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Review

How Oral Contraceptives Impact Social-Emotional Behavior and Brain Function

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Millions of women worldwide use oral contraceptives ('the pill'; OCs), often starting at a pubertal age when their brains are in a crucial developmental stage. Research into the social-emotional effects of OCs is of utmost importance. In this review, we provide an overview of studies that have emerged over the past decade investigating how OCs, and their main ingredients estradiol (E) and progesterone (P), influence social-emotional behaviors and underlying brain functions. Based on this overview, we present a heuristic model that postulates that OCs modulate core social-emotional behaviors and brain systems. Research domains and challenges for the future, as well as implications, are discussed.

Trends

Strong indications exist that OCs, by actions of their main ingredients, the ovarian hormones estradiol and P, affect social-emotional behavior and brain function.

Despite millions of users worldwide, neuroscientific research on the social-emotional effects of OCs is just starting to emerge.

The current literature demonstrates effects of OCs on emotional functions such as fear and stress, and on the social functions of partner preference and social reward.

Neuroimaging research on ovarian hormones predicts that OCs: impact emotional reactivity and fear-learning systems, such as amygdala, hippocampus, and ventromedial prefrontal cortex; potentially modify emotion regulation via changing amygdala-prefrontal connectivity; and could influence social functions, such as partner preference, by altering striatal reward processing.

The Potential of OCs to Impact Social-Emotional Behavior

Worldwide more than 100 million women use OCs ('the pill'), which contain synthetic forms of the ovarian hormones E and P, as an effective way to prevent pregnancy [1]. OCs have been on the market for half a century, and they are among the best-researched drugs in the history of medicine. However, remarkably little neuroscientific research has been done on the effects of OCs on social-emotional behavior and brain function [2,3]. This is particularly surprising since there are strong indications that OCs, via actions of E and P, impact social-emotional behavior and brain function. OCs alter the hormonal profile of their user, because endogenous levels of ovarian hormones are substantially suppressed via negative feedback mechanisms [4] (Box 1). The role of E and P in regulating social-emotional behaviors is suggested by menstrual cycle studies that have linked the fluctuations in ovarian hormones to changes in social-emotional behavior and brain function (reviewed in e.g., [5,6]). In addition, animal research supports a regulatory role of E and P in various social-emotional behaviors, such as social learning, social recognition, anxiety, and aggression [7–9]. E and P can bring forth such effects by acting on the E receptors (ER_{α} and ER_{β}) and P receptors (PR-A and PR-B) in brain regions that regulate social-emotional behaviors, such as amygdala, hypothalamus, hippocampus, and cerebral cortex [10,11]. Thus, lowering E and P by OC treatment has the potential to change a range of social-emotional behaviors and brain functions. In addition to suppressed female sex steroids in OC users, levels of testosterone are also strongly reduced, irrespective of the dosage of E or the type of synthetic P [12] (Box 2). Low levels of testosterone in OC users can also cause changes in social-emotional behavior, as suggested by a rich human literature (reviewed in e.g., [13,14]). Finally, OC use is associated with structural brain changes in regions relevant to social-emotional behavior (reviewed in [2]).

The suppression of ovarian hormones could underlie the behavioral effects of OCs and, therefore, in this review, we first give an overview of studies investigating the effect of E and P on social-emotional behavior and its underlying neural circuitries. Next, we highlight recent insights into how OCs impact these processes. Finally, to guide future neuroscience and

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Box 1. The Menstrual Cycle and OC Use

The typical menstrual cycle has a length of 28 days, but there is variability in cycle length [97]. The menstrual cycle is characterized by fluctuations of the ovarian hormones E and P (Figure IA), which are regulated by the hypothalamus–pituitary–ovarian axis. At the beginning of the first half of the cycle, during the follicular phase, E and P are low. At the end of this phase, E starts to rise, peaking at ovulation. After ovulation, during the luteal phase, P rises and normalizes again before the onset of the next follicular phase. The exogenous E and P in OCs suppress the hypothalamus–pituitary–ovarian axis through negative feedback, leading to lower endogenous levels of E and P and minimizing the fluctuations of these hormones over the cycle [4,98]. Specifically, E primarily inhibits the secretion of follicle-stimulating hormone (FSH) and P mainly inhibits the secretion of luteinizing hormone (LH), leading to less ovarian activity and release of E and P [99]. Thus, the hormonal profile of OC users differs substantially from that of naturally cycling women in that endogenous levels are lowered and fluctuations are suppressed (Figure IB). The low ovarian hormone levels and absence of fluctuations might be important mechanisms in the long-term effects of OC use on behavior and brain function.

