistic, while women also worked more for smaller rewards. In turn, women ascribed higher value to small rewards than men, which was also corroborated by women's higher subjective wanting and exertion ratings for smaller rewards compared with men. On a more general level, one might say that the extrinsic influence of higher reward magnitude was stronger for men than for women.

Of note, invigoration refers to automatic processes related to motivational drive, while effort maintenance rather describes an active decision of allocating physical effort [11, 22]. Moreover, effort maintenance refers to how much effort one is *willing* to spend to gain rewards, rather than how much effort one is (physically) *able* to exert. Since we did not find a sex difference in invigoration, but only in effort maintenance, we can assume that women actively chose to put in effort for both small and high rewards. Women weighed the benefits of smaller rewards higher than men, but women may have also valued effort itself higher than men. Effort can add substantial value to both rewards and to effort itself ('The Effort Paradox' [11, 23]). We can not rule out that women in our study might have valued the rewarding experience of exerting effort higher than men, which boosted the valuation of smaller rewards. Regarding the total points won, the female strategy of putting in effort also for small rewards can be seen as more successful than the male strategy of presumably saving effort costs for small rewards. Another line of argument was the possibility that women and men allocate physical effort differently depending on task demands, such as difficulty, e.g., Treadway et al. [16] found that women preferred easy trials with smaller rewards and men preferred difficult trials with higher rewards. However, we did not find a sex difference in effort maintenance depending on difficulty to obtain a reward. Our results were further corroborated by experiences from previous studies, in which behavioral differences in effort allocation became evident in the face of small rewards, whereas for larger rewards, most individuals give their very best (e.g., [15]). Taken together, our results suggest that sex differences in instrumental physical effort depend on reward magnitude, with women weighing the benefits of smaller rewards higher than men.

Moreover, we found that women had significantly higher BIS and BAS Drive scores than men. Higher BIS scores in women have repeatedly been shown in validation samples (e.g., [19, 21]). BIS stands for the motivation to avoid aversive outcomes, and, thus, women in our study felt 'worried when they thought they have done poorly at something', more than men. Also, compared with men, women in our

study ‘went out of their way to get things they wanted’, as described by higher BAS Drive scores (motivation to pursuit desired goals). The sex difference in both behavioral inhibition and activation may thus contribute to the finding that women in our study generally put in more effort for rewards than men. In the same sample, we previously reported a positive correlation of average effort with BIS scores [20]. Consequently, higher BIS scores in women in our analysis may further explain why women had overall higher effort maintenance than men: women avoided an aversive situation, i.e., ‘doing poorly at something’, by ramping up their effort to fulfill the task requirements. This fits well with the finding that effort can have signaling functions in social settings, as it is easily detected by self and others: by putting in more effort, women may express more commitment and dedication to the task [24, 25]. Men, with lower BIS scores, might have been less affected by this, and, thus, had a rather opportunistic motivation in performing the task.

The present study has several limitations which could guide future research. First, we did not measure sex hormone levels, e.g., estradiol, progesterone, or testosterone. Sex hormone receptors are densely present along midbrain areas and thereby modulate decision-making processes by interacting with relevant neurotransmitter systems (for review, see [5, 26]). It remains an open question if and how sex hormones also influence physical effort expenditure and thereby contribute to sex differences. Second, we did not assess gender-related attributes and merely split the sample into biological females and males. However, we can not rule out if self-perceived feminine or masculine traits may also contribute to behavioral differences between women and men, i.e., if individuals allocate physical effort differently if they consider themselves as being for example more risk-taking (typically male) or more conscientious (typically female).

Value-based decision-making shows sex differences in the integration of benefits and costs, but potential biases in the allocation of physical effort when rewards are at stake were largely elusive. We investigated sex differences in instrumental physical effort and found that women showed overall higher effort maintenance than men. More specifically, women had higher effort maintenance than men for small rewards, while for higher rewards, men adjusted their effort to match women’s performance. In line with behavioral differences, women also reported higher wanting and exertion for smaller rewards compared with men. Taken together, our results highlight sex differences in instrumental physical effort and subjective wanting and

exertion that are explained by an elevated subjective value of small rewards in women compared with men. Since these sex differences were not specific to task difficulty or reward types, we conclude that sex differences in instrumental physical effort depended on the encoding of potential benefits, not costs. We thereby contribute to the understanding of sex-specific behavioral variability on motivated behaviors and underline the potential of cost-benefit decision-making to understand potential mechanisms in several domains, such as education and mental health.

Methods

Participants

85 individuals participated in the study and completed two sessions each: one session took place during stimulation of the cymba conchae (taVNS) and the other one during sham stimulation at the earlobe. Methods and results of the taVNS stimulation are reported elsewhere [14, 27] and are thus not further reported in this manuscript. The total sample size for the current analysis was N = 81 after exclusion of 4 participants (n=3: did not finish the second experimental session, for example due to sick leave, n=1: was assigned an incorrect maximum of button press frequency precluding comparison of the two sessions). Half of the participants completed the effort task during left-sided taVNS and the other half completed the effort task during right-sided taVNS. As determined by a telephone interview, participants were physically and mentally healthy, German speaking, and right-handed (47 women: M_{age}= 24 ± 3 years, M_{BMI}= 22.4 ± 2.9 kg/m^2; 34 men: M_{age}= 25 ± 4 years, M_{BMI}= 24.0 ± 3.0 kg/m^2). The study was approved by the local ethics committee (the institutional review board of the Faculty of Medicine, University of Tübingen) and was conducted in accordance with the ethical code of the World Medical Association (Declaration of Helsinki). Participants took part voluntarily and provided written informed consent at the beginning of Session 1. They received either monetary compensation (32€ fixed amount) or course credit for their participation. Moreover, depending on their task performance, participants received money and a breakfast (cereal + chocolate bar).

Experimental procedure

The study was designed so that experimental sessions were conducted in a randomized, single-blind crossover fashion. Experimental session started between 7:00 am and 10:15 am and lasted about 2.5 h for each session. Participants were asked to fast overnight (>8 h hours prior to the visit). In the beginning of the first session, participants selected their preferred type of cereal out of four options (dried fruits, chocolate, cookies, or honey nut; Peter Kölln GmbH & Co. KGaA, Elmshorn, Germany). It was explained that participants would collect energy and money points depending on their performance in the effort allocation task. The participant's breakfast

serving would consist of cereal and milk scaled according to the energy points earned during the task. During the session, participants could drink water *ad libitum*.

First, participants completed a set of state ratings [27] followed by practice trials of the effort allocation task to estimate the maximum frequency of button presses for every individual. A blue ball depicted within a tube appeared on the screen for two initial trials of 10 s length each. By repeatedly pressing a button on the Xbox 360 controller (Microsoft Corporation, Redmond, WA) with their right (dominant) index finger, participants could move the ball upwards within the tube. A blue tangent line on the vertical axis was also moved by moving the ball upwards, marking the highest position reached by the ball so far. This line would depict the maximum frequency of button presses achieved so far ("peak") even when participants stopped pressing the button and remained at the highest position, in contrast to the ball. Participants were encouraged to push the line as high as they could. Next, participants completed a short practice analogous to the effort task consisting of eight trials that comprised all possible combinations of reward magnitude (low vs. high), difficulty (easy vs. hard), and reward type (food vs. money) presented in a randomized order including a short break after half of the trials. By use of these practice trials, the maximum frequency of button presses was updated if participants exceeded the previous level achieved during training. After completing the practice trials, participants received feedback about the reward they would have won as a reference for the following experiment (for details, see [14]).

After the tasks, participants received their breakfast and a snack according to the food reward ("energy") points earned. At the end of the first session, participants received their monetary wins as part of the compensation. Both sessions took place within a week (usually within 3-4 days), were conducted at approximately the same time, and followed the same standardized protocol. Participants either received monetary compensation (32€ fixed amount + wins of Session 2) or course credit (+ wins of Session 2) after the second session.

Effort allocation task

By exerting effort (i.e., repeatedly pressing a button with the right index finger), participants collected food and money tokens throughout the effort allocation task. Analogous to preclinical studies of lever pressing [17], the task used frequency of

button presses instead of grip force to measure physical effort (adapted from [13]). Tokens were exchanged for calories (cereal + chocolate bar as snack) or money at a rate of 1 kcal or 1 cent per 5 tokens at the end of the session.

A prospective reward, which could be either food (indicated by a cookie) or money (indicated by a coin), was presented for 1 s at the start of every trial. The magnitude of the reward at stake was varied as one symbol signaled a low magnitude (1 point/s) whereas several symbols indicated a high reward magnitude (10 points/s). Participants won 362.8 kcal and €3.78 per session on average. Following, a blue ball contained within a tube was presented on the screen. Participants were instructed to vertically move the ball above a certain difficulty level by repeatedly pressing a button on the controller with the right index finger to earn reward points. Difficulty corresponded to a relative frequency threshold and was indicated by a red line. Reward points were accumulated and tracked by a counter in the upper right corner of the screen (Figure 3) for every second that the ball was kept above the threshold (indicated by a change of color from dark to light blue). By alternating the red threshold line between 75% and 85% (counterbalanced order across participants) of the individual maximum frequency, difficulty was varied. We used a moving average algorithm with exponential weighting ($\lambda = 0.6$) to smooth the movement of the ball for display on screen. Hence, the ball fell quickly yet slowed down when participants stopped working or reduced the frequency.

Participants were presented sequentially with two visual analogue scales inquiring about exertion and wanting of the reward at stake after every effort phase of each of the 48 trials comprised in the task. Participants were encouraged to take breaks at their convenience to recover during trials, so that they could try to exceed the threshold again, as the task was too difficult to always keep the ball above the red line, as was emphasized in the instructions. Participants could take a short break to recuperate after completing the first half of the task. The total amount of tokens they had collected was shown on the screen after completing the task. Only completed sessions were rewarded in tokens. The task was presented using Psychophysics toolbox v3 [28] in MATLAB v2017a.

