Embodied emotions: The role of sex hormones in emotional processing

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List of abbreviations used in the general introduction and discussion

BPD	borderline personality disorder
E2	17β-estradiol
ER	estrogen receptor
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
HPA	hypothalamic-pituitary-adrenocortical
LH	luteinizing hormone
MET-core-2	Multifaceted Empathy Test condensed and revised version 2
MR	mineralocorticoid receptor
OC	oral contraceptive
P4	progesterone
PR	progesterone receptor
SCR	skin-conductance response
TSST	Trier Social Stress Test

Abstract

Emotion, as well as cognition, are often understood as a manifestation of brain activity. However, bodily processes are also involved in mental functioning, referring to the concept of embodiment. Embodied emotion, traditionally, implies that experiencing an emotion involves perceptual, somato-visceral, and motor aspects. Within the frame of the *Research Training Group " Situated Cognition*", we here extend the concept of embodiment by considering the role of hormones in the processing of emotional content. Importantly, hormones allow a bidirectional body-to-brain and brain-to-body coupling. The endocrine system, e.g., steroid sex hormones, produced in the gonads, send feedback to the brain by binding at their receptors. These receptors are relatively abundant in the brain regions associated with emotional processing, memory, and executive functions (i.e., amygdala, hippocampus, and prefrontal cortex). Moreover, peripheral hormone secretion is modulated via actions from the central nervous system. We intended to characterize the role of sex hormones, and partly also of stress hormones, on different components of emotion as a hormonal embodiment of emotion.

Thus, we examined emotional processing in different sex hormone-status groups. To account for different levels of sex hormones, we used a quasi-experimental approach by comparing women in different cycle phases, women using hormonal oral contraceptives (Study 1), and additionally men (in Study 2). The female menstrual cycle is characterized by fluctuating sex hormone levels. On the peripheral gonadal level, these are 17β-estradiol and progesterone. These hormones are low at the beginning of the cycle (early follicular phase). Estradiol rises towards the middle of the cycle (mid-cycle) and stays moderately high until the next cycle. Progesterone levels are high after mid-cycle in the luteal phase until the end of the cycle. Hormonal contraceptives suppress the endogenous production of estradiol and progesterone, keeping the hormone levels low during the whole cycle. Estradiol and progesterone are also present in males, however, at low levels with no sign of cyclical fluctuations.

In Study 1, we examined three independent groups of women in the mid-cycle (n = 24), in the luteal phase (n = 24), and women using hormonal oral contraceptives (n = 24). We assessed different measures of emotional processing, i. e. emotional memory, cognitive and affective empathy-related measures (emotion recognition and ratings for feeling with a protagonist´s emotion, respectively), as well as mimic and skin-conductance responses to affective stimuli. Additionally, we addressed interactions of experimental stress (cold pressor test vs. control) with sex hormones in emotional memory. Our data demonstrated the role of hormones in empathy-related measures and skin-conductance responses depending on the stimulus characteristics (valence, the gender of the protagonist). *Emotional memory* was not affected by hormone status, stressor or salivary hormone levels. In the *cognitive empathy-related measure*, women in the luteal phase, as well as oral contraceptive users, identified emotions depicted by female protagonists more accurately than those by male protagonists. On the other hand, estradiol correlated positively with recognition of emotions depicted by males in the total sample. In the *affective empathy-related measure*, oral contraceptive users rated negative emotions higher than the positive ones. Finally, in the luteal phase *skin-conductance responses* to negative stimuli

were heightened, also supported by a positive correlation with the salivary progesterone levels. The *mimic responses* remained unaffected. None of the remaining associations with the salivary hormone levels were significant. These results indicate that sex hormones modulated emotional processing by interacting with the stimulus features, as evident in the negativity bias under oral contraceptive use and in the luteal phase in the affective empathy-related measure and sympathetic autonomous reactivity, respectively. However, emotional memory and mimic activity to affective stimuli were not affected.

In Study 2, we extended the initial scope to examine the role of sex hormones and olfaction in empathy-related measures. Reports of female advantage in empathy-related measures suggest a role for sex hormones, although data are inconsistent. Studies also report similar sex differences in human olfactory perception. In rodents, olfaction is involved in detecting and integrating socially-relevant information and is modulated by the brain-actions of estrogens. Based on this background, we hypothesized that olfaction may untangle the mixed evidence regarding the relationship between sex hormones and empathy-related measures (cognitive, affective). Thus, we measured odor discrimination ability, empathy-related measures, and facial mimic activity (also associated with affective empathy-related measures) in free-cycling women in high sex-hormone phases (n = 20), oral contraceptive users (n = 19), and men (n = 21). Free-cycling women outperformed only men in the recognition of emotions depicted from the eye region. Oral contraceptive users showed higher scores in the affective empathy-related measure towards negative emotions. Free-cycling women exhibited the strongest facial mimicry (viewing female, but not male protagonists), positively associated with progesterone. Finally, the groups differed in odor discrimination, with free-cycling women outperforming men. However, odor discrimination ability and empathy-related performance were not correlated. Our results support the role of sex hormones in odor perception and empathy-related measures, to a certain extent. However, no common underlying mechanism was found.

Finally, we conducted a systematic review (Study 3) aiming to elucidate factors contributing to the inconsistent results concerning the role of sex hormones in the two most addressed areas of emotional processing, emotion recognition (empathy-related measure) and emotional memory. Thereby, we extended previous reviews that address single areas of emotion processing. Moreover, we systematically addressed the role of situational features (mainly emotion-type and/or stimulus valence). All studies included healthy women of reproductive age either in stages of their natural menstrual cycle or using oral contraceptives, and measured or at least estimated levels of ovarian sex hormones. We document the methodological diversity in the field, presumably contributing to the heterogeneity of results. We recognized the need for studies explicitly contrasting the early follicular, mid-cycle, and mid-luteal phases, as well as OC-intake and using standardized tasks. Research would take advantage of using within-subject design more frequently and account for the recognition of complex emotions.

In sum, our data suggest that sex hormones differentially modulate the cognitive and affective empathy-related performance and skin-conductance responses by interacting with situational variables, such as the emotional valence of the stimuli and the gender of the protagonist. Women in the luteal

phase and under oral contraceptive use demonstrated better recognition of emotions depicted by female protagonists. By contrast, estradiol levels positively correlated with the recognition of emotions depicted by male protagonists. Sex-hormone status main effects only manifested in the emotion recognition advantage of free-cycling women over men (Reading the Mind in The Eyes Test; Study 2). In both studies, affective empathy ratings towards negative emotions were higher in the oral contraceptive users. Moreover, although mimic activity was not associated with sex hormones, skin-conductance responses to negative stimuli were heightened in the luteal phase. On the other hand, the performance in empathy-related measures in different hormone-status groups was not related to odor discrimination ability. Additionally, the inconsistencies of the sex hormone and emotion research could be the result of variations of designs and tasks used across studies from a similar field. This is also indicated in our findings from the empathy-related measures differing in tasks and hormone-status groups in two studies. Finally, our findings provide evidence that emotional processes under sex-hormone modulation are situated, i.e., subject to the influence of the stimulus valence. Furthermore, they are embodied via coupling between the endocrine system and the brain as evident in hormone status and valence interactions in empathy-related measures and sympathetic reactivity.

1. Introduction

1.1. Overview

The lifetime prevalence of affective and stress-related disorders is about twice as high in women as in men (Maeng & Milad, 2015; Tolin & Foa, 2006). One of the approaches to understanding the underlying mechanisms is studying emotions from the embodied perspective. Traditionally, embodied emotion implies that experiencing an emotion involves perceptual, somato-visceral, and motor aspects (Wiswede et al., 2009; Niedenthal, 2007). We here extend the concept of embodiment by considering the role of hormones in the processing of emotional stimuli.