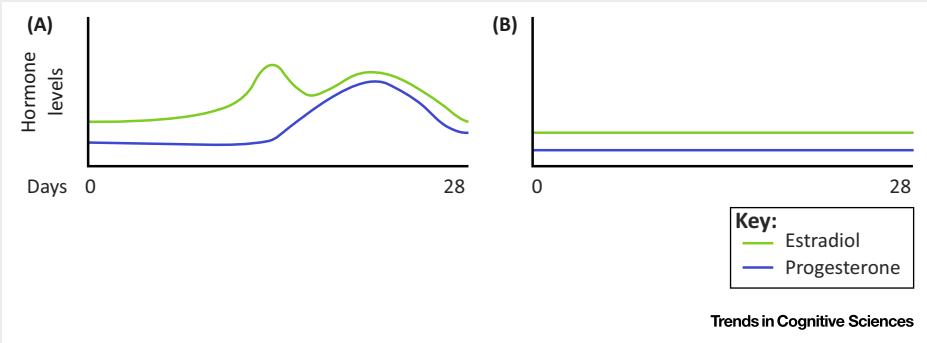

Figure I. Schematic Representation of the Fluctuations of Estradiol (E) and Progesterone (P) during (A) the Regular Menstrual Cycle and in (B) Oral Contraceptive (OC) Use. Some residual ovarian activity might exist during the pill-free week in OC treatment because of an increase in follicle-stimulating hormone (FSH), and suppression of ovarian activity can differ between OCs with varying doses of E [99].

Box 2. OCs

Different types of OC exist; there are P-only pills and combination pills that contain estradiol (E2) and a variant of a progestin, that is, synthetic P (P4). Combination pills are the most frequently used OCs worldwide [100,101], but there is substantial variety in the type of progestin that is used. Second-generation OCs, containing the progestin levonorgestrel, are mostly used in The Netherlands, whereas third-generation OCs containing progestins such as gestodene and norgestimate are mostly used in Italy [101] and the USA, respectively [100]. In the UK, both second- and third-generation OCs are frequently used [101]. The type of progestin in OCs is relevant in the context of effects on social-emotional behavior, because it determines their androgenic properties (e.g., the older progestin levonorgestrel used in second-generation OCs) or antiandrogenic properties (e.g., the newer progestins, such as drospirenone, used in third-generation OCs). Thus, different neural and behavioral effects can be expected on the basis of the type of progestin in the OC, and is an important, yet often ignored factor, to take into account in studies [2].

Glossary

Fear conditioning: form of learning in which a neutral stimulus is paired with an aversive stimulus and presentation of the neutral stimulus eventually leads to generation of fear responses.
Fear extinction: the decline in the conditioned fear response after several exposures to a nonreinforced fearful stimulus.
Follicular phase: first stage of the menstrual cycle, characterized by low ovarian hormone levels.
Hypothalamus-Pituitary-Adrenal (HPA) stress system: endocrine system that regulates stress reactivity and produces the hormone cortisol.
Luteal phase: second stage of the menstrual phase, characterized by high ovarian hormone levels.
Premenstrual dysphoric disorder: disorder that comprises a cluster of affective, behavioral, and somatic symptoms that recur monthly during the luteal phase of the menstrual cycle.

behavioral studies, we present a heuristic model of the behaviors and brain systems targeted by OC use, and outline research domains for future investigation. Considering the millions of women who take OCs on a daily basis, often starting at a young age when sex hormones have important organizational effects on brain structure [15,16], the social-emotional effects of OC use can have important implications for users and society. An overview of studies and future directions in this field is of utmost importance, because research will aid in understanding the consequences of OC use for the mental health and the social-emotional wellbeing of present and future users.