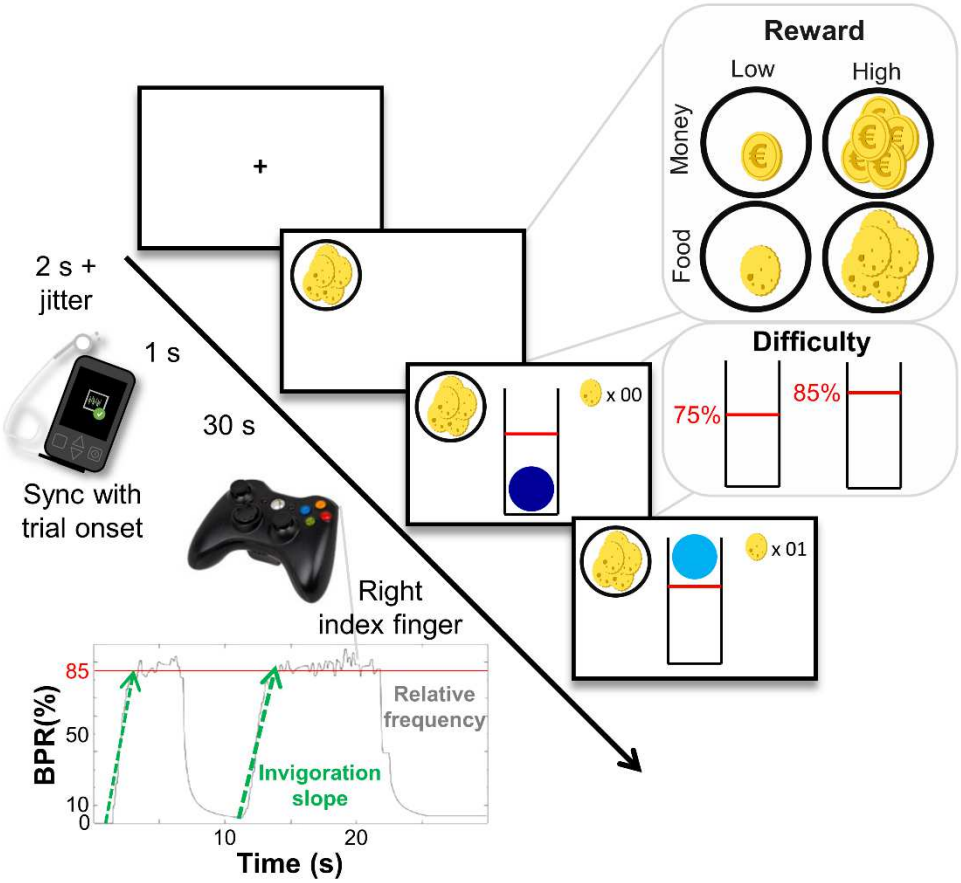

Figure 3. Schematic depiction of the effort allocation task. First, fixation cross is shown, followed by the reward cue. To earn reward, participants have to keep a ball above the red line by repeatedly pressing a button with their right index finger. Reward magnitude (low vs. high), difficulty (easy vs. hard), and reward type (food vs. money) were manipulated as task conditions. The lower left graph shows a representative time series of a high-difficulty trial, depicting effort output as button press rate, BPR, in % relative to the maximum frequency of the participant. Invigoration slopes captured how quickly participants reach effortful behavior during a trial to collect the reward. Effort maintenance relates to the average relative frequency on the trial. Figure taken from [14] under CC BY license (https://creativecommons.org/licenses/by/4.0/); no changes have been made to the figure.

BIS/BAS scale

We used the German version of the BIS/BAS scale [21], originally developed by Carver and White [19]. The BIS/BAS scale measures two motivational systems: the behavioral inhibition system (BIS), which corresponds to motivation to avoid aversive outcomes, and the behavioral activation system (BAS), which describes motivation to approach goal-oriented outcomes. The questionnaire has 24 items with 4-point Likert scale responses (from 1 = ‘very true for me’, to 4 = ‘very false for me’). One of the four subscales correspond to the BIS and comprises items like ‘I worry about making

mistakes' or 'I feel worried when I think I have done poorly at something'. The three components of BAS compose the remaining three subscales. BAS Drive measures the motivation to pursuit desired goals, e.g., 'I go out of my way to get things I want'. BAS Reward Responsiveness focuses on positive responses to pleasant reinforcers, e.g., 'When I'm doing well at something, I love to keep at it'. BAS Fun Seeking comprises items that measure the motivation to approach new rewards spontaneously, e.g., 'I crave excitement and new sensations'. We previously reported associations of invigoration and effort maintenance with BIS/BAS in the same sample, but did not examine sex differences [20].

Data analysis

To isolate the facets invigoration and effort maintenance, we divided the behavioral data into work and rest segments (see also [14]). Invigoration was estimated with the slope of the transition between relative frequency of button presses during a rest segment and their initial plateau during the following work segment (MATLAB findpeaks function). Effort maintenance was the average frequency of button presses during a trial capturing how much effort participants produce over time.

Invigoration and effort maintenance estimates at the trial level were then entered in a mixed-effects analysis as implemented in hierarchical linear models (HLM; [29]). We used two univariate mixed-effects models, as both outcomes were only moderately correlated, r = 0.286, 95% CI [0.25, 0.32]. We predicted either invigoration or effort maintenance using the following predictors: stimulation (sham vs. taVNS), reward magnitude (low vs. high), difficulty (easy vs. hard), reward type (food vs. money, all dummy coded), the interaction between reward magnitude × difficulty, as well as interactions of stimulation with all these terms. At the participant level, we included stimulation order, stimulation side (both mean centered), BMI, and sex. Intercepts and slopes were modeled as random effects to account for individual deviations from fixed group effects. As detailed in [14], the taVNS stimulation effect was accounted for by including stimulation condition (taVNS vs. sham) together with all interactions of stimulation with the other predictors of the model. The order of stimulation conditions and stimulation side were controlled for at the participant level and results of the taVNS stimulation were already reported elsewhere [14]. We found no sex-specific effects of

taVNS vs. sham, stimulation order, or stimulation side, and thus pooled both sessions in our current analysis.

Moreover, to assess specific associations of sex with the subjective ratings of wanting (related to benefits of action) and exertion (related to costs of action), we used mixed-effects models as implemented in R (lmerTest), predicting wanting or exertion as outcomes, respectively, and using sex and reward magnitude as predictors.

Statistical threshold and software

We used a two-tailed $\alpha \leq .05$ for the analyses of our main research question: Do women and men differ in invigoration or effort maintenance? Mixed-effects analyses were conducted with HLM v7 [30] and lmerTest in R [31]. To determine the evidence for the alternative hypothesis provided by our results, we calculated corresponding BFs based on individual empirical Bayes estimates. Effort data was processed with MATLAB vR2017-2019a and SPSS v24. Results were plotted with R v4.1.0 (R Core Team, 2017).

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Author contributions

NBK was responsible for the study concept and design and supervised data collection. NBK conceived the method and AK processed the data. CAL performed the data analysis and AK and NBK contributed to analyses. CAL wrote the manuscript, and MG contributed to the Methods section. All authors contributed to the interpretation of findings, provided critical revision of the manuscript for important intellectual content, and approved the final version for publication.

Data availability

Source data are provided with a previous publication [14]. Trial-based behavioral data that was used to conduct all analyses are publicly available on OSF:

https://osf.io/58r3c/?view_only=5d1ccee7d67b464bb6f40ebe7ebc844b

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The authors declare no competing financial interests.

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2.3. No differences in Value-Based Decision-Making Due to Use of Oral Contraceptives

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No Differences in Value-Based Decision-Making Due to Use of Oral Contraceptives

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Fluctuating ovarian hormones have been shown to affect decision-making processes in women. While emerging evidence suggests effects of endogenous ovarian hormones such as estradiol and progesterone on value-based decision-making in women, the impact of exogenous synthetic hormones, as in most oral contraceptives, is not clear. In a between-subjects design, we assessed measures of value-based decision-making in three groups of women aged 18 to 29 years, during (1) active oral contraceptive intake (N = 22), (2) the early follicular phase of the natural menstrual cycle (N = 20), and (3) the periovulatory phase of the natural menstrual cycle (N = 20). Estradiol, progesterone, testosterone, and sex-hormone binding globulin levels were assessed in all groups *via* blood samples. We used a test battery which measured different facets of value-based decision-making: delay discounting, risk-aversion, risk-seeking, and loss aversion. While hormonal levels did show the expected patterns for the three groups, there were no differences in value-based decision-making parameters. Consequently, Bayes factors showed conclusive evidence in support of the null hypothesis. We conclude that women on oral contraceptives show no differences in value-based decision-making compared to the early follicular and periovulatory natural menstrual cycle phases.

Keywords: oral contraceptives, ovarian hormones, value-based decision-making, impulsive choice, delay discounting, probability discounting, risk, loss

INTRODUCTION

Our everyday life is determined by the decisions and choices which we have made or did not make – no matter how big or small. To make these decisions, we often draw on the cognitive process of value-based decision-making. In this complex cognitive process, potential rewards are balanced against their potential costs, i.e., a certain delay or probability of obtaining or losing something. Value-based decision-making comprises different facets, in which the dimensions amount, delay, or

probability differ (1). We speak of *delay discounting* if a person is faced with the decision between a smaller, sooner reward and a larger, later reward. Risk-aversion/seeking and loss aversion are captured in *probability discounting* which is a decision between a sooner, small certain reward (or loss) and a later, less certain but larger reward (or loss). Choice behavior is considered more impulsive if a person tends to choose smaller, sooner rewards over larger, later rewards.

Women and men differ in some aspects of value-based decision-making [for review, see Ambrase et al. (2)]. For example, women show bias towards frequent but smaller rewards, while men tend to maximize rewards even if their strategy is not optimal. Women also tend to regret suboptimal changes in their decision-making strategy and thus are more sensitive to information about previous rewards (3–5). Emerging evidence suggests that ovarian hormones, such as estradiol and progesterone, affect value-based decision-making in women (2). Ovarian hormones fluctuate across the menstrual cycle [~ 28 days; Bull et al. (6)]: In the *follicular* phase, both estradiol and progesterone levels are low in the beginning, with estradiol slowly rising and surging before *ovulation* (periovulatory phase, ~ day 14). Following ovulation, estradiol and progesterone rise again in the *luteal* phase, peaking bluntly. It has been shown that women made more impulsive choices in the early follicular phase, i.e., when both estradiol and progesterone were low, while at the same time women were less likely to wait for a higher reward, compared with the periovulatory phase (7). Similarly, women were also less sensitive for immediate rewards with rising estradiol levels, but this effect was mainly driven by women with lower frontal dopamine levels (8). Hence, decision-making processes may be affected by the interaction between ovarian hormones and neurotransmitter systems involved in decision-making – especially the dopaminergic system (9).

While most studies focused on menstrual cycle related effects on decision-making as the menstrual cycle provides a natural experimental model for investigating influences of endogenous ovarian hormones in women, we know only little about possible effects of exogenous ovarian hormones, such as in oral contraceptives (OCs). More than 100 million women worldwide use OCs (10), as OC-use provides an effective option for contraception as well as for managing cycle-related physiological symptoms. While the physiological side effects of OC-use are relatively well understood (e.g., cardiovascular risk), only little research has been dedicated to the effects of OCs on behavior, brain function or their association with psychopathology [but see (11–14)]. Steep delay discounting, risk-seeking and insensitivity to loss characterize mental disorders such as attention-deficit hyperactivity disorder (15), bipolar disorders (16), or substance use disorders (17). To give but one example, substance use disorders are two times more prevalent in men than in women (18), but women show more severe illness courses [for review see Becker (19)]. In women, drug use escalates more quickly and shows patterns of bingeing more often; moreover, women have poorer outcomes regarding quitting and treatment (20, 21). Evidence from rodent and human studies suggests that effects of ovarian hormones on underlying mechanisms of decision-making contribute to these differences (as reviewed by 2): Women have higher ratings of craving and show greater subjective responses to drug stimuli in the follicular phase compared with the luteal phase. However, a recent review of the relationship between OC-use and smoking-related symptoms found only mixed results, e.g., for craving, and could not report about any published data on OC-use and smoking cessation outcomes (22). Given the fact that one out of four smokers use OCs and that OC-use is related to increased nicotine metabolism (22), further research is needed to explore hormonal treatment developments and, more specifically, to investigate potential benefit/harm and secondary effects of OC-intake.

The most widely prescribed OCs contain a synthetic estrogen (ethinyl estradiol) and a synthetic progesterone (progestin) (10). These combined formulations prevent pregnancies by inhibiting ovulation because endogenous estradiol and progesterone fluctuations are suppressed. While endogenous estradiol and progesterone levels are constantly low in OC-users (23, 24), exogenous hormone levels are on a steadily high level (25). This substitution with higher-affinity, synthetic hormones has been shown to lead to structural brain differences in OC-users compared with naturally cycling women: e.g., OC-users had smaller right putamen volumes (26) as well as lower thickness of the lateral orbitofrontal cortex and the posterior cingulate cortex (27). Especially the lateral orbitofrontal cortex region is essential for the cognitive control of behavior, including response inhibition to stimuli with changing reward value (28). Besides its impact on brain structure, OC-use has also been found to increase resting state functional connectivity in the salience network, central executive network, reward network, as well as in the subcortical limbic network (26), which provides a mechanistic insight for putatively altered value-based decision-making in OC-users.