To study the role of female sex hormones (17-ß estradiol [E2] and progesterone [P4]), we take advantage of the natural phasic fluctuations of E2 and P4 during the menstrual cycle and examine women in different cycle phases, but also women using oral hormonal contraceptive (OC) that suppress natural E2- and P4 production. Moreover, in one of the studies (Study 2), we also included men and addressed testosterone actions. Additionally (Study 1), women were exposed to a stressor inducing first-wave stress response.

Taking into account that emotional processing is a multifaceted function, we measure three important aspects within the same sample, i.e., *emotional memory, empathy-related measures* (i.e., cognitive and affective), as well as and mimic and *skin-conductance responses* to affective stimuli. Additionally, the interaction of sex-hormone status and stress in emotional memory is examined (Study 1). Since hormone status played a role in empathy-related measures in Study 1, it is further investigated in women and men, also accounting for the mediating role of olfactory performance for empathy-related performance in different sex hormone states (Study 2). Finally, considering the inconsistent results in sex-hormone and emotion research, we systematically review the literature addressing hormone-status-related effects on emotion recognition (empathy-related measure) and emotional memory (Study 3).

The subsequent introduction first derives the hormonal perspective of embodiment as an extension of the traditional view of embodiment (1.2.1). Then, the pattern of sex-hormone conditions during the natural menstrual cycle, and under OC-use, and additionally stress-induced changes are described (1.2.2) followed by an overview of sex-hormone actions in the brain (1.2.3). The main areas of emotional processing are defined and the main results of the existing literature are summarized to deduce the own studies (1.2.4). Finally, the role of olfaction and sex hormones in empathy-related measures is addressed (1.3).

1.2. Embodiment of emotion

1.2.1. Traditional and hormonal perspective on embodiment

The concept of embodiment implies that an agent´s body, beyond the brain, strongly influences mental processes (Wilson & Foglia, 2011). From the perspective of embodied emotions, experiencing an emotion may involve perceptual, somatovisceral, and motor feedback aspects, which is traditionally referred to as embodiment (Wiswede et al. 2009; Niedenthal, 2007). In the embodied view, emotions

are grounded in internal systems including the motor, sensory, and autonomic nervous systems (Winkielman et al., 2015). This traditional understanding of embodiment is based on the evidence that manipulations of the afferent (sensory) and efferent (motor) features of the somatic nervous system contribute to modulating emotional states and influence how affective information is processed (for review see: Fuchs & Koch, 2014). E.g., Williams & Bargh (2008) demonstrated that temperature sensation (holding a cup of hot vs. iced coffee, hot vs. cold therapeutic pad) affected the judgment of personality traits of others (generous, caring or foe, untrustworthy), or choosing a gift for others vs. themselves. Referring to the facial feedback hypothesis, manipulations of motor responses via inhibiting vs. facilitating facial muscles involved in smiling, affected the judgment of humorous content (funny vs. not funny) (Strack et al., 1988; for registered replication report see: Wagenmakers et al., 2016; for response see: Strack, 2016). Moreover, e.g. botulinum toxin injections between the eyebrows, to hinder frowning, elevated depressive symptoms (e.g. Wollmer et al., 2012).

So far, the role of hormones is not established in the embodiment concept, although there is some evidence that certain body postures (i.e. a motor action expected to induce emotions) are associated with changes in hormonal levels. E.g., Carney et al. (2010) showed that a high-power posture (expended posture showing dominance), in contrast to low-power body posture (slumped position), was associated with decreased stress hormone (cortisol) and increased sex-hormone (testosterone) levels in saliva, as well as with feeling more powerful and in charge. Moreover, androgens (male sex hormones) played a role in the modulation of social decision-making processes (Oliveira & Oliveira, 2014). In line with the consideration of hormones in the embodiment literature, Oliveira & Oliveira (2014) noted that neuroendocrine axes are a part of the brain-body-environment coupling, where brain-to-body and body-to-brain feedback processes integrate information to allow organism`s appropriate adaptation.

Thus, bidirectional body-brain feedback processes represent a valid basis for considering the role of hormones in the embodied-emotion concept to better understand the impact of bodily processes on cognitive and affective functions.

1.2.2. Menstrual cycle, oral contraceptives, and stress responses

Studying how bodily processes that are related to sex-hormone actions affect emotional processing, requires understanding the hormonal mechanisms of the menstrual cycle and oral contraceptive use. Moreover, because of their interactions with the sex hormones, peripheral and endocrine stress responses will be introduced as well.

Menstrual cycle and oral contraceptives

The female menstrual cycle is regulated by the hypothalamic-pituitary-gonadal axis with the release of gonadotropin-releasing hormone from the hypothalamus, and of gonadotropins, i.e., luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. Steroid sex

hormones, including E2, P4, and testosterone, are primarily produced in the peripheral gonads, i.e., in the ovaries and testes (Becker et al., 2005) but also for example in the adrenal cortex.

Female sex hormones, E2 and P4, fluctuate during the menstrual cycle (Becker et al., 2005). Referring to an idealized cycle length of 28 days, the subsequent changes occur: After menstruation onset (day 1), E2 and P4 concentrations are low in the early follicular phase (approx. cycle days 1–8). During the late follicular phase (also labeled mid-cycle or peri-ovulatory, days 9–14), P4 remains low, while E2 rises to reach its peak shortly before ovulation (approx. days 13–14). Ovulation is triggered by the sudden rise of the gonadotropins, i.e., LH and FSH. P4-synthesis increases in the luteal phase initiated by the rapid LH increase at the end of the late follicular phase (Ney et al., 2019). P4-levels peak during the mid-luteal phase, accompanied by a second less prominent E2-peak. Thus, the mid-luteal phase constitutes a condition with high P4- and moderate E2-levels.

The primary source of testosterone secretion is gonads in males and the adrenal cortex in both sexes (see: McHenry et al., 2014). While the focus here is on the actions of estrogens and progesterone, we extend the scope to testosterone actions in Study 2 by adding a male participant sample, further focusing on empathy-related measures. Testosterone is also present in females via the production in the adrenal cortex. However, males have about ten times higher concentrations of testosterone compared to women.

Primarily to avoid pregnancy, hormonal contraceptives were introduced in the 1960ies. OCs were designed to change the natural production of sex hormones. Most OCs combine synthetic estrogen (i.e., usually Ethinyl estradiol) and progestins, a synthetic form of progesterone. OCs suppress the release of LH and FSH and thus inhibit the production of endogenous estrogen and progesterone. OCs prevent pregnancy by inhibiting ovulation, changing the lining of the uterus to inhibit implantation of a fertilized egg, and altering cervical mucus to hinder sperm from entering (Beltz et al, 2015).

Stress responses

Under stress, the sympathetic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis are activated. Concerning their onset, neuroendocrine changes comprising the stress response include a first-wave and a second-wave stress response (Sapolsky, Romero, & Munck, 2000). Sympathetic nervous system activation leads to *the first-wave stress response*, peaking within seconds and fading quickly after the termination of a stressor. The response includes (a) increased release of noradrenaline, dopamine, and serotonin in the brain (Joëls & Baram, 2009); (b) of corticotropin-releasing and adrenocorticotropic hormones in the hypothalamus and the pituitary, respectively; and (c) a reduced secretion of gonadotropin-releasing hormone resulting in reduced release of gonadotropins (for additional changes see: Stockhorst & Antov, 2016). In the periphery, the *first-wave stress response* includes a rapid increase in sympathetic tone and secretion of adrenaline and noradrenaline from the adrenal medulla (Sapolsky et al., 2000). *The second-wave stress response* is triggered by HPA activation. The response involves increased peripheral secretion of glucocorticoids (i.e., cortisol) from

the adrenal cortex and reduced secretion of gonadal steroid hormones (i.e., estrogens, progesterone, and testosterone) (Sapolsky et al., 2000). Glucocorticoid concentration starts slow and peaks after about 20-30 minutes. Glucocorticoids quickly pass the blood-brain barrier and exert negative feedback on the hypothalamus and the pituitary gland reducing HPA axis activity (Stockhorst & Antov, 2016).

The first-wave stress response can be elicited by physiological stressors, such as skin contact with ice-cold water using a cold pressor test developed by Hines & Brown, (1932) and successfully used in a large number of studies (e.g., Antov et al., 2013, 2015; Andreano et al., 2008; Felmingham et al., 2012; Nielsen et al., 2013, 2014).

Also, sex hormone- and stress circuits in the brain are related and set the stage for their interactions.

1.2.3. Sex-hormone actions in the brain

E2 and P4 not only regulate the female reproductive function but also contribute to cognitive and mainly affective processes via acting on genomic (nuclear) and non-genomic (transmembrane) receptors in brain areas associated with emotion, memory, and executive functions (e.g., Gasbarri et al., 2012; Sundström-Porooma, 2018). This allows bidirectional communication between the brain and the body. Estrogen receptors (ERs; α, β and G-protein coupled ERs) are located in the hypothalamus, amygdala, hippocampus, cerebral cortex, in the striatum, basal forebrain, midbrain, cerebellum, and brainstem, as well as in glial cells and central grey matter (Gasbarri et al., 2012). The ERα subtype dominates in hypothalamic regions, whereas the ERβ type is more frequent in the hippocampus and ventromedial prefrontal cortex. Progesterone acts at progesterone receptors, PR-A and PR-B, (similarly in hypothalamus and hippocampus, amygdala, frontal cortex, forebrain, midbrain, brainstem). Moreover, female sex hormones modulate synaptic transmission in the noradrenergic, dopaminergic, serotonergic, glutamatergic, and GABAergic systems and thereby affect cognitive and affective processes (Toffoletto et al., 2014).

E2 was shown to improve hippocampus-dependent memory in rodents and humans, and to stimulate neural transmission in the hippocampus while decreasing neuronal excitability in the amygdala (Womble et al., 2002; Walf & Frye, 2006; Foy et al., 1999). Correspondingly, imaging data reveal *reduced* activation of the brain-stress circuitry (covering bilateral amygdala, hippocampus, and hypothalamus), e.g., to a mild stress challenge in phases of high as compared to low E2-levels (Jacobs et al., 2015). This suggests some capacity for stress regulation via natural E2 fluctuations which were missing in women with major depressive disorder (Jacobs et al., 2015). For the high-P4 mid-luteal phase, instead, there is evidence for heightened stress responsivity. E.g., stimuli of negative valence were shown to increase activation in the brain stress-circuitry (amygdala, hippocampus) compared to the low-P4, early-follicular phase (Andreano & Cahill, 2009). However, rising P4 levels also stimulate the production of its active metabolite allopregnanolone, which binds to GABA-A receptors. Allopregnanolone effects appear to vary dose-dependently, inducing inhibitory, anxiolytic effects at

high levels and anxiogenic effects at low levels (e.g., Barros et al., 2015). Moreover, allopregnanolone exerts negative feedback effects on the stress HPA axis via GABA-ergic signaling. (Ney et al., 2019). This could explain the results of a reduced amygdala activation after exogenous administration of P4 (Wingen et al., 2007). However, further studies are necessary to disentangle its action profile.

Ethinyl estradiol and progestins in the combined OC pills act at ERs and PRs, respectively. Androgenic type of progestins (e.g. levonorgestrel, desogestrel) also activate androgen receptors, whereas antiandrogenic progestins (e.g., dienogest, drospirenone) only bind to ERs and PRs (Pletzer & Kerschbaum, 2014). Data on the neuronal effects of OCs mainly stem from human fear conditioning studies. Here, OC-users (compared to men and women in the luteal phase) show higher differential BOLD responses in fear and stress circuits as evident in higher activity to the conditioned stimulus (previously paired with the unconditioned stimulus) in the amygdala, anterior cingulate cortex, and ventromedial prefrontal cortex (Merz et al., 2012, see Stockhorst & Antov, 2016 for a review). Considering stress-hormone responsivity, OC-use is often accompanied by a blunted cortisol response to psychosocial stress as compared to men and women in the luteal phase (e.g., Kudielka & Kirschbaum, 2005).

Finally, since the brain areas containing E2- and P4-receptors also contain adrenergic receptors as well as mineralocorticoid receptors (MRs) and glucocorticoid receptors, the interactions of stress and sex hormones are of great interest.

In sum, sex hormones as well as stress hormones share brain circuits and act on corresponding receptors present in brain areas relevant for emotional processing. Thus, it should be also addressed in which way they modulate emotional processing.

1.2.4. Emotional processing and sex hormones

As early as 1884, William James proposed that emotions are physiological and behavioral responses preceding subjective experience that is characterized by "distinct bodily expression“. He defined emotion as the experience of bodily changes, which follow directly after the perception of an exciting stimulus. Emotional stimuli evoke physiological reactions, both autonomic and somatic, and the perception of these changes evoke the feeling of an emotion, so-called affect (for review see: Friedman, 2010).

Integrating various ways to describe emotion, one working definition would be that “emotion is a complex set of interactions among subjective and objective factors, mediated by neural-hormonal systems, which can (a) give rise to affective experiences such as feelings of arousal, pleasure/displeasure; (b) generate cognitive processes such as emotionally relevant perceptual effects, appraisals, labeling processes; (c) activate widespread physiological adjustments to the arousing conditions; and (d) lead to behavior that is often, but not always, expressive, goal-directed, and adaptive” (Kleinginna & Kleinginna, 1981, p. 355).

In line with this working definition, Scherer (2005) proposes five components of emotion: (a) subjective (feeling), (b) cognitive (appraisal and cognitive processing), (c) physiological aspects (bodily reactions), (d) action tendencies (motivational preparation and direction of an emotional response) and (e) motor (mimic and vocal expressions, gesture, posture, etc.).

Taking into account that emotion is a multifaceted phenomenon and manifests in various ways, (experimental) studying of emotional processing should include these different components. Moreover, these components should be assessed independently but be related to each other. As mentioned above, the cognitive component of emotion implies appraising and labeling information e.g. evident in labeling a particular input positive, negative, or neutral. One of the cognitive processes that are involved in the generation of appraisal is *emotional memory* (a). On the other hand, *empathy-related measures* provide information about different facets of empathy, e. g., cognitive (emotion recognition) as well as subjective (affective ratings) components (b). Furthermore, emotions are normally accompanied by *facial mimic expressions* and *sympathetic physiological reactivity* that belong to a motor and physiological components respectively (c).

a) Emotional memory

Memory is an essential adaptive function of our brain and entails three distinct processes: encoding, consolidation, and retrieval. During encoding, the multisensory input is integrated and processed, which leads to forming memory traces. During consolidation, memory traces are strengthened over time and stored permanently. During retrieval, the stored information is accessed to create a conscious representation of the memory trace (Gazzaniga, Irvy & Mangun, 2014).

It is well established that emotional content can affect memory processes and enhance recollection of emotional rather than neutral material as mediated by the activation of arousal systems via heightened adrenergic activity (e.g., Cahill et al. 1994). In addition to the emotional valence of the stimuli (aversive stimuli might be also stressful), it has been consistently reported that stress affects memory consolidation and recall, depending on the timing and placement of the stressor relative to memory encoding (Schwabe et al., 2012).