Overall, results from studies investigating the impact of OCs on value-based decision-making are mixed [for review, see Lewis et al. (29)]. OC-users were more sensitive to monetary rewards and had enhanced blood-oxygen level dependent (BOLD) responses during reward expectation in the anterior insula and inferior prefrontal cortex compared with naturally cycling women (30). Another study found greater neural activation in the amygdala, putamen, and executive frontal areas to food stimuli in OC-users compared with naturally cycling women in the follicular phase, but no differences between OC-users and naturally cycling women in the luteal phase (31). However, these studies were limited by their small sample size [N = 24; (30)] or lack of behavioral outcome measures (31). Two other studies found blunted reward responses in OC-users compared with naturally cycling women: Scheele et al. (32) reported enhanced attractiveness ratings of the partner's face together with increased BOLD responses in nucleus accumbens and ventral tegmental area in naturally cycling women after oxytocin administration, but not in OC-users. Jakob et al. (33) found that only naturally cycling women showed a significant effect of polymorphisms of the dopamine transporter (DAT1-genotype) on reinforcement learning, while OC-using women did not show any such behavioral variations according to DAT1-genotype differences. Especially the latter study provides a first hypothesis about how decision-making processes may be affected by the interaction

between ovarian hormones and neurotransmitter systems involved in decision-making, namely the dopaminergic system. Based on these previous studies, we expect OC-users to show differences in value-based decision-making compared with naturally cycling women. However, we cannot hypothesize the direction of this difference, i.e., if OC-users show more or less impulsive decision-making compared with naturally cycling women.

To this end, we investigated value-based decision-making in women using OCs and compared this group with two other groups of naturally cycling women with different hormonal profiles. In this study, three groups of women underwent a value-based decision-making test battery (34), which measured different facets of value-based decision-making: delay discounting, risk-seeking for gains/losses, and loss aversion. The three hormonal profile groups comprised (1) women using OCs (active pill intake, OC group), (2) women in the early follicular phase (days 2-5 of their cycle, fNC group), and (3) women during the periovulatory phase (± 3 days around ovulation, oNC group). Based on the literature reported earlier, we hypothesized (a) less impulsive choices in the fNC group compared with the oNC group, and (b) differences in value-based decision-making between the OC-group and both naturally cycling groups; the direction of this difference, however, remained exploratory.

MATERIALS AND METHODS

Sample Description

A total of 67 healthy female students were recruited from the University of Tübingen and participated in the study. We excluded five participants: three women did not show a luteinizing hormone (LH) surge in the predefined time frame, two women used progestogen-only contraception or recently switched the OC brand. The remaining 62 participants formed three hormonal profile groups, (1) the OC group (n = 22, mean age = 22 ± 2), (2) the fNC group (n = 20, mean age = 22 ± 3), and (3) the oNC group (n = 20, mean age = 24 ± 4). Inclusion criteria were 18-35 years of age, no history of any neurological or mental disorders and no (other) hormonal treatment within the past three months. For the OC group, we included women using monophasic OCs (containing a synthetic estrogen and a synthetic progesterone; an overview of the oral contraceptives and their compounds used by the study participants can be found in **Supplementary Table 2**) for at least six months (mean duration: 3.3 years ± 1.7 years) and measured them during their active pill intake phase (days 2-21). Inclusion criteria for the fNC and oNC groups were an average cycle length of 21-35 days and no hormonal contraception for the past six months. We tested women in the oNC group during their fertile period, i.e., ± 3 days around the detection of the LH peak (predicting ovulation within 2 days, using NADAL hLH ovulation strips, nal von minden GmbH, Moers/Germany). Women in the oNC group reported the first day of bleeding after the measurement to confirm the test results. We measured women in the fNC group on days 2-5 of their menstruation. All women were comparable in age, verbal intelligence, and executive functioning. **Table 1** shows all sociodemographic and neuropsychological characteristics as well as the serum hormone profiles.

Experimental Procedure

After we received written informed consent from participants, we checked all inclusion and exclusion criteria and asked for menstrual cycle features, OC intake history, as well as gynecological characteristics (e.g., premenstrual syndrome, pregnancies, endometriosis, polycystic ovary syndrome etc.). The German version of the Structured Clinical Interview

TABLE 1 | Sample description (mean and standard deviation) and hormone profiles per hormonal profile group.

Demographic information and questionnaires	OC	fNC	oNC	*p*-value
N	22	20	20	
Age (years)	22 (2)	22 (3)	24 (4)	.208
Impulsiveness (BIS-15)	29.0 (6.4)	28.7 (5.1)	33.0 (7.0)	**.058**†
State anxiety (STAI)	34.9 (9.6)	33.2 (4.8)	33.1 (7.0)	.99
Positive mood (PANAS)	31.9 (6.0)	31.2 (6.2)	30.3 (7.2)	.72
Negative mood (PANAS)	13.8 (4.2)	12.9 (4.0)	12.7 (4.6)	.44
Verbal intelligence (WST)	31.8 (3.2)	32.5 (2.4)	31.7 (3.6)	.69
Executive functioning (TMTB-A in sec)	15.5 (9.5)	15.1 (13.5)	16.2 (12.5)	.96
Hormone profiles	**OC**	**fNC**	**oNC**	***p*-value**
Estradiol (pmol/l)	67.0 (30.1)	165.9 (45.8)	516.7 (352.2)	**<.001**, OC = fNC < oNC
Progesterone (nmol/l)	1.3 (0.7)	2.1 (0.9)	6.6 (8.0)	**<.001**, OC = fNC < oNC
Testosterone (nmol/l)	0.8 (0.2)	1.1 (0.3)	1.2 (0.3)	**<.001**, OC < fNC = oNC
SHBG (nmol/l)	182.0 (107.1)	65.1 (33.0)	53.9 (23.2)	**<.001**, OC > fNC = oNC

OC, women using oral contraceptives; fNC, naturally cycling women in the early follicular phase; oNC, naturally cycling women during periovulatory phase; BIS-15, German short version of the Barrat Impulsiveness Scale; STAI, State-Trait Anxiety Inventory; PANAS, Positive and Negative Affect Scale; WST, Wortschatztest; TMTB-A, Trail Making Test; SHBG, sex hormone binding globulin; bold values indicate statistically significant differences; †*Marginally significant.*

[SCID; Wittchen et al. (35)] was used to exclude any history of mental disorder. Neuropsychological tests comprised verbal intelligence [Wortschatztest WST; Schmidt and Metzler (36)] and executive functioning [trail making test TMT; Reitan (37)]. Affective functioning was assessed with the Positive and Negative Affect Scale [PANAS; Watson et al. (38)], state anxiety with the State-Trait Anxiety Inventory [STAI; Laux et al. (39)]. Impulsiveness was assessed with the German short version of the Barrat Impulsiveness Scale [BIS-15; Meule et al. (40)]. Thereafter, participants underwent the value-based decision-making battery (34), as well as two other behavioral tasks (Tübinger Empathy Test and a sexual approach avoidance task; reported in (41). The Ethics committee of the Medical Faculty of Tübingen approved the study.

Value-Based Decision-Making Battery

The value-based decision-making battery measured different facets of impulsive choice, which were implemented in four tasks: delay discounting, probability discounting for gains, probability discounting for losses, and mixed gambles (34).

Participants repeatedly had to decide for one of two offers, which were presented simultaneously on a computer screen for 5 seconds. Offers were randomly assigned to the left or to the right of the screen and participants had to decide by pressing the respective button. For each trial, the participant's choice was indicated with a frame before presenting the next offer. The test battery took about 20 minutes. All task choices were hypothetical and participants were not informed about outcomes. Since hypothetical monetary rewards have been shown to produce similar results as real monetary rewards [e.g., (42, 43)], participants were paid a fixed amount of money for compensation after completing the test battery.

The delay discounting (DD) task consisted of 50 trials in which participants had to choose between a smaller, immediate amount of money and a larger, later amount (3-50 €; delays of 3 days, 1 week, 2 weeks, 1 month, 2 months, 6 months or 1 year). This task measured the extent to which individuals discount rewards as a function of delay, where stronger discounting is described by higher k values.

In the probability discounting for gains (PDG) and probability discounting for losses (PDL) tasks, participants had to decide between a small, but sure gain or loss of money and a larger amount of money with changing probabilities (3-50 €, probabilities of 2/3, 1/2, 1/3, 1/4, 1/5; 50 trials respectively). The PDG task measured risk-aversion, described by the preference for sure over probabilistic amounts, which is indicated by higher k values. Higher k values in the PDL task describe a preference for the probabilistic offer over the certain one and therefore captured risk-seeking.

In the mixed gambles (MG) task, participants had to gamble for winning (1-40 €) or losing (5-20 €) money or to reject to gamble over the course of 50 trials. This task measured loss aversion. Higher λ values resulted from participants who tended to reject gambles and therefore weighed losses relatively higher.

The tasks used a trial-by-trial adaptive Bayesian approach, that allows an efficient and precise estimation of the impulsive choice parameters k or λ (34). After each trial, the individual indifference point is estimated based on previous choices and informs the options in the next trial. Additionally, a consistency parameter β was computed for each task. Large values of β describe consistent choices, i.e., a higher probability of choosing the option with a higher value; small values of β represent inconsistent choices. The mathematical modeling and parameter estimation for the four tasks can be found in the **Supplementary Material**, together with the posterior distributions of the estimated parameters k and λ.

The value-based decision-making battery, including instructions, binary choices, outcomes, and the parameter estimation algorithm was implemented using MATLAB, Release 2010a (The MathWorks, Inc., Natick, MA) and Psychotoolbox 3.0.10, based on the Psychophysics Toolbox extensions (44, 45).

Hormone Sampling and Analysis

Blood levels of estradiol, progesterone, testosterone, and sex hormone binding globulin (SHBG) were assessed to confirm cycle phase and inter-individual differences in sex steroid concentrations. Samples were analyzed using chemiluminescence immunoassays (CLIA; Centaur, Siemens). Measurement units were nmol/l for progesterone, testosterone and SHBG, and pmol/l for estradiol. The analytical sensitivity of the assays is 27.2 pmol/l for estradiol, 0.67 nmol/l for progesterone, 0.09 nmol/l for testosterone, and 1.6 nmol/l for SHBG. For the intra-assay accuracy, the maximum coefficient of variation is 11.1% for estradiol, 12.4% for progesterone, 8.5% for testosterone, and 3.8% for SHBG. The reported overall variation of the assays is 13.3% for estradiol, 12.7% for progesterone, 12.6% for testosterone, and 6.5% for SHBG.

Data Analysis

Analyses were conducted using R version 3.6.2 (46), using parametric statistical methods with two-tailed significance at $p < .05$. We used log transformations of k, λ, and β to fulfill the assumptions of parametric testing; BIS-15 total scores were centered to the mean. Mean differences between groups in age, questionnaire data, and hormonal profiles were analyzed using univariate ANOVAs. Each task of the battery (DD, PDG, PDL, and MG) was analyzed in separate univariate ANOVAs, with *group* (OC, fNC, and oNC) as between-subjects factor and η_p^2 as a measure of effect size. In an exploratory analysis, we also included BIS-15 scores as covariate. We used Pearson's r to characterize the correlations between k/λ and β. We conducted a sensitivity power analysis using G*Power version 3.1.9.4 (47) to calculate the critical population effect size with 80% power. Our remaining sample ($N = 62$) was sufficiently powered to detect a small to medium effect ($f^2 = 0.21$).