Some evidence suggests that variations of sex hormones during the natural menstrual cycle are associated with emotional changes. Progesterone is related to more negative affect, whereas high E2 levels are associated with a positive affect (for review see: Sundström-Poromaa, 2018).

For emotional memory, women seem to have an advantage over men recalling emotional content (Cornelisse et al., 2011, Felmingham et al., 2012). Relatively little is known about the role of high E2-phases in emotional memory, although some evidence suggests enhanced recall of positive contents in the peri-ovulatory phase (Pompili et al., 2016). So far, the effects of positive valence have been mainly investigated between OC users and non-users (Nielsen et al, 2013, 2015; Mordecai et al., 2017; Spalek et al., 2019). A larger number of studies indicates enhancing effects of P4, or the corresponding luteal phase, for recall of negative content, especially intrusions (Ferree et al., 2011; Soni et al., 2013; Ertman

et al., 2011, Ferree et al., 2009; Nielsen et al., 2015). Also, stressor administration is reported to enhance negative recall in the high P4-state (Felmingham et al., 2012, Nielsen et al., 2015). Similarly, enhanced trauma memory and subsequent intrusive recollections are facilitated by high (vs. low) P4 levels during trauma (high stress) exposure (Bryant et al., 2011; Ferree et al., 2011).

In sum, P4 is often but not always linked to negative memory bias. On the other hand, the effects of E2 on emotional memory are not well established thus far.

b) Empathy-related measures

Emotional processing also manifests in empathic behavior. There is no consensus on the definition of empathy (Preston & de Waal, 2002; Cuff, Brown, Taylor, & Howat, 2014). This concept rather entails multiple facets, including recognition of basic and complex emotions, perspective-taking, the theory of mind, mentalizing, cognitive and affective aspects, facial mimicry, factors such as state and trait, intention, etc. (Cuff, Brown, Taylor, & Howat, 2014; Neumann et al., 2015). Thus, the term "empathy-related measures" is used here to refer to different tests assessing aspects of empathy. Cognitive aspects of empathy cover one´s ability to infer another person´s mental state, whereas the affective aspect involves responding to others' emotional state with a suitable affect (Dziobeck et al, 2008). The cognitive aspect of empathy entails comprehensive recognition of emotions. Basic emotion recognition implies identifying basic emotions (happiness, fear, sadness, anger, etc.) usually measured using extreme full-face emotional expressions without any context (Derntl et al., 2008a; 2008b; 2013). Whereas, complex emotion recognition is often referred to as cognitive empathy (overlapping with mentalizing, the theory of mind) and can be measured using images depicting human facial expressions of emotion in a context (Dziobeck et al., 2008) or even using eye pairs expressing complex emotions (Baron-Cohen et al., 2001).

Cognitive empathy-related measures here are referred to as basic and complex facial emotion recognition. Notably, cognitive empathy-related measures are far more often addressed in sex–hormone research than affective empathy-related measures (affective response to others' emotions). In emotion recognition studies, positive (vs. negative) emotions are better differentiated (Derntl et al., 2008a, 2013; Zhang et al., 2015; Pahnke et al., 2019) and female (vs. male) facial expressions are better identified (Guapo et al., 2009). Data on emotion type and hormone status interactions suggest that naturally fluctuating levels of sex hormones are associated with facilitation or impairment of recognition depending on the *specific* emotions. E.g., for negative emotions, E2 levels were associated with better fear recognition (Pearson & Lewis, 2005; Guapo et al., 2009), as well as, with sadness and happiness recognition (Hamstra, de Kloet, Quataert, Jansen, & Van der Does, 2017). On the other hand, OC use appears to be associated with an impaired recognition accuracy of basic emotions, mainly negative emotions (Hamstra et al., 2014; 2016; Pahnke et al., 2019). Importantly, there is a lack of studies examining recognition of complex emotions. Data on the role of P4 is rather contradictory. Studies report impaired (Derntl et al., 2008a, 2013), as well as improved emotion recognition under high vs. low

P4-levels (Conway et al., 2007). Little is known so far about sex-hormone actions and affective empathy-related measures. Data only indicates higher affective reactivity in their pill-on vs. pill-off phase in OC users (Radke & Derntl, 2016).

Apart from elucidating mixed results, complex emotion recognition and affective empathy-related measures deserve more attention when examining the sex-hormone status-related modulations, especially to understand empathy in a comprehensive fashion.

c) Mimic and sympathetic physiological responses

Emotional processing is often accompanied by bodily responses such as physiological arousal and facial mimic responses. Mimic reactions can be regarded as an explicit indicator of both, the subjective evaluation of an emotional event and empathetic processing by responding to others' emotions. *E.g., facial mimicry*, i.e., facial expressions that match the expressed emotional valence of the counterpart was shown to be stronger than baseline muscle activity during an affective empathy task (Drimalla et al., 2019). Research on sex-hormone related differences in facial mimic expression are extremely limited thus far. There are first data on the higher mimic activity of facial muscles involved in smiling to positive stimuli during low P4 states (Mass et al., 2009; Armbruster et al., 2017). Moreover, mimic expression of negative affect via corrugator activity was shown to be downregulated by E2 and P4 in the follicular and luteal phases respectively (Armbruster et al., 2018). Further research should elucidate the role of sex hormones in mimic activity to emotional stimuli and thus further contribute to understanding of the embodiment of emotions from the hormonal perspective.

1.3. Role of olfaction in empathy-related measures

In rodents, features of *social behavior*, including social recognition, social preferences, and social learning is strongly "olfactory-mediated" (Ervin et al., 2015). (Body) odor identification and discrimination are essential providers of social information, such as "demographics" of the encounter, emotional and motivational state (Brown, 1979; Ervin et al., 2015). Moreover, in rodents, *estrogens* are involved in different indicators of social behavior from detecting and integrating socially relevant olfactory information, up to learning and memory for social stimuli (Ervin et al., 2015), in both, males and females. Indeed, ERs are present throughout the olfactory system, allowing estrogens to modulate olfactory activity and chemical sensitivity (Ervin et al., 2015). Correspondingly, ER (α and β) knockout leads to deficits in olfactory-mediated social recognition in females (Choleris et al., 2003; 2006) as well as in males (Imwalle, Scordalakes, & Rissman, 2002).

In humans, women display a sense of smell superior to men, with better identification/discrimination and lower thresholds, although the effect sizes in a recent meta-analysis are small (Sorokowski et al., 2019). However, women show enhanced central-nervous system odor processing (Evans, Cuin, & Starr, 1995; Pause, Storch, & Lübke, 2020), and their olfactory perception advantage is the clearest during the fertile years (Hummel, Kobal, Gudziol, & Mackay-Sim, 2007). Odor

perception also varies across the menstrual cycle with evidence of increased performance around ovulation (Navarrete-Palacios, Hudson, Reyes-Guerrero, & Guevara-Guzmán, 2003). Moreover, women using oral contraceptives have a lower sensitivity for pheromone-related and musk odors than free-cycling women with high or rising E2 and P4 (Renfro & Hoffmann, 2013), and olfactory effects are associated with E2-levels (Lübke & Pause, 2014). This might indicate that E2 also improves olfaction in humans as well as explains the small effect sizes in studies that did not account for different, precisely defined menstrual-cycle phases and/or oral contraceptive use.

Human social behavior entails more complex processing, e.g., empathy-related behavior. Generally, research shows a female advantage (over men) in cognitive empathy-related performance (Wingenbach, Ashwin, & Brosnan, 2018; Wright, Riedel, Sechrest, Lane, & Smith, 2018; Hoffmann, Kessler, Eppel, Rukavina, & Traue, 2010). Fairly, sex hormones are of great interest in understanding these sex differences. According to experimental data, testosterone, when administered to women, impairs cognitive empathy-related performance (van Honk et al., 2011), as well as facial mimicry (Hermans, Putman, & van Honk, 2006), whereas E2 administration promotes emotional responsiveness in men (Olsson, Kopsida, Sorjonen, & Savic, 2016). Investigating cognitive empathy-related performance during the E2 and P4 fluctuations in the menstrual cycle yields mixed results. Women with increasing E2 and low P4 (first half of the cycle) show better basic-emotion recognition than women with high P4 and low to moderate E2 (second half) (Pearson & Lewis, 2005; Guapo et al., 2009; Derntl, Hack, Kryspin-Exner, & Habel, 2013), leading to the idea that P4 has an impairing effect. However, several studies report no differences between women in different cycle phases (Kamboj, Krol, & Curran, 2015; Dan et al., 2019; Zhang, Zou, & Ye, 2013). Finally, the suppressed production of E2 and P4 (under OC use) is often associated with impaired performance in cognitive empathy-related measures (Hamstra et al., 2014; 2016; 2017), although not supported by Shirazi et al., 2020. On the other hand, affective empathy-related performance during the menstrual cycle is poorly understood.

The inconsistencies in the sex hormone and empathy-related research might be partly due to methodological differences, and partly due to the mediating role of other variables such as odor discrimination ability. Preliminary evidence from correlational studies in humans supports a link between empathy-related measures and olfactory perception. A higher affective empathy-related score is associated with a lower olfactory threshold in women (Spinella, 2002) as well as better odor identification and discrimination in both sexes (Mahmut & Stevenson, 2016). Performance in noticing and identifying others' facial expressions is positively associated with the recognition of sociochemosensory stimuli i.e., natural body odor (Zhou & Chen, 2009). Complex emotion recognition correlates positively with odor discrimination in women, but not men (Blum, Lübke, & Pause, 2018). Furthermore, patients with dysosmia (impaired olfaction) after brain injury have reduced visual and vocal emotion recognition compared with brain-injured controls without dysosmia (Neumann et al., 2012).

Furthermore, affective empathy-related measures and accompanied facial mimicry are rarely taken into account. Therefore, investigating the role of olfaction particularly for empathy-related measures in different sex-hormone states might elucidate some of the inconsistencies.

2. Objectives

The main aim of the conducted studies was to demonstrate the role of sex hormones in emotional processing to extend the concept of embodied emotions to a hormonal perspective. To measure emotional processing, we selected several areas, i.e., *emotional memory*, *empathy-related measures*, as well as *mimic and skin-conductance responses to affective stimuli*. The evidence partly suggests the role of sex hormones but requires elucidation of inconsistent results. To account for different conditions of hormone status (relying on E2, P4, and testosterone), women in the mid-cycle and the luteal phase of the menstrual cycle, as well as hormonal contraceptive users and men were tested. Men and testosterone were addressed only in Study 2. We also addressed interactions of stress (hormones) (Study 1) and olfactory ability (Study 2) with sex hormones in emotional memory and empathy related measures, respectively.

2.1. Study 1: Sex-hormone status in emotional processing in healthy women

Emotional memory and emotion recognition (cognitive empathy-related measure) are often addressed in sex-hormone research. Importantly, some aspects of emotion, including cognitive and affective empathy-related measures for complex emotions, as well as mimic and skin-conductance responses to affective stimuli are rarely studied. Thus, Study 1 aimed to investigate the role of sex-hormone status in emotional memory, empathy-related measures for complex emotions, as well as in mimic and skin-conductance responses to emotional stimuli *within the same sample*. As a between-subject factor of hormone status, 1) mid-cycle (high E2 and low P4 state), 2) luteal phase (moderate E2 and high P4 state), and 3) OC use (low E2 and P4 state) were quasi-experimentally chosen. As an additional between-subject factor, stressor (cold pressor test vs. warm water control) effects were measured for emotional memory (post-encoding). The above emotion measures represented dependent variables from different areas of emotional processing. Furthermore, mimic and skin-conductance responses to affective stimuli were recorded. These emotion measures represented dependent variables from different areas of emotional processing. For memory encoding and stimulus-triggered mimic and skin-conductance responses, pictures from the international affective picture system were presented. To examine empathy-related performance, the cognitive and affective empathy subtests of the Multifaceted Empathy Test – condensed and revised version 2 (MET-core-2) were used (Drimalla et al., 2019; Dziobeck et al., 2008). The emotional aspect of the measures was the within-subject factor of stimulus valence (negative, positive, neutral). We tested hormone-status main effects and their interactions with the stimulus valence in the emotional memory recall, in empathy-related measures, as well as in mimic and skin-conductance responses. Additionally, stressor effects and interactions with hormone status, as well as with valence

were investigated only for emotional memory task. Finally, correlations between emotion measures and salivary E2- and P4-levels were addressed.

2.2. Study 2: The role of olfaction and sex-hormone status in empathy-related measures

We focused on empathy-related measures in Study 2. Evidence suggests an association between sex or sex hormones and both olfaction and empathy-related measures. However, data on cognitive empathy-related measures are inconsistent and studies on affective empathy-related measures are missing. Here, we addressed three main questions: Do cognitive and affective empathy-related scores vary with sex hormones? Are sex hormones related to odor perception? Is there a link between odor perception and empathy-related measures? To address these questions, we examined healthy participants in three independent *sex-hormone-status* groups: free-cycling women (examined in cycle phases with higher E2 and P4), OC users (low expected E2 and P4), and men (low E2 and P4, but high testosterone).

In this study, to address above questions we measured empathy-related performance in the hormone-status groups using (1) As *empathy-related measures*, the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001), (measuring the recognition of complex emotions depicted by eye pairs, related to the theory of mind or mentalizing), along with MET-core-2 (also in Study 1); additionally, (3) *facial mimicry*, as inferred from facial muscle responses during the presentation of the MET-core-2 material was assessed. Hormone-status group differences in odor discrimination ability was measured in a standardized test (Weierstall & Pause, 2012). The correlations between these measures and salivary hormone levels were also addressed. Finally, the link between odor discrimination ability and empathy-related measures were investigated through correlations.

2.3. Study 3. The role of sex hormones in emotion recognition and emotional memory: A systematic review

Based on the first two studies we conducted a systematic review on the emotion recognition (empathy-related) and emotional memory studies that addressed the role of sex hormones. In sex-hormone research, these two areas appear to be examined most often. With this systematic review, we aimed to address the mechanisms behind inconsistent and sometimes contradictory findings in these research areas and additionally provide the current picture of the role of sex hormones in emotion recognition and emotional memory. The focus was on healthy women of reproductive age with measured or estimated sex-hormone levels.