RESULTS

Demographics and Hormone Concentrations

The hormonal profile groups did not differ in age, mood and anxiety scores, verbal intelligence, and executive functioning (**Table 1**). Impulsiveness differed marginally between groups, as

measured with the BIS-15 questionnaire, $F(2,59) = 2.99$, $p = .058$. Hormone concentrations varied as expected across the hormonal phases which were examined (**Table 1** and **Figure 1**): estradiol, $F(2,59) = 28.08$, $p < .001$, progesterone, $F(2,59) = 7.95$, $p < .001$, testosterone, $F(2,59) = 15.95$, $p < .001$, and SHBG, $F(2,59) = 23.28$, $p < .001$ (**Supplementary Table 3** contains single serum hormone profiles for all participants).

Delay Discounting

Running a one-way ANOVA with *group* as between-subjects factor, we found no significant group effect for the DD task, $F(2,59) = .59$, $p = .560$, $\eta_p^2 = .019$ (**Figure 2**). Adding BIS-15 as a covariate did not show any association with parameter k (delay discounting), $F(3,58) = .42$, $p = .738$.

To substantiate the null effect observed in the DD task, a Bayesian analysis approach using the Bayesian information criterion BIC (as described by 48) was applied to allow for the evaluation of the probability of the null hypothesis being true (i.e., that there is no difference between the groups). We provide a detailed description of the approach in the **Supplementary Material**. Bayesian analyses revealed that the probability of the null hypothesis was $p_{BIC} = .97$. According to criteria suggested by Masson [see also (49)], this reflects strong evidence for the null hypothesis (.50-.75 weak,.75-.95 positive,.95-.99 strong, >.99 very strong).

Correlation analyses showed significant correlations of k and β for the fNC ($r = -.48$, $p = .033$) and oNC ($r = -.51$, $p = .021$) groups, but not for the OC group ($r = -.02$, $p = .919$; **Figure 3**). In other words, stronger discounting correlated with more inconsistent choices for the naturally cycling groups (fNC and oNC), but not for the OC group. However, the correlation coefficients between groups did not differ significantly (fNC vs. OC, $z = 1.51$, $p = .13$; fNC vs. oNC, $z = 0.12$, $p = .91$; oNC vs. OC, $z = 1.63$, $p = .1$; Bonferroni-corrected at $\alpha = .017$).

Probability Discounting of Gains

We found no significant differences between groups for the PDG task, using a one-way ANOVA with *group* as between-subjects factor, $F(2,59) = .55$, $p = .560$, $\eta_p^2 = .019$ (**Figure 2**). Adding BIS-15 as a covariate did not show any association with parameter k (risk-aversion), $F(3,58) = 1.17$, $p = .330$.

For the PDG task, Bayesian analyses revealed that the probability of the null hypothesis was $p_{BIC} = .97$. This reflects strong evidence for the null hypothesis.

Correlation analyses showed no significant correlations of k and β for any of the groups (OC $r = -.13$, fNC $r = .05$, oNC $r = -.33$; all $p > .05$).

Probability Discounting of Losses

Running a one-way ANOVA with *group* as between-subjects factor, we found no significant group effect for the PDL task, $F(2,59) = .67$, $p = .517$, $\eta_p^2 = .022$ (**Figure 2**). Adding BIS-15 as a covariate did not show any association with parameter k (risk-seeking), $F(3,58) = .44$, $p = .722$.

For the PDL task, Bayesian analyses revealed that the probability of the null hypothesis was $p_{BIC} = .97$. This reflects strong evidence for the null hypothesis.

Correlation analyses showed no significant correlations of k and β for any of the groups, (OC $r = .15$, fNC $r = -.10$, oNC $r = .14$; all $p > .05$).

Mixed Gambles

We found no significant differences between groups for the MG task, running a one-way ANOVA with *group* as between-subjects factor, $F(2,59) = 1.83$, $p = .169$, $\eta_p^2 = .058$ (**Figure 2**). BIS-15 as a covariate was significantly associated with parameter λ (loss aversion) for all three groups, $F(3,58) = 2.87$, $p = .044$, $\eta_p^2 = .071$ (**Figure 4**). This means that less impulsive participants tended to reject gambles and therefore weighed losses higher, regardless in which group they were in.

For the MG task, Bayesian analyses revealed that the probability of the null hypothesis was $p_{BIC} = .91$. This reflects positive evidence for the null hypothesis.

Correlation analyses showed no significant correlations of λ and β for any of the groups, (OC $r = -.33$, fNC $22r = -.09$, oNC $r = -.12$; all $p > .05$).

DISCUSSION

In the present study, we investigated value-based decision-making in women with different hormonal profiles. We

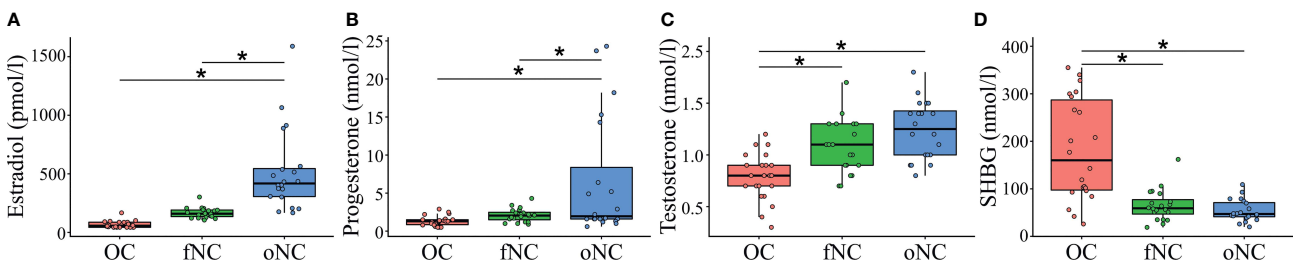

FIGURE 1 | Serum hormone profiles for each hormone profile group, showing **(A)** estradiol in pmol/l and **(B)** progesterone, **(C)** testosterone, and **(D)** sex hormone binding globulin (SHBG) in nmol/l. OC, women using OCs; fNC, women in the early follicular phase; oNC, women during periovulatory phase. Whiskers indicate variability outside the upper and lower quartiles, '*' denote significance levels at $p < .05$.

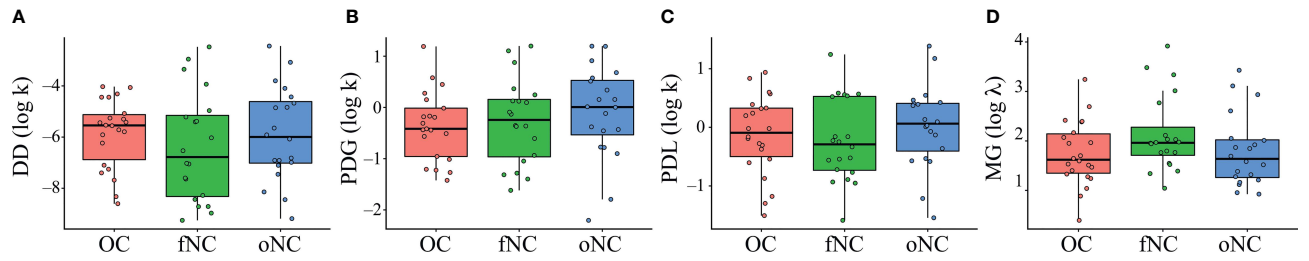

FIGURE 2 | Boxplots showing outcomes for the parameter k of the **(A)** delay discounting (DD), **(B)** probability discounting for gains (PDG), and **(C)** probability discounting for losses (PDL) tasks, and λ of the **(D)** mixed gambles (MG) task. Each dot represents an individual subject. OC, women using OCs; fNC, women in the early follicular phase; oNC, women during periovulatory phase. Whiskers indicate variability outside the upper and lower quartiles.

measured the value-based decision-making constructs delay discounting (DD), risk-seeking for gains (PDG) and losses (PDL), and loss aversion (MG). The three groups did not differ in the main outcome parameters k for the DD, PDG, and PDL tasks, and λ for the MG task. We substantiated these null effects using a Bayesian analysis approach, which reflected positive to strong evidence for the null hypothesis, i.e., that there are no differences between groups. The BIS-15 total score as a covariate was not associated with the k parameters of the DD, PDG, and PDL tasks, only with parameter λ (loss aversion) of the MG task. Here, more impulsive participants in all groups tended to reject gambles, which means that they weighed uncertain losses higher than uncertain gains. In a more exploratory fashion, we also ran correlation analyses between k and β to learn more about decision behavior. For the DD task, k and β significantly correlated for the fNC and the oNC groups, but not for the OC group. This means that in naturally cycling women, steeper discounting correlated with more inconsistent choice behavior – but not in women using OCs. Inconsistent choices describe a lower probability of choosing the option with a higher value.

Based on the current literature, we hypothesized (a) less impulsive choices in the fNC group compared with the oNC group, and (b) differences in value-based decision-making between the OC-group and both naturally cycling groups; however, the direction of this difference remained exploratory. Our results did not confirm these hypotheses. One explanation might be the relative scarcity of studies investigating value-based decision-making in different hormonal profile groups. Therefore, formulating straightforward hypotheses might have been premature. Most results so far came from small samples [e.g., Bonenberger et al. (30)], using different tasks, characterizing hormonal profile groups differently [for review, see (29)], and, in general, replication studies are missing [but see Diekhof et al. (50)]. Diekhof et al. (50) replicated results from a within-subjects design in a between-subjects design and showed that avoidance learning capacity is reduced when women were in the high estradiol state of the late follicular phase as compared to the mid luteal phase with more progesterone influence. Although this probabilistic feedback learning task differed in some aspects to the task battery used in our study, the similarity between these tasks lies in maximizing reward by choosing a certain option and, thus, falls within the concept of value-based decision-making. The study by Diekhof et al. (50) not only supports that choice behavior is influenced by hormonal fluctuations, but also confirms the use of between-subjects designs in studies investigating different hormonal states.

Still, in the present study we did not find an effect of different hormonal states on value-based decision-making, especially no difference between the naturally cycling groups and the OC group. One explanation might be a possible hormone-genotype interaction. Jakob et al. (33) investigated how estradiol levels and polymorphisms of the dopamine transporter (DAT1) interact: only naturally cycling women showed a significant effect of DAT1-genotype on reinforcement learning, i.e., a decrease in the ability to avoid punishment with rising estradiol levels in 9RP carriers, while OC-using women did not show any such behavioral variations according to DAT1-genotype differences. This hints at a first hypothesis about how decision-making processes may be affected by the interaction between ovarian hormones and neurotransmitter systems involved in decision-making, namely the dopaminergic system. In the same vein, Jacobs and D'Esposito (51) showed how the interaction between baseline dopamine and estradiol can shape prefrontal cortex dependent working memory performance across the cycle. Here, the effect of estradiol was beneficial or detrimental, depending on the catechol-O-methyltransferase (COMT) genotype, which is involved in metabolizing released dopamine. However, this coupling seems to work differently in women using OCs, leading to no observable variation in behavior (33). The hypothesis of more general differences between naturally cycling women and women using OCs is still uptrend and has been confirmed for several cognitive and behavioral processes [emotion recognition: (13, 52–54); memory performance: (55); fear conditioning and extinction: (56)], however, based on our results, it might not hold true for value-based decision-making.

Evidence increasingly points to considerable effects on brain circuitry and structure following administration of metabolic hormones in form of OC-use [e.g., (26, 27, 57)], however, we do not fully understand the action of OCs on brain and behavior.