3. Research papers

Paper status at the time of submitting the dissertation (Dec 15, 2020)

Study 1:

Gamsakhurdashvili, D., Antov, M. I., & Stockhorst, U. (*under review*). Sex-hormone status and emotional processing in healthy women. *Psychoneuroendocrinology.*

Study 2:

Gamsakhurdashvili, D., Antov, M. I., Lübke, K. T., Pause, B. M., & Stockhorst, U. (*accepted*). The role of olfaction and sex-hormone status in empathy-related measures. *Physiology & Behavior.*

Study 3:

Gamsakhurdashvili, D., Antov, M. I., & Stockhorst, U. (*submitted*). Emotion recognition and emotional memory from the sex-hormone perspective: A systematic review. *Frontiers in Psychology.*

Paper status by the time of publishing the dissertation in the repository

Study 1:

Gamsakhurdashvili, D., Antov, M. I., & Stockhorst, U. (*in press*). Sex-hormone status and emotional processing in healthy women. *Psychoneuroendocrinology.* https://doi.org/10.1016/j.psyneuen.2021.105258

Study 2:

Gamsakhurdashvili, D., Antov, M. I., Lübke, K. T., Pause, B. M., & Stockhorst, U. (2021). The role of olfaction and sex-hormone status in empathy-related measures. *Physiology & Behavior, 230*:113289. https://doi.org/10.1016/j.physbeh.2020.113289

Study 3:

Gamsakhurdashvili, D., Antov, M. I., & Stockhorst, U. (2021). Facial emotion recognition and emotional memory from the ovarian-hormone perspective: A systematic review. *Frontiers in Psychology, 12*:641250. doi: 10.3389/fpsyg.2021.641250

3.1. Sex-hormone status and emotional processing in healthy women

Gamsakhurdashvili, D., Antov, M. I., & Stockhorst, U. (*in press*). Sex-hormone status and emotional processing in healthy women. *Psychoneuroendocrinology*. https://doi.org/10.1016/j.psyneuen.2021.105258

Abstract: Fluctuations of sex hormones across the menstrual cycle allow investigating the role of 17-β estradiol and progesterone in emotional processing. We examined emotional memory, empathy-related measures, as well as mimic and skin-conductance responses to affective stimuli in 72 women either in the mid-cycle (MC-group: moderate to high estradiol, low progesterone), the later cycle (LC-group: high progesterone, moderate estradiol), or during oral contraceptive use (OC-group: low endogenous ovarian-hormone levels). In the first session, affective pictures were presented (memory encoding) while recording mimic and skin-conductance responses. Additionally, participants were exposed to a post-encoding stressor (cold pressor test). After 24 hours, we tested surprise recall as well as empathy-related performance. *Emotional memory* was not affected by the hormone-status group, stressor, or salivary hormone levels. For the *cognitive empathy-related* measure, hormone status interacted with the protagonist gender. Women in the LC- and OC-groups identified emotions more accurately if depicted by female protagonists, yet the MC-group identified emotions depicted by men and women equally well. Correspondingly, the number of correctly identified emotions from male protagonists correlated positively with estradiol levels. In the *affective empathy-related* ratings, the OC-group showed a negativity bias, rating negative (vs. positive) emotions higher, although not associated with hormone levels. *Mimic responses* were not modulated by hormone-status group or related to hormone levels. S*kin-conductance responses* to negative pictures were heightened in the LC-group and correlated positively with progesterone levels. These data suggest a differential impact of female sex hormones on emotional processing, i.e., empathy-related performance and affective sympathetic reactivity, but not in emotional memory or affective mimic reactivity.

Keywords: Cognitive empathy, affective empathy, emotional memory, estrogen, progesterone, oral contraceptives.

Full text and online supplementary material (when published) can be found at: https://doi.org/10.1016/j.psyneuen.2021.105258

3.2. The role of olfaction and sex-hormone status in empathy-related measures

Gamsakhurdashvili, D., Antov, M. I., Lübke, K. T., Pause, B. M., Stockhorst, U. (2021). The role of olfaction and sex-hormone status in empathy-related measures. *Physiology & Behavior*, *230*:113289. https://doi.org/10.1016/j.physbeh.2020.113289

Abstract: Reports of a female advantage in empathy-related measures suggest a role for sex hormones, although the data are inconsistent. Studies also report similar sex differences in human olfactory perception. In rodents, olfaction is involved in detecting and integrating socially relevant information and is modulated by the brain actions of estrogens. We hypothesized that olfaction may untangle the mixed evidence on the relationship between sex hormones and empathy-related measures (cognitive and affective) in humans. To test this, we examined 60 healthy participants in three sex-hormone-status groups: free-cycling women tested in cycle phases with higher 17-β estradiol and progesterone, oral-contraceptive users (low estradiol and progesterone), and men. We assessed empathy-related measures, facial mimicry (from zygomaticus and corrugator muscle activity), and odor discrimination ability. In the empathy-related measures and facial mimicry, we did not find overall group effects or meaningful associations with salivary levels of estradiol, progesterone, or testosterone. Free-cycling women only outperformed men in the recognition of emotions from pictures of the eye region, but sex hormones were unrelated to emotion recognition performance. Oral contraceptive users showed higher scores in the affective empathy-related measure when viewing negative emotions, with no relation to hormone levels. Free-cycling women exhibited the strongest facial mimicry (viewing female, but not male protagonists), positively associated with progesterone. Finally, the groups differed in odor discrimination, with free-cycling women outperforming men. However, odor discrimination ability and empathy-related performance were not correlated. Our results support a role of sex hormones in odor perception and in empathy-related measures, to a certain extent. However, no common underlying mechanism was found.

Keywords: Cognitive empathy, affective empathy, olfaction, estradiol, testosterone, oral contraceptives.

Full text and online supplementary material can be found at:
https://doi.org/10.1016/j.physbeh.2020.113289

3.3. Emotion recognition and emotional memory from the sex-hormone perspective: A systematic review

Gamsakhurdashvili, D., Antov, M. I., & Stockhorst, U. (2021). Facial emotion recognition and emotional memory from the ovarian-hormone perspective: A systematic review. *Frontiers in Psychology, 12*:641250. doi: 10.3389/fpsyg.2021.641250

Abstract: **Background:** We review original papers on ovarian-hormone status in two areas of emotional processing: facial emotion recognition and emotional memory. Ovarian-hormone status is operationalized by the levels of the steroid sex hormones 17β-estradiol (E2) and progesterone (P4), fluctuating over the natural menstrual cycle and suppressed under oral contraceptive (OCs) use. We extend previous reviews addressing single areas of emotional processing. Moreover, we systematically examine the role of stimulus features such as emotion type or stimulus valence and aim at elucidating factors that reconcile the inconsistent results. **Methods:** We followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines and included papers published until September 2020 indexed in PubMed and Web of Science databases. Search terms were MeSH terms (emotional OR emotion) AND (*X*) AND (estrogen OR progesterone OR menstrual cycle OR oral contraceptives) with (*X*) representing our separately searched areas, resulting in (processing OR recognition OR empathy), and (memory OR recall). To be included, articles had to (1) be written and published in English, (2) examine healthy, non-pregnant adult women in their reproductive age, and (3) measure or at least estimate levels of E2 and P4. In PubMed, the search was (4) limited to humans and (5) to the search term present in the title or abstract. **Results:** Features of the provided stimulus material (emotion type and/or valence) constitute a relevant influence that interacts with E2- and P4-related ovarian-hormone status. For instance, recognition of basic emotions appears to be more related to P4- than E2-levels. Quite consistent, OC intake (vs. natural menstrual cycling) was accompanied by impaired recognition accuracy of basic and also complex emotions, although not in a recent large-sample study assessing complex emotions. Memory recall of negative content was mainly enhanced by P4, especially after having been stressed. **Discussion and Conclusion:** We document the methodological diversity in the field, presumably contributing to the heterogeneity of results. More studies explicitly contrasting the early follicular phase, mid-cycle phase, mid-luteal, and OC intake while standardizing tasks are needed. Research would take advantage of using within-subject designs and accounting for the recognition of complex emotions.

Keywords: Emotional memory, emotion recognition, menstrual cycle, estrogen, progesterone, oral contraceptives, ovarian hormones, sex hormones.

Full text can be found at: doi: 10.3389/fpsyg.2021.641250

4. General discussion

This thesis aimed to investigate the embodiment of emotion via the endocrine system. Specifically, the relation between female sex hormones, 17β-estradiol (E2) and progesterone (P4), and different components of emotional processing was investigated. To answer this, not only the main effects but also the interactions between sex hormones and the emotional valence of the stimulus were addressed. Additionally, the effects of stress and its interactions with hormone status and valence were investigated in the emotional memory task. Moreover, the role of olfaction in empathy-related measures in different hormone-status groups was studied. The first part of the general discussion will serve to summarizing and interpreting the results of two quasi-experimental studies and the systematic review. It is arranged according to addressed measures of emotional processing, i.e., emotional memory, empathy-related measures, as well as mimic and skin-conductance responses to affective stimuli. Then I will summarize the role of sex hormones in embodied emotion. Moreover, I will discuss some important limitations of the conducted studies and outline directions for future research. Lastly, I will derive conclusions.

4.1. Summary and discussion of the main findings

4.1.1. Role of sex hormones in emotional processing

Emotional context

The emotional valence of the stimuli was used to elicit emotions in subjects in different hormone-status groups and measure their responses/performance. Our data confirm that affective stimuli improve performance in all measures of emotional processing. This indicates the role of contextual factors in information processing, as they trigger emotions and affect behavior. However, the question is whether the emotion elicitation during these tasks and followed emotional processing is modulated by hormone status.

Emotional memory

In Study 1, we examined women in distinct female sex-hormone states on several measures of emotional processing, including emotional memory, empathy-related measures, as well as mimic and skin-conductance responses to affective stimuli. Additionally, a stress reaction was experimentally induced to investigate its interaction with sex-hormone status and stimulus valence in emotional memory. Our data show that memory is not affected by the hormone status, nor does it interact with the emotional valence of the stimuli, stress, or both. These results contradict some of the data published previously (Ertman et al., 2011; Felmingham et al., 2012; Pompili et al., 2016; Nielsen et al., 2013). Instead, our data reveal that free-cycling women in high and low P4 phases, as well as OC users, perform similarly in free recall of encoded emotional material. The correlational data revealed no significant associations between subjects' salivary E2- or P4-levels and memory recall. Notably, the difference in E2 levels between mid-cycle (high E2) and luteal (moderately high E2) groups was not significant, which might

have resulted in missing differences between the groups of free-cycling women. On the other hand, OC users with significantly lower endogenous E2 levels did not perform differently from the free-cycling women. Overall memory recall was impaired in the low-hormone cycle phases and enhanced in the peri-ovulatory (Pompili et al., 2016) or luteal phases (Zoladz et al., 2015; Ertman et al., 2011). The hormone status effects in the emotional memory studies were additionally reported as more frequent intrusions in the luteal phase (Ferree et al., 2009, 2011; Soni et al., 2013) but not in the free recall. However, this evidence comes from single studies, not supported widely. One can speculate, that the differences in emotional memory rather arise between low and high hormone (either estradiol or both) groups but the line is blurring out between mid-cycle and luteal phases, both characterized with rather high levels of estradiol, only distinct in progesterone levels. On the other hand, the differences are again not evident between OC users and free-cycling women in high hormone phases, possibly due to compensating effects of synthetic ethinyl estradiol and progestins ingested through oral contraceptives. Moreover, we could not replicate hormone status, stressor, and valence interactions reported in a few studies. This could also be due to differences in hormone-status groups among the studies. As discussed in the systematic review (Study 3), the emotional memory tasks across the studies varied in several procedural features including not only the type of stimuli (videos, words, pictures), but also the temporal delay between encoding and recall of the material (10 min to 1 week), placement and variation of other factors such as stress, etc. The differences in hormone-status group definition across the studies of both areas also indicate that varying results might just come from the overall design. This problem points out the need for replications studies, instead of continuous modification of study designs to provide novelty.

Empathy-related measures

In both studies, hormone status did not modulate empathy-related performance as measured by cognitive and affective empathy tasks. In the first study, we observed an interaction between hormone status and the gender of the protagonist in the cognitive empathy-related measure. This effect was driven by the luteal and the OC groups identifying emotions of female protagonists better. This is in line with evidence from face recognition data, where women identified the face of their gender more accurately than male subjects (Cellerino et al., 2004; Lewin & Herlitz, 2002). In Study 2, although the hormone-status main effect was absent, the high hormone group of free-cycling women outperformed men in the recognition performance of complex emotions (depicted in eye pairs). This is in line with the Reading the Mind in the Eyes Test meta-analyses reporting rather a small advantage of women over men (Kirkland et al., 2013). As for associations with hormone levels, E2 and P4 did not play any role in empathy-related performance, whereas testosterone negatively correlated with cognitive empathy in men and positively in OC-women. This might indicate the interaction of baseline cortisol levels with testosterone in cognitive empathy (Zilioli et al., 2015). In both studies, the cognitive subtest of MET-core2 did not provide hormone status effects nor trend effects. Notably, it was used as a consequent task after the emotion recognition test (see study timelines in Paper 1 and Paper 2) in both cases. The absence of

effects in MET-core-2 cognitive subtest might stem from the fact that it followed other cognitive-empathy related tasks in both studies. An unspecific training effect might have contributed to blurring the differences between the hormone status groups, whereas the novelty effect of the task might have contributed to detect trend group differences in the first task (see supplementary results 2.2 in paper 1). On the other hand, several reports of impairing effects of OC use on emotion recognition, i.e., cognitive empathy-related performance (Hamstra et al., 2014, 2017, Pahnke et al., 2019) was not supported. Instead, our results are in line with Radke & Derntl (2016) as well as with the recent large sample study, dismissing the disadvantage of OC users in emotion recognition (Shirazi et al., 2020).

Our systematic review suggest that in negative emotion recognition, P4 might have facilitating effects but high P4-phases coincide with moderate E2-levels. Our data partly support this conclusion. However, we have to be aware that emotion recognition studies nearly exclusively rely on the identification of basic, not complex emotions. Moreover, importantly, the causal role of hormone status cannot be deduced, especially due to its quasi-experimental character.

As for the affective empathy-related measure, in both experiments, hormone status and valence interactions indicated higher ratings in OC users towards negative emotions. While OC-use was associated with impaired basic emotion recognition for several times (e.g., Hamstra et al., 2014, 2016; Pahnke et al., 2019), OC-users appear to show higher affective responsiveness during their pill-on vs. off-phase (Radke and Derntl, 2016), or higher affective responses to emotional stimuli (e.g., Armbruster et al., 2017). Moreover, this pattern might indicate that cognitive and affective empathy-related performance, as independent aspects, is differentially modulated by hormone status. However, this line of research is still quite limited and requires further investigation.

Besides, we pioneered to address odor discrimination ability as a factor to elucidate the link between empathy-related performance and sex-hormone status. Although high-hormone free-cycling group showed clear olfactory advantage, the performance did not predict empathy-related performance, other than unexpected negative correlation in oral contraceptive users. This indicates that olfaction does not improve empathy-related performance in women. However, so far, there are no other data to support or dismiss this result.

Mimic responses and SCR

Mimic responses to emotional stimuli did not yield hormone-status main effects in either study. Notably, this line of research remains very limited with only one report of a direct hormone-status effect. The reports of the higher zygomaticus major activity to positive stimuli in high estradiol state (Mass et al., 2009) or higher zygomaticus activity in OC users (Armbruster et al., 2018) was not replicated in our studies. In Study 2, hormone status played a role in facial mimicry towards female protagonists, where free-cycling women showed stronger mimicry than OC users. This new effect might have appeared in the second study due to the task difference. In the second study, we used pictures with complex emotions depicted by humans and considered the protagonist gender as a within-subject factor along with the

stimulus valence. Thus, the gender of a person depicted in the stimulus material was an important factor. Indeed, in face recognition tasks women (vs. men) identify the face of their gender more accurately (Cellerino et al., 2004; Lewin & Herlitz, 2002). This could have resulted in stronger mimicry as a function of recognition for something familiar or something the female subjects identified themselves with (Hess & Fischer, 2013). This indicates that, in addition to the sex differences reported previously, hormone status can be a modulator factor in mimic activity to facial emotions interacting with the protagonist gender.