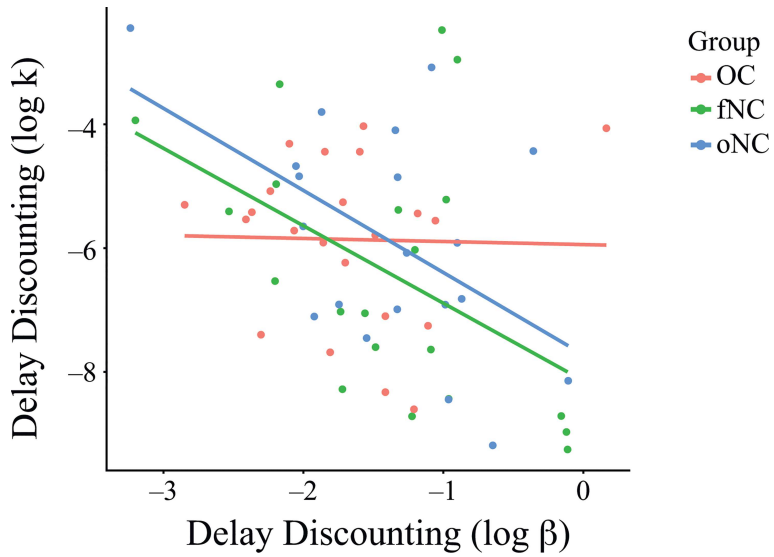

FIGURE 3 | Relationship between the parameters k and β of the delay discounting task per group. Correlation analyses showed significant correlations of k and β for the fNC (r = -.48, p = .033) and oNC (r = -.51, p = .021) groups, but not for the OC group (r = -.02, p = .919; **Figure 3**). However, the correlation coefficients between groups did not differ significantly (fNC vs. OC, z = 1.51, p = .13; fNC vs. oNC, z = 0.12, p = .91; oNC vs. OC, z = 1.63, p = .1; Bonferroni-corrected at α = .017). Each dot represents an individual subject. OC, women using OCs; fNC, women in the early follicular phase; oNC, women during periovulatory phase.

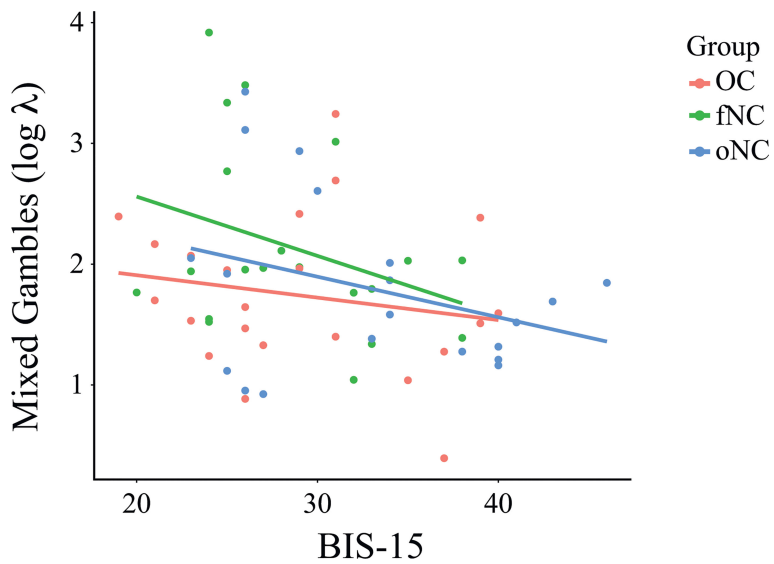

FIGURE 4 | Relationship between the parameter λ (loss aversion) of the mixed gambles task and BIS-15 total score per group. BIS-15 as a covariate was significantly associated with loss aversion for all three groups, $F(3,58)$ = 2.87, p = .044, η_p^2 = .071 Each dot represents an individual subject. OC, women using OCs; fNC, women in the early follicular phase; oNC, women during periovulatory phase.

The present null finding extends the scarce literature on OC-effects on value-based decision-making, especially on the behavioral level. Here, we found no differences between naturally cycling women and women using OCs in making value-based decisions. This result is important for understanding female-specific development, maintenance, and treatment trajectories in mental disorders which are characterized by steep delay discounting, risk-seeking, and

insensitivity to loss, as e.g., reported in patients with substance use disorders. It is just as important to know if and how OC-use impacts behavior related to mental health as well as to highlight which behavior is potentially not affected. Still, further research is needed to investigate potential benefit/harm as well as secondary effects of OC-intake on female behavior.

Limitations

Some limitations have to be noted for the present study. We only used hypothetical monetary rewards. Although hypothetical monetary rewards have been shown to produce similar results as real monetary rewards [e.g., (42, 43)], it would have also been interesting to use real monetary rewards as well as food stimuli. Moreover, we used a relatively new task approach, which has only been used by few studies so far [e.g., (58)]. However, this new approach for adaptive parameter estimation and offer presentation is quick, reliable, and outperforms the most widely used classical approaches.

Also, OC-users in our study had a quite varying mean intake duration of 3.3 years ± 1.7 years. We ruled out a possible impact of these varying intake durations on the results of our study by correlating duration of OC-use with task performance (DD r = -.16, PDG r = -.12, PDL r = .42, MG r = -.33; all p >.05).

Another limitation is that we only tested young female university students, a group with a presumably very good ability to wait for rewards in the first place. They probably did not differ much in the tested value-based decision-making facets at baseline. One solution would be to use a within-subjects design. However, Diekhof et al. (50) could replicate their results of a within-subjects design in a between-subjects design on avoidance learning capacity and therefore provide first evidence for using between-subjects designs in studies investigating influences of different hormonal states.

Another limitation concerning the study design is that we compared OC-users only with the early follicular and periovulatory phases of naturally cycling women, and not with the luteal phase. Firstly, we aimed at contrasting naturally cycling women, i.e., women with a fluctuating hormonal milieu, with women which do not have hormonal fluctuations, at least over certain period, i.e., during active pill intake. Secondly, we further divided the naturally cycling women in a group with overall low endogenous hormone levels, here the fNC group, and a group with high endogenous estradiol levels, here the oNC group, as we had specific hypotheses based on prior knowledge about the impact of endogenous estradiol on value-based decision-making [e.g., (7, 8)]. The luteal phase of the menstrual cycle shows elevated levels of both estradiol and progesterone, which makes it difficult to disentangle specific effects of either one. To this end, we decided to measure a group with overall low endogenous hormone levels (fNC group) and a group with high endogenous estradiol levels only (oNC group), and compare these groups with women with overall low endogenous hormone levels and high exogenous hormone levels (OC group). Therefore, we could ground our hypotheses about the naturally cycling groups on existing literature on estradiol effects on decision-making and focus on the rather exploratory hypotheses about OC effects in this domain. To substantiate the null findings in our study, we encourage to use larger sample sizes and measure women in a longitudinal design, e.g., a naturally cycling group measured at several time-points during the menstrual cycle in comparison with OC-users measured across a similar time-scale.

Conclusion

We investigated the impact of different hormonal profiles on the value-based decision-making constructs delay discounting, risk-aversion, risk-seeking, and loss aversion in women. The three groups – early follicular, periovulatory, and OC-using women – did not differ in the main outcome parameters. We underpinned these null effects using a Bayesian analysis approach, i.e., that there are no differences between groups. While more general differences between naturally cycling women and women using OCs have been confirmed for several cognitive and behavioral processes, it might not be the case for value-based decision-making. Understanding the influence of endogenous and exogenous hormones is important in the context of mental disorders with a focus on decision-making deficits and a known sexual dimorphism.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Medical Faculty of Tübingen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CL, NK, MS, JS, and BD designed the study. SP designed the task. CL and A-CK coordinated the study and acquired the data, which CL analyzed. NK, SP, and MS critically revised the analysis. CL wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.817825/full#supplementary-material

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The reviewer JB declared a past collaboration with one of the authors BD to the handling editor.

Supplementary Material

1 Mathematical modeling and parameter estimation of the value-based decision-making battery

Delay discounting is described by the function from Mazur (1987):

$$V = \frac{\mathrm{A}}{1 + k_0\,\mathrm{D}} \quad (1)$$

where the subjective value *V* of an outcome of amount *A*, delivered after a delay *D,* declines hyperbolically according to the discounting rate $k_0 > 0$.
With a transformation of the probability to the odds against winning *(1 – p)/p*, the same hyperbolic discounting function is used to describe subjective values of probabilistic outcomes (Rachlin et al., 1991), in our case for the probability discounting of gains and losses tasks:

$$V = \frac{\mathrm{A}}{1 + k_0 \frac{[1 - \mathrm{p}]}{\mathrm{p}}} \quad (2)$$

To estimate a behavioral measure of loss aversion, the equation

$$V = \frac{1}{2}(\mathrm{G} - \lambda\,\mathrm{L}) \quad (3)$$

was used in which loss aversion λ is the ratio of the contribution of the loss magnitude *L* to the contribution of the gain magnitude *G* to the participant's decisions (Frydman et al., 2011; Tom et al., 2007).

In the following, we describe the mathematical modeling and parameter estimation algorithm for the case of delay discounting. A Bayesian approach was used to estimate the discounting parameter *k* trial-by-trial by using choices that a person makes between a smaller immediate and a larger delayed reward.
The offers are chosen between r_1 and r_2, measured in a currency unit, and the delays are selected from the set $D = \{d_1, d_2, \ldots, d_7\}$, in days. We assume that the likelihood of choosing between the two offers follows a softmax probability function with an inverse temperature parameter, $\beta_0 > 0$,

$$\boldsymbol{P(a_d|k_0, \beta_0) = 1 - P(a_i|k_0, \beta_0).} \quad \mathbf{(4)}$$

Large values of β describe consistent choices, i.e., a higher probability of choosing the option with a higher value; small values of β represent inconsistent choices.

The parameters k_0 and β_0 are nonnegative and positively skewed. Parameters were therefore transformed to the natural-logarithmic scale and defined $k = ln(k_0)$ and $\beta = ln(\beta_0)$. The parameters space was discretized over an equally spaced 2-D region, $\boldsymbol{R}$, with $-8 \leq k \leq 2$ and $-5 \leq \beta \leq$

5. To simplify, the two parameters were assumed to be independent and liberal univariate priors were imposed on the parameters, such that *k* and *β* had a Beta and a uniform distribution. By assuming independence, a joint probability distribution *P(k, β)* served as a prior for the Bayesian framework.

Given the prior distribution, the immediate and delayed offers were presented to the participant. The prior was updated after the choice at the first trial, using Bayes's rule:

$$\boldsymbol{P(k,\beta|a) = \frac{1}{Z} - P(a|k,\beta)P(k,\beta),} \quad \mathbf{(5)}$$

With the joint distribution over the parameters $P(k,\beta)$ and the likelihood $P(a|k,\beta)$ of observing the action a, which results from Eq. 4. For every trial *t*, the posterior distribution over the parameters, $P(k,\beta|a)$, is updated by multiplying the prior by the likelihood of the participant's action and then becomes the prior for the following trial. In Eq. 5, 1/Z is a normalization factor over the discrete domain $\boldsymbol{R}$. The expected values of *k* and *β* served as current parameter estimations $\hat{k}_t$ and $\hat{\beta}_t$ at the end of each trial. By using the current estimates based on the previous choice, the upcoming offers were close to the indifference point, i.e., the probability of choosing the immediate or the delayed offer was equally likely. This approach is considered to provide the most informative data (Lewi et al., 2008; Sebatiani & Wynn, 2000).