On the other hand, SCR responses to affective stimuli as measured in the first experiment indicate that women in the luteal phase are more sensitive to negative stimuli, also supported by the positive correlation with the salivary P4 levels in the total sample. This is in line with the luteal phase described as "window of vulnerability" because of the negativity bias (Andreano et al., 2018). Thus, a better understanding of the relation between P4 and negative stimuli has an important clinical implication.

4.1.2. Embodiment of emotion from a hormonal perspective

Understanding the specific role of sex hormones in emotional processing is a complex topic and requires the results of extensive research to establish solid conclusions. So far, the data suggest the role of sex-hormone status in emotional processing with mixed results. Our research provides further evidence on the sex-hormone related modulation of emotion. Despite the limitations of the above-discussed experiments (see 4.2. below), our data demonstrate the role of sex hormones in the embodiment of emotion. Specifically, our findings show that the luteal phase, characterized by high sex-hormone levels, is associated with enhanced processing of negative emotions, as suggested in the SCR data. On the other hand, in the cognitive empathy-related measure, women in the luteal phase and under OC use identified emotions of female (vs. male) protagonists better. Moreover, OC use showed a negativity bias in the empathy-related measure. Besides, free-cycling women showed stronger mimicry to female protagonists. Valence and the gender of the protagonist represent situational factors that not only affect emotional processing but also interact with sex hormones. This suggests that such contextual characteristics of stimuli can be prioritized while stimulus processing and modulate effects of hormone status. Thus, our results indicate that in specific measures of emotional processing sex hormones interact with contextual factors and modulate emotional processing.

4.2. Limitations

Firstly, we are aware that the size of our first sample could be increased in further studies. However, we have to consider the strict definition of cycle-phase ranges in our sample with women in their peri-ovulatory and mid-luteal phase. Moreover, subjects had to fulfill a larger number of exclusion and inclusion criteria. Nonetheless, the sample size was comparable to some of the studies in this field (for emotion recognition: e.g., Derntl et al., 2013; Kamboj et al., 2015, or even exceeds the sample size: e.g., (Derntl et al., 2008a; Guapo et al., 2009; for emotional memory under stress: e.g., Felmingham et

al., 2012; Maki et al., 2015; Mordecai et al., 2017). Notably, our second sample did not reach the planned 96 participants because of the coronavirus pandemic. Previously, the relationship between odor sensitivity and self-reported empathy-related performance was measured in a smaller sample with an evident role of olfaction in this regard (Spinella, 2002). However, previous studies addressing olfaction and empathy-related measures were conducted between men and women – not differentiated between free-cycling women vs. oral contraceptive users.

Secondly, we purposely decided to limit our sample to healthy subjects of reproductive age not exhibiting pregnancy or lactation. However, this way, we fail to cover large groups of the population representing other age groups characterized by distinct concentrations of ovarian hormones, including puberty and menopause but also women during pregnancy and post-partum (for facial emotion recognition see: Osorio et al., 2018). Besides, clinical subgroups with anxiety and affective disorders should be considered, as vulnerable affective states may demonstrate the role of sex hormones in a more specific way.

Moreover, although we aimed to measure different emotional tasks within one sample, the overwhelming amount of different tasks (see the study timeline in Paper 1) may generally generate an interference risk and affect participant's motivational state to work thoroughly through the tasks to perform well.

Finally, we have to be aware that natural hormone-status conditions in both experiments were a quasi-experimental factor as commonly used in this field. Thus, we are confined to make conclusions about causal inferences of hormone-status effects and hormone actions. Therefore, consideration of the experimental administration of sex hormones is worthwhile to enable causal E2- and P4 action profiles. E.g., E2 administration proved to be a successful approach improving extinction recall in fear-conditioning studies (Graham & Milad, 2013). Despite its restrictions, the quasi-experimental approach has a major advantage of the natural and *physiological* hormone fluctuations which is a major characteristic of the menstrual cycle (Gasbarri et al., 2012). Additionally, we have to be aware that exogenous administration distorts natural hormone fluctuations and thus is limited when extrapolating results to natural hormone effects.

4.3. Future directions

As already mentioned above, studies investigating sex hormones and empathy-related measures, mostly focus on basic emotions and cognitive empathy-related tasks. Thus, more research is required in complex emotions, as well as in affective empathy-related measures. Moreover, empathy-related research should address the role of experimentally-induced stress while accounting for sex-hormone status. So far, there are first data examining men and women without accounting for sex-hormone status. E.g., Daudelin-Peltier et al., (2017) submitted healthy men to psychosocial stress (TSST) or a control condition, followed by a basic-emotion recognition task. Stress reduced the sensitivity to identify disgust but improved the sensitivity to identify surprise. These findings were interpreted to suggest that a stress-

induced increase in the sensitivity to surprise is adaptive for detecting novel and threatening events. There are initial data on the effects of stress-induction via the TSST and measurement of both, cognitive and affective empathy-related measures within healthy men (Wolf et al., 2015) and in healthy women compared to women with a borderline personality disorder (BPD) (Wingenfeld et al., 2018). In both studies, psychosocial stress enhanced emotional (affective), but not cognitive empathy-related performance. However, sex hormones were not measured here. Results induced by the psychosocial stressor were comparable to the effects of a pharmacological MR-receptor stimulation via fludrocortisone (vs. placebo) in healthy women and BPD women (Wingenfeld et al., 2014). Higher glucocorticoid activity at MR-binding sites led to higher affective, not cognitive empathy-related performance, while healthy vs. BDP participants per se did not differ in empathy-related measures. Psychosocial stressors, as used in studies mentioned above, and pharmacological interventions are known to induce the second-wave stress response with activation of the HPA-axis. Data on the effects of a first-wave stressor often used in emotional memory studies are missing in emotion recognition research. Including experimental stress manipulations in the empathy-related research should also help to disentangle the *adaptive value* of empathy-related behavior. Here the differential response profile of cognitive vs. affective empathy-related measures is of special importance.

4.4. Conclusions

Female sex hormones, estrogen and progesterone play a role in different measures of emotional processing by interacting with contextual and situational factors such as emotional valence of stimuli or the gender of the protagonist. Our data indicate negativity bias in the luteal phase and under oral contraceptive use in skin-conductance responses and the affective empathy-related measure, respectively. Considering olfaction as a mediating factor between emotion and sex hormones suggests no association between olfactory ability and empathy-related measures. Furthermore, the systematic review of the studies regarding the role of sex hormones in emotion recognition and emotional memory indicates that mixed results might be a result of methodological variations in measures used. Given that existing research struggles to establish the specific role of sex hormones in emotional processing, we suggest an approach that combines several measures and chooses distinct hormone status conditions. Finally, our findings allow a specific characterization of embodiment as coupled embodiment. Namely, brain-body-coupling shows that cognition and emotion not only rely on brain states but also on bodily states and that there is a coupling loop between the endocrine system and cognitive and affective processes. The standard understanding of embodiment ignores the feedback loop between brain processes and hormonal bodily states. Instead, it either highlights the role of the activation of corresponding areas in the brain through the somatosensory, motor, or visceral feedback (neural embodiment) or describes the role of out of brain bodily processes as constitutive of cognition and affect (strong embodiment). Our approach provides a new perspective for the body to brain coupling by considering endocrine processes and expends the concept of embodiment.

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