In order to present two offers with the same subjective values, the condition

$$\boldsymbol{r_1 \leq \frac{r_2}{1+kd} \leq r_2 - \delta, \quad i = 1, \ldots, m,}$$

holds for all feasible delays, where δ is the minimum difference between the two offers. A feasible delay was chosen randomly, and the following offers were presented such that they differed at least by δ and had the same subjective values according to the current estimate $\hat{k}_t$. After a certain number of trials, *N*, the resulting $\hat{k}_N$ was considered the estimated parameter. To reduce the probability of participants learning the pattern, random offers were presented throughout the trials.

The same framework is applicable to the concepts of probability discounting of gains/losses and loss aversion.

Please refer to Pooseh et al. (2018) where, through simulations and real data, it has been shown that this method gives similar results compared to standard methods.

1.1 Posterior distributions of the estimated parameters *k* and *λ*

Supplementary Table 1. Posterior distributions of the estimated parameters *k* and *λ* for each participant (posterior means and posterior variances).

Subject ID	mean *k* DD	var *k* DD	mean *k* PDG	var *k* PDG	mean *k* PDL	var *k* PDL	mean *λ* MG	var *λ* MG
fNC_01	-6.03	0.17	-0.61	0.04	-0.56	0.16	1.39	0.05
fNC_02	-5.22	0.08	0.13	0.17	-0.16	0.04	2.77	0.21
fNC_03	-9.25	0.09	0.88	0.12	-1.59	0.15	3.34	0.06
fNC_04	-7.05	0.48	0.25	0.27	-0.52	0.40	1.95	0.08
fNC_06	-5.41	0.85	0.37	0.66	-0.16	0.12	1.55	0.17
fNC_07	-6.53	0.72	-1.31	0.11	0.58	0.23	1.79	0.04
fNC_08	-8.72	0.21	-1.62	0.23	0.56	0.60	1.04	0.01
fNC_09	-8.71	0.09	-0.13	0.05	-0.89	0.27	3.92	0.01
fNC_10	-3.93	1.63	-0.36	0.13	0.52	0.33	1.94	0.42
fNC_11	-3.35	0.28	1.11	0.45	-0.93	0.55	3.01	0.49
fNC_12	-7.64	0.25	-0.94	0.12	-0.23	0.05	2.03	0.002
fNC_13	-5.38	0.29	-0.35	0.32	-0.77	0.09	1.98	0.44
fNC_14	-2.95	0.09	-0.09	0.60	-0.95	0.04	1.97	$9.64\ e^{-5}$
fNC_15	-7.03	0.48	0.12	0.07	-0.25	0.64	1.34	0.01
fNC_16	-4.96	0.62	-1.05	0.01	1.24	0.18	1.76	0.19
fNC_17	-2.48	0.04	0.10	0.12	-0.33	0.53	2.11	0.07
fNC_19	-8.43	0.22	-1.28	0.27	0.57	0.37	1.52	0.26
fNC_20	-8.28	0.38	-0.37	0.10	0.54	0.22	1.77	0.003
fNC_21	-8.97	0.09	1.20	0.003	-0.72	0.34	3.48	0.03
fNC_22	-7.60	0.37	-1.40	0.04	-0.54	0.02	2.03	0.02
OC_01	-4.03	0.27	-0.42	0.05	-0.19	0.11	1.33	0.18
OC_02	-7.40	0.65	-1.22	0.75	-1.30	0.17	1.64	0.36
OC_03	-5.79	0.31	-0.17	0.56	-0.87	0.23	2.42	0.27
OC_04	-6.23	0.33	NA	NA	0.39	0.12	1.47	0.04
OC_06	-5.91	0.51	-0.57	0.02	0.24	0.02	2.07	0.02
OC_08	-4.44	0.14	-0.18	0.67	0.57	0.26	0.88	0.16
OC_09	-5.53	0.59	-0.96	0.62	-0.02	0.01	1.95	0.05
OC_10	-5.08	1.11	-1.42	0.13	-0.31	0.34	1.40	0.03
OC_11	-7.25	0.16	-0.19	0.007	-0.16	0.19	1.04	$9.67\ e^{-4}$
OC_12	-4.06	0.02	0.28	0.34	0.84	0.28	1.96	0.003
OC_13	-5.30	1.70	-1.21	0.66	-0.02	0.45	1.59	0.02
OC_15	-7.10	0.28	-0.44	0.02	-0.37	0.10	2.38	0.05
OC_16	-5.26	0.65	-0.31	0.50	0.33	0.38	1.24	0.005
OC_17	-8.33	0.29	0.58	0.66	-1.51	0.70	3.24	0.16
OC_18	-5.56	0.11	-0.51	0.06	0.32	0.12	1.70	$4.67\ e^{-4}$
OC_19	-5.44	0.17	-0.01	0.07	-0.28	0.02	2.17	0.23
OC_20	-4.44	0.42	0.15	0.28	-0.60	0.26	2.39	0.24
OC_21	-5.72	0.75	0.45	0.16	-1.18	0.09	2.69	0.12
OC_22	-5.42	1.14	-1.01	0.14	-0.54	0.40	1.53	0.002
OC_23	-8.60	0.21	-0.44	0.39	0.60	0.26	0.39	0.04

Subject ID	mean *k* DD	var *k* DD	mean *k* PDG	var *k* PDG	mean *k* PDL	var *k* PDL	mean *λ* MG	var *λ* MG
OC_24	-4.31	0.55	1.19	0.49	0.94	0.12	1.51	0.19
OC_25	-7.68	0.47	-1.27	0.02	0.20	0.11	1.28	0.02
oNC_01	-7.10	0.41	0.58	0.11	-0.53	0.35	1.38	0.05
oNC_02	-5.91	0.09	-0.38	0.07	-0.57	0.10	2.61	0.28
oNC_04	-6.91	0.20	-0.43	0.05	-1.54	0.03	1.69	0.004
oNC_05	-8.45	0.19	0.68	0.50	-0.13	0.45	3.11	0.18
oNC_06	-6.08	0.19	-0.78	0.21	0.42	0.19	1.21	0.04
oNC_07	-4.09	0.20	-0.12	0.37	0.09	0.82	0.95	0.07
oNC_08	-2.44	2.11	0.16	0.11	0.55	0.02	1.28	0.25
oNC_09	-7.45	0.25	0.91	0.56	1.39	0.03	1.92	0.44
oNC_11	-4.67	0.55	0.34	0.52	-0.58	0.12	2.94	0.02
oNC_12	-3.08	0.14	0.16	0.001	0.01	0.17	2.01	0.01
oNC_13	-9.19	0.11	1.20	0.03	0.40	0.25	1.52	0.07
oNC_14	-4.43	0.04	0.51	0.08	0.03	0.39	1.85	0.09
oNC_17	-4.84	0.32	-0.90	0.60	0.37	0.64	0.92	0.18
oNC_18	-6.91	0.41	-1.79	0.04	1.18	0.17	1.32	0.05
oNC_19	-8.14	0.05	0.01	0.33	0.39	0.004	1.12	0.03
oNC_20	-6.82	0.14	1.19	0.68	-1.21	0.13	3.43	0.05
oNC_22	-5.65	0.81	-0.46	0.50	-0.36	0.53	1.87	0.01
oNC_23	-4.85	0.27	0.002	0.66	0.46	0.29	2.05	0.42
oNC_24	-3.80	0.47	-0.77	0.03	-0.07	0.29	1.16	0.07
oNC_25	-6.99	0.25	-2.20	0.01	0.13	0.09	1.58	0.04

2 Bayesian alternative to null-hypothesis significance testing using the Bayesian information criterion

The approach described by Masson (2011) provides evidence regarding which model, i.e., effect absent (null hypothesis) vs. effect present (alternative hypothesis), is more strongly supported by the data. This is in contrast with classic null hypothesis significance testing, which does not allow investigating the degree of support favoring the null hypothesis. This approach uses the Bayesian information criterion (BIC) approximation of Bayesian posterior probabilities introduced by Wagenmakers (2007).

First, we compute ΔBIC, by

$$\Delta BIC = n\, ln\frac{SSE_1}{SSE_0} + (k_1 - k_0)\, ln(n) \quad (1)$$

where SSE_1 and SSE_0 are the sums of squares for the error terms in the alternative and the null hypothesis models. The term SSE_1/SSE_0 is simply the complement of partial eta-squared η_p^2, an effect size measure which describes the proportion of variability accounted for by the independent variable ($SSE_1/SSE_0 = 1 - \eta_p^2$). The term $k_1 - k_0$ corresponds to the difference in the number of free parameters between the two models, i.e., the degrees of freedom associated with an effect when null and alternative hypotheses are contrasted.

The ΔBIC value can then be used to generate an estimate of the Bayes factor

$$BF = \frac{p_{BIC}(D|H_0)}{p_{BIC}(D|H_1)} = e^{(\Delta BIC)/2} \quad (2)$$

In a final step, the Bayes factor is converted into the posterior probabilities for the two competing hypotheses

$$p_{BIC}(H_0|D) = \frac{\mathrm{BF}}{\mathrm{BF} + 1} \quad (3)$$

Given the fact that posterior probabilities will not always clearly favor one hypothesis over the other, it is recommended to use the convention for labeling the strength of evidence provided by Raftery (1995). Here, p_{BIC} values of .50-.75 are considered as weak, .75-.95 as positive, .95-.99 as strong, and >.99 as very strong.

Please refer to Masson (2011) for example applications of the approach and an Excel worksheet for computing p_{BIC} values.

3 Oral contraceptives used by the study participants

Supplementary Table 2. Overview of the oral contraceptives and their compounds used by the study participants.

Generation	Compounds	Androgen/Antiandrogen	Used by participants
2nd	Ethinylestradiol (20-30 µg), Levonorgestrel, Norethisteron	androgen	11
3rd	Ethinylestradiol (20-30 µg), Desogestrel, Gestoden,	neutral	1
4th	Ethinylestradiol (20-30 µg), Drospirenon, Chlormadinon, Dienogest, Nomegestrol	antiandrogen	10

4 Serum hormone profiles for all participants

Supplementary Table 3 Serum hormone profiles for all participants. Measurement units were pmol/l for estradiol and nmol/l for progesterone, testosterone and serum hormone binding globulin (SHBG).

Subject ID	Age	Estradiol	Progesterone	Testosterone	SHBG
fNC_01	22	137	2.00	1.10	51
fNC_02	20	185	1.20	1.10	70
fNC_03	27	170	4.30	1.30	64
fNC_04	19	117	1.60	1.10	26
fNC_06	23	149	3.40	1.70	95
fNC_07	20	140	2.80	0.90	55
fNC_08	25	204	1.70	1.00	90
fNC_09	24	209	1.00	0.70	94
fNC_10	24	127	0.90	0.80	56
fNC_11	29	121	1.20	0.80	19
fNC_12	20	184	2.20	1.30	35
fNC_13	21	157	2.10	1.30	67
fNC_14	22	207	1.80	1.20	51
fNC_15	25	122	1.00	0.90	73
fNC_16	19	137	2.70	1.70	60
fNC_17	22	302	2.40	1.30	34
fNC_19	24	190	2.40	0.90	106
fNC_20	19	193	2.20	1.40	162
fNC_21	22	161	1.90	0.70	58
fNC_22	19	105	3.10	1.00	35
OC_01	23	91	1.40	0.70	103
OC_02	24	87	2.90	1.00	42
OC_03	23	43	1.10	0.70	300
OC_04	21	43	1.20	0.40	96
OC_06	24	43	1.60	0.60	201
OC_08	20	65	1.20	0.60	93
OC_09	19	87	1.30	0.80	261
OC_10	24	101	2.30	1.10	26
OC_11	19	86	2.20	1.20	119
OC_12	21	47	1.30	0.90	105
OC_13	20	43	1.40	0.80	294
OC_15	22	62	1.50	0.90	208
OC_16	24	43	0.50	0.30	266
OC_17	23	43	2.50	0.80	340
OC_18	20	167	1.30	0.90	102
OC_19	19	43	0.50	1.00	355
OC_20	22	95	1.00	1.10	56
OC_21	23	52	0.60	0.70	177
OC_22	22	53	1.50	0.90	143
OC_23	25	48	0.50	0.80	304

OC_24	25	71	0.80	0.50	84
OC_25	24	60	0.80	0.70	328
oNC_01	23	403	1.70	0.80	44
oNC_02	27	1589	1.60	1.00	44
oNC_04	29	564	2.20	1.50	79
oNC_05	18	307	1.60	1.60	48
oNC_06	19	436	2.90	1.40	93
oNC_07	24	889	4.90	1.40	26
oNC_08	25	206	1.60	1.50	30
oNC_09	25	538	6.40	1.40	46
oNC_11	29	515	1.30	1.30	74
oNC_12	27	1065	1.00	0.90	109
oNC_13	21	167	1.60	1.00	20
oNC_14	22	401	15.30	0.90	58
oNC_17	23	201	1.60	1.40	43
oNC_18	25	302	5.20	1.20	39
oNC_19	29	913	0.60	0.90	79
oNC_20	18	485	18.20	1.50	70
oNC_22	26	370	23.70	1.00	50
oNC_23	22	176	1.20	1.80	48
oNC_24	21	432	14.30	1.10	42
oNC_25	19	374	24.30	1.20	35

3. Discussion

3.1. Serotonergic modulation of reward responsiveness

Reward responsiveness is reflected in neural activity to reward and punishment cues, which regulates responses to positive and negative reinforcers, their receipt as well as processes following repeated receipt of reinforcers (National Advisory Mental Health Council Workgroup on Changes to the RDoC Matrix, 2018). Reward responsiveness can be disrupted in several mental disorders. One prominent example is a blunted hedonic response to rewards and/or an enhanced sensitivity to punishment, which describes a negative bias in reward responsiveness that is common in major depressive disorder (Eshel & Roiser, 2010), obsessive-compulsive disorder (Fullana et al., 2004), or eating disorders (Monteleone et al., 2018). Although a negative bias in reward responsiveness describes a transdiagnostic symptom in several disorders, there are almost no trials specifically focused on pharmacological treatment of this motivational deficit (Husain & Roiser, 2018).

To this end, it is important to (1) understand basic mechanisms of reward responsiveness on a neurobehavioral level, and (2) extend our knowledge of neurotransmitters and modulators involved in reward responsiveness to develop treatments specifically targeting motivational deficits. In study 1, we found reduced BOLD responses to punishment cues in the right caudate nucleus and the right thalamus after acute administration of the SSRI escitalopram. We found no changes in BOLD response to reward cues, which pointed to serotonin's role in aversive processing only. The SSRI-induced modulation of functional responses to negative reinforcers targeted brain areas typically involved in processing loss, an important process in negative bias.

Psychological and neurocognitive approaches consider negative biases of information processing to play a key role in maintaining motivational deficit symptoms (for review see Harmer et al., 2017). Studies investigating the effect of SSRIs on negative biases in emotional processing in patients found that already acute single doses of SSRIs have a normalizing effect on responses to negative emotional stimuli (e.g., Godlewska et al., 2016; Harmer et al., 2009). Importantly,

these effects on emotional processing are seen much earlier than changes in mood, which substantiated the hypothesis that reducing negative biases contributes and eventually leads to improvements in mood (Harmer et al., 2017). A blunted response to rewards as well as enhanced sensitivity to punishment similarly describes a negative bias in reward processing, which is common in several mental disorders (Eshel & Roiser, 2010). However, the effect of SSRIs on the negative bias in processing rewards is far from clear (Husain & Roiser, 2018). We provide additional support for the neuropsychological theory of acute SSRI action and extend those findings for negative biases in reward processing.

In study 1, we replicated the finding that serotonin modulates processing of punishment cues in brain areas which have been identified as transdiagnostic neural markers of disrupted reward responsiveness (Zhang et al., 2016). We contributed to the understanding of acute SSRI effects in the healthy human brain to the processing of negative bias in reward responsiveness. In general, and in accordance with the RDoC framework, this study aimed at extending our knowledge of basic mechanisms in reward responsiveness on a neurobehavioral level in healthy humans and provided a first approach for refining treatment strategies, which could be beneficial for a group of symptoms rather than for a specific disorder.

3.2. Sex-specific modulation of reward valuation

Reward valuation is based on cost-benefit weighing, in which the subjective value of a choice results from evaluation of costs (e.g., probability, delay, effort) and benefits (food, money, sex, and hedonic experience in general). Aberrant reward valuation in form of steep delay discounting, risky behavior, or insensitivity to loss are characteristic features of e.g., attention-deficit hyperactivity disorder (Jackson & MacKillop, 2016), bipolar disorders (Chandler et al., 2009), and substance use disorders (Amlung et al., 2017). Sex differences in these mental disorders do not only exist in prevalence, but also in illness progression and treatment trajectories. For example, in substance use disorders, drug use

escalates more quickly and more often tends to have bingeing patterns in women than in men (Becker, 2016; Becker & Chartoff, 2019). Evidence from animal and human studies support the hypothesis that ovarian hormones may contribute to this behavioral variability (Ambrase, Lewis et al., 2021), e.g., women show higher craving ratings and greater subjective responses to drug stimuli in the follicular phase compared with the luteal phase. Understanding basic mechanisms in cost-benefit valuations in women and men and if and how sex-specific behavioral variability in reward valuation depends on hormonal fluctuations has the potential to influence clinical decisions, e.g., scheduling a quit date during a menstrual cycle phase in which craving is expected to be less intense.

To this end, we conducted two studies to examine sex-specific and hormonal modulators of reward valuation. In study 2, we tested women and men in an effort allocation task and found that women had higher effort maintenance than men for small rewards, while effort maintenance for higher rewards was comparable between sexes. Women also reported higher wanting and exertion ratings compared with men for small rewards. To summarize, we found that sex differences in instrumental physical effort depended on reward magnitude and, thus, were explained by an elevated subjective value of small rewards in women. To conclude, these sex differences in *effort* depended on the encoding of benefits, not costs, because women and men did not differ regarding task difficulty or reward type.

In study 3, we examined sex-specific behavioral variability in reward valuation in more depth and investigated the influence of different hormonal profiles on the subconstructs *probability* and *delay* in women. We found no difference between early follicular, periovulatory, and OC-using women in the main outcome parameters of the value-based decision-making tasks. Only for delay discounting we found that steeper discounting correlated with more inconsistent choice behavior in naturally cycling women, but not in OC-users. In sum, endogenous and exogenous hormonal milieus did not lead to substantial differences in reward valuation in women.

To summarize, we found that sex is a modulator of reward valuation, whereas different hormonal states did not substantially modulate reward valuation in women. We identified which components of effort-based reward valuation differed between sexes and, thus, contributed to the understanding of basic mechanisms of reward valuation on a behavioral level. This knowledge could be beneficial for testing in clinical translation, e.g., refining PVS-based behavioral treatment strategies for women and men.

3.3. Serotonin, sex, and sex hormones as transdiagnostic modulators of PVS

Disruptions in one or more PVS constructs are shared behavioral symptoms in several mental disorders. Fractioning symptoms into PVS constructs and investigating different modulators is a main idea of the RDoC initiative. Understanding basic mechanisms already in healthy human subjects is an important first step for transdiagnostic clinical translation (Morris et al., 2022).

Anhedonia is a typical example for disrupted PVS and is a shared behavioral symptom in schizophrenia, substance use disorders, and major depressive disorder (Baskin-Sommers & Foti, 2015; Hallford & Sharma, 2019; Lambert et al., 2018). Anhedonia as a symptom itself can be reflected in deficits across all PVS constructs (Der-Avakian & Markou, 2012). Thus, in order to fully understand the underlying mechanisms of the symptom anhedonia and how it manifests in each of the above-mentioned disorders, a separate investigation of PVS constructs is crucial. By fractioning anhedonia into components referring to PVS constructs, we can see how multifaceted this reward-related motivational deficit may be. Anhedonia may affect the ability (1) to anticipate rewards (reward responsiveness), (2) to associate values and costs with rewards as well as (3) to determine the effort needed to obtain rewards (both reward valuation), and (4) to integrate this information and learn from outcomes of their actions to guide future behavior (reward learning) (Der-Avakian & Markou, 2012; Husain & Roiser, 2018). So far, computational modelling revealed that reward learning is not affected in anhedonia, but instead anticipation and valuation of rewards is blunted

(Collins et al., 2014; Huys et al., 2013). In study 1, we specifically focused on the anticipation of reward and punishment cues and found that SSRIs modulated functional responses to punishment in brain areas typically involved in anhedonia. For example, caudate and ventral striatal gray matter volume was negatively correlated with self-reported anhedonia (Harvey et al., 2007; Pizzagalli et al., 2009). Furthermore, a meta-analysis of 33 studies in major depressive disorder and 24 studies in schizophrenia identified caudate and putamen as transdiagnostic neural markers of anticipatory anhedonia (Zhang et al., 2016). The lack of biological markers by which to select treatment is a current limitation in the field (Rush & Ibrahim, 2018). The findings of study 1 contribute to the understanding of relevant PVS brain circuits and provide first indications for treatment targets.

In study 2, we found a sex-specific behavioral variability in a PVS subconstruct, which contributes to the understanding of sex differences in basic mechanisms of motivated behaviors. This finding is in accordance with recent literature in the field, e.g., a recent study found that dynamic neural correlates of PVS constructs and depressive traits were significantly different in healthy women and men (de Lacy et al., 2021). Here, intrinsic brain dynamism was positively correlated with PVS constructs in women, but not with depressive traits. In men, intrinsic brain dynamism was positively correlated with depressive traits, but not PVS constructs. Another study reported that PVS-related symptoms (operationalized as impaired motivation, impaired energy, and anhedonia) were associated with female gender and were more responsive to antidepressants such as escitalopram compared to negative valence system symptoms in depressed patients (e.g., anxiety, interpersonal sensitivity) (Medeiros et al., 2020). However, PVS-related symptoms were overall less responsive to antidepressants than other depressive symptoms, which is in accordance with the clinical observation that anhedonia is a difficult-to-treat symptom. Yet, a recent review suggests that – especially in women – targeting the reward circuitry may be most promising to alleviate anhedonic symptoms (Bangasser & Cuarenta, 2021). Taken together, current literature together with the findings from study 1 and 2 suggest that assessment of PVS-related symptoms may be of use

in clinical practice to promote symptom- and sex-specific treatment selection and prognosis.

Considering sex differences and sex hormones is important for optimizing both basic research and clinical translation (Shansky & Murphy, 2021). Modulation of the serotonergic neurotransmitter system may serve as one mechanism via which sex and sex hormones exert effects on PVS constructs. Sex hormones modulate the serotonergic system from the level of serotonin synthesis to binding and reuptake (for review, see Spies et al., 2020). For instance, serotonin transporter (5-HTT) activity offers a peripheral marker for sex and sex hormone effects on serotonin reuptake. Estradiol is by far the most thoroughly studied sex hormone in this field, whereas only few studies examined progesterone and testosterone. Yet, the effects of estradiol on serotonin are not clearly excitatory or inhibitory: Most studies found estradiol to increase serotonin expression in many brain areas, whereas some evidence showed a decrease in serotonergic activity after estradiol treatment (for review see Ambrase, Lewis et al., 2021). A pharmacologically induced reduction in estradiol levels was associated with an increase in 5-HTT binding and depressive symptoms in women (Frokjaer et al., 2015). Similarly, testosterone treatment led to an increase in 5-HTT binding in the amygdala, putamen, caudate, and median raphe nuclei, whereas antiandrogen and estradiol treatment led to a decrease in 5-HTT binding in insula and cingulate regions in transgender people (Kranz et al., 2015). Furthermore, 5-HTT levels vary across the menstrual cycle in women. 5-HTT levels were higher in the follicular than in the luteal phase, and 5-HTT binding correlated positively with estradiol levels in the early follicular phase and during ovulation (Wihlback et al., 2004). In contrast to estradiol, progesterone has been found to reliably increase serotonergic neurotransmission by regulating expression of serotonin-related genes and proteins (for review see Barth et al., 2015). Taken together, the effects of sex hormones on the serotonin system appear to be sexually dimorphic, region specific, as well as time-dependent, or more specifically cycle-dependent in women. Moreover, hormonal effects most likely do not function in isolation from each other. Sex hormone effects on the

serotonin system may be an important mechanism to understand sex differences in PVS constructs and are an area ripe for further investigation.

Understanding sex-specific and hormonal modulations of the serotonergic neurotransmitter system is also relevant for research on SSRI treatment response. There is evidence that women may respond better to SSRIs than men, based on greater reductions in depressive symptoms (Berlanga & Flores-Ramos, 2006; Joyce et al., 2003; Khan et al., 2005) (for review see Sramek et al., 2016). However, other studies found no sex differences in SSRI treatment response (Gougoulaki et al., 2021; Parker et al., 2003; Pinto-Meza et al., 2006; Thiels et al., 2005). One hypothesis is that men have a higher rate of serotonin synthesis than women, which potentially blunts the pharmacological effects of SSRIs in men (Nishizawa et al., 1997). Another line of argument is based on evidence that estradiol-induced expression of mood-related neuropeptides drives sex differences in SSRI treatment response (Unschuld et al., 2010). In general, sex differences in SSRI treatment response are still under debate. Explanations for conflicting results might be due to variance in the measurement of treatment responses (e.g., different depression scales), disregarding menstrual cycle phases in women, and not defining subgroups of symptoms (e.g., alleviation of mood or anhedonic symptoms). For instance, sex differences in SSRI treatment response may be different if alleviation of PVS-related symptoms such as anhedonia would be examined as treatment response, rather than only mood. To summarize, the serotonergic neurotransmitter system as well as response to treatments targeting this system (i.e., SSRIs) may be modulated by sex and sex hormones. A better understanding of both the discrete mechanisms and the interactions between these complex systems is necessary to understand potential differences in treatment response.

3.4. General conclusion

The RDoC initiative promotes an integrative approach to investigate basic psychological and biological mechanisms from normal to abnormal behavior. A

main goal is to identify core features relevant for a group of disorders or syndromes (Insel, 2014). My thesis builds upon the first pillar of RDoC, which takes a translational perspective: “psychopathology research should start with what is known about normative neurobehavioral processes” (Morris et al., 2022). The RDoC initiators name anhedonia as one example, which benefited from basic behavioral and neuroscience research in animals and humans and contributed to the understanding of anhedonia as multi-component phenotype across several psychiatric conditions (Arrondo et al., 2015; Freed et al., 2019) and potential driver of heterogeneity in major depressive disorder (Pizzagalli, 2014).

Disruptions in PVS constructs, i.e., common syndromes of motivation, comprise not only anhedonia, but also apathy, amotivation, avolition, abulia, anergia, and fatigue, which are associated with several mental conditions (Pelizza & Ferrari, 2009; Yuen et al., 2015), stroke (Caeiro et al., 2013), traumatic brain injury (Starkstein & Pahissa, 2014), and neurodegenerative diseases (Chow et al., 2009; den Brok et al., 2015; Zhao et al., 2016). Especially apathy and anhedonia also occur in milder forms in otherwise healthy individuals (Bonnelle et al., 2016). An important question is whether there are central aspects and neural markers which contribute to these motivational symptoms, which appear to be disabling for numerous people.

In my thesis, I focused on the PVS constructs *reward responsiveness* and *reward valuation* and contributed to the understanding of basic mechanisms of motivational aspects and neural markers. The contributions of my thesis are three-fold. (1) I replicated the finding that the caudate region is a transdiagnostic neural marker of reward responsiveness and extended our understanding of serotonergic neurotransmission in response to punishment. (2) These findings suggest a specific and acute SSRI effect on a transdiagnostic neural marker of reward responsiveness, which might be a promising treatment specifically targeting this aspect of disrupted PVS. (3) Sex appeared to be a modulator of reward valuation, but not sex hormones. Sex differences depended on the encoding of potential benefits, not costs. This may have implications for treatments targeted to components of effort-based behavior, such as behavioral activation therapy (Richards et al., 2016).

My thesis presents an example of the heuristic value of the RDoC initiative in understanding basic mechanisms of the PVS domain in terms of shared behavioral symptoms. In accordance with the RDoC initiative, my work provides a crucial next step toward (1) testing clinical translation for PVS paradigms in patients with motivational symptoms in order to personalize treatment selection and (2) considering sex as important modulator of the PVS domain.

4. Summary

The Positive Valence Systems (PVS) are a major domain of the Research Domain Criteria framework (RDoC), which aims at promoting precision medicine for psychiatry, based on a profound understanding of the psychological and biological basis of shared behavioral symptoms. The PVS domain describes basic processes of reward processing, which can be disrupted in several mental disorders, such as schizophrenia, substance use disorders, and major depressive disorder. Investigating basic mechanisms of PVS constructs is important to understand central aspects which contribute to these transdiagnostic motivational syndromes.

In my doctoral thesis, I investigated pharmacological, sex-specific, and hormonal modulators of PVS constructs. I focused on the constructs *reward responsiveness* and *reward valuation* in the context of motivational behavior in healthy humans. In study 1, I examined the neurotransmitter serotonin, and in particular a selective serotonin reuptake inhibitor (SSRI) as modulator of reward responsiveness on a neural level, using functional magnetic resonance imaging (fMRI). In studies 2 and 3, I inquired into sex-specific and hormonal modulators of reward valuation to elucidate sex-specific integration of benefits and costs on a behavioral level.

In study 1, I found that an acute SSRI dose modulated the processing of punishment cues in caudate and thalamus brain regions, which have been identified as transdiagnostic neural markers of disrupted reward responsiveness. In study 2, I identified sex differences in reward valuation, which depended on different encoding of benefits, not costs. Study 3 did not yield substantial differences in reward valuation depending on different hormonal states in women.

The RDoC initiative aims at understanding core features and modulators of shared behavioral symptoms, ranging from normal to abnormal behavior. Understanding basic mechanisms is an important first step towards transdiagnostic clinical translation. Within this scope, my work has implications for testing clinical translation of pharmacological and behavioral treatments

specifically targeted to PVS constructs, which take sex-specific behavioral variability into account.

5. German summary

Die Research Domain Criteria (RDoC) Initiative strebt Präzisionsmedizin in der Psychiatrie an, die auf einem tiefgreifenden Verständnis der psychologischen und biologischen Grundlagen von Verhaltenssymptomen basieren soll. Die Positiven Valenzsysteme (PVS) sind eine Hauptdomäne der RDoC und umfassen grundlegende Prozesse der Belohnungsverarbeitung, die bei verschiedenen psychischen Erkrankungen wie z.B. Schizophrenie, Substanzkonsumstörungen und depressiven Störungen beeinträchtigt sein können. Die Untersuchung grundlegender Mechanismen von PVS-Konstrukten trägt dazu bei, zentrale Aspekte von transdiagnostischen motivationalen Syndromen besser zu verstehen.

In der vorliegenden Doktorarbeit wurden pharmakologische, geschlechtsspezifische sowie hormonelle Modulatoren von PVS-Konstrukten in gesunden Personen untersucht. Der Fokus lag dabei auf den Konstrukten *Belohnungsreaktionsfähigkeit* (reward responsiveness) und *Belohnungsbewertung* (reward valuation). Studie 1 untersuchte den Neurotransmitter Serotonin und insbesondere einen selektiven Serotonin-Wiederaufnahmehemmer (SSRI) als Modulator der Belohnungsreaktion auf neuronaler Ebene mittels funktioneller Magnetresonanztomographie (fMRT). In den Studien 2 und 3 wurden geschlechtsspezifische sowie hormonelle Modulatoren der Belohnungsbewertung betrachtet, um Geschlechtsunterschiede in der Integration von Kosten und Nutzen auf Verhaltensebene aufzuklären.

Die Ergebnisse von Studie 1 ließen darauf schließen, dass eine akute und einmalige SSRI-Dosis die Verarbeitung von Bestrafungshinweisen in den Hirnregionen Nucleus caudatus und Thalamus modulierte, die als transdiagnostische neuronale Marker für eine gestörte Belohnungsreaktionsfähigkeit gelten. Studie 2 zeigte, dass Geschlechtsunterschiede in der Belohnungsbewertung von einer geschlechtsspezifischen Kodierung des Nutzens abhingen, und nicht der Kosten. In Studie 3 fanden sich bei Frauen keine wesentlichen Unterschiede in der Belohnungsbewertung in Abhängigkeit von Zyklusphase oder der Einnahme oraler Kontrazeptiva.

Die RDoC-Initiative zielt darauf ab, Kernmerkmale und Modulatoren gemeinsamer Verhaltenssymptome zu verstehen, die von gesundem bis zu auffälligem Verhalten reichen. Das Verständnis grundlegender Mechanismen von Verhaltenssymptomen ist ein wichtiger erster Schritt für die transdiagnostische klinische Translation. In diesem Hinblick hat die vorliegende Doktorarbeit Implikationen für die klinische Translation pharmakologischer und verhaltensbasierter Behandlungen, die speziell auf PVS-Konstrukte abzielen und geschlechtsspezifische Verhaltensvariabilität berücksichtigen.

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7. Declaration of contribution of others

A single dose of escitalopram blunts the neural response in the thalamus and caudate during monetary loss

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C. Lewis, E. Forbes, A. Villringer, and J. Sacher were responsible for the study concept and design. C. Lewis, R. Regenthal, H. Okon-Singer, E. Forbes, and J. Sacher selected the research methods. R. Regenthal and J. Sacher acquired the data, which C. Lewis, K. Mueller, J. Reinelt, and J. Sacher analyzed. C. Lewis, K. Mueller, and J. Sacher interpreted the results. C. Lewis wrote the original draft of the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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Women compared with men work harder for small rewards

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C. Lewis, B, Derntl, and N. Kroemer were responsible for the study concept and design. C. Lewis and N. Kroemer selected the research methods. A. Kühnel and N. Kroemer supervised data collection. C. Lewis performed the data analysis and A. Kühnel and N. Kroemer contributed to analyses. C. Lewis, A. Kühnel, B. Derntl, and N. Kroemer interpreted the results. M. Grahlow contributed to preparing the Methods section. C. Lewis wrote the original draft of the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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C. Lewis, N. Kroemer, M. Smolka, J. Sacher, and B. Derntl were responsible for the study concept and design. S. Pooseh designed the task. C. Lewis and A-C. Kimmig coordinated the study and acquired the data, which C. Lewis analyzed. N. Kroemer, S. Pooseh, and M. Smolka critically revised the analysis. C. Lewis, N. Kroemer, S. Pooseh, J. Sacher, and B. Derntl interpreted the results. C. Lewis wrote the original draft of the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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