Social-Emotional Effects of E, P, and OCs

Since E and P are not only both main ingredients of OCs, but also strongly suppress the endogenous production and fluctuations of E and P (Box 1), we provide here an overview of the evidence from menstrual cycle studies that capitalize on the cyclic fluctuations in these ovarian hormones. In addition, we discuss single-administration studies on E and P that show important causal evidence for their role in social-emotional behavior.

Fear and Stress

Menstrual cycle studies have demonstrated that ovarian hormones modulate fear- and stress-related behavior. Fear processing in particular has received substantial attention from researchers, possibly because anxiety disorders are twice as prevalent in women compared with men [17], indicating a role of sex hormones in this behavior. E can reduce fear, particularly via facilitating **fear extinction** (see Glossary). A single administration of E increases fear extinction in women and high endogenous E levels are associated with enhanced fear extinction memory [18,19]. By contrast, low E levels are related to higher **fear conditioning** responses during fear extinction and intrusive memories [20].

In line with evidence that high E levels are associated with enhanced fear extinction, high E is accompanied by increased activation of the ventromedial prefrontal cortex (vmPFC)-amygdala circuit during fear extinction [19,21] and the anterior cingulate cortex (ACC) and dorsolateral PFC during emotional response inhibition [22]; both circuits are crucial in fear regulation. By contrast, high E levels coincide with downregulated emotional and stress reactivity in hypothalamus, hippocampus, amygdala, ACC, and orbitofrontal cortex (OFC) [23,24]. Moreover, high E modulates hippocampus activation, which has protective effects on stress and memory for negative stimuli [25,26]. Finally, actions of E on the amygdala and prefrontal sites can influence connectivity between these regions. This was illustrated by a study showing that women with high E levels have higher basolateral amygdala resting-state functional connectivity with prefrontal and other cortical areas, implied in emotion regulation, compared with women with low E levels, who display higher connectivity with ACC, a connection implicated in negative affect [27]. Putatively, high E protects against the effects of stress and facilitates fear extinction by influencing prefrontal regulation and the reactivity of stress and fear circuitry, and modulating hippocampal activation [19,23]. To date, there are no published single-administration studies investigating the effect of E on the neural activation of the emotion circuitry in healthy premenopausal women, but such studies are crucial for progress in this field.

The role of P in fear extinction is less clear (reviewed in [28]); however, P can potentially reduce stress and anxiety via its metabolite, allopregnanolone (ALLO) (Box 3). Yet, effects of P are complex because anxiogenic effects are also observed (Box 3). This is reflected by mixed findings from two single-administration studies, in which one demonstrated decreased amygdala activation during memory for faces [29] and the other showed increased amygdala reactivity and amygdala-ACC connectivity towards emotional faces following P administration, a finding that could imply an anxiogenic response or stronger emotional control [30]. Increased neural reactivity of amygdala is also observed during the **luteal phase** compared with the **follicular phase**, characterized by higher P levels but no difference in E levels [31]. This concurs with findings from subjects with **premenstrual dysphoric disorder** (PMD), in which P levels positively predicted dorsolateral PFC and amygdala activity in the anticipation and presentation of emotional stimuli [32,33]. Thus, discrepancies in neuroimaging findings on P might reflect nonlinear and hormonal state-dependent effects of P (Box 3).

Due to the suppression of endogenous levels of E and P, OC use could result in the dysregulation of fear- and stress-related mechanisms, which appears to be the case. Translational work demonstrated impaired fear extinction recall in OC-treated animals, which was rescued in animals by terminating treatment or administering an E agonist. Correspondingly, fear extinction in female OC users is impaired and, in naturally cycling women, a single administration of E enhanced fear extinction recall [18]. In line with this evidence, OC users displayed different activation in fear conditioning and extinction networks compared with naturally cycling women [21,34]. During fear extinction, women taking OCs displayed higher activation in amygdala, thalamus, ACC, and vmPFC, and also demonstrated slower habituating skin conductance responses, suggesting impaired fear extinction [34]. Yet, when comparing women taking OCs

Box 3. Possible Mechanisms of E, P, and OCs

Ovarian hormones are steroids that can cross the blood–brain barrier. After binding to their receptors, P and E can not only quickly affect the brain (seconds to minutes) via nongenomic pathways, but also have slower effects based on gene transcription [9,102]. Knowledge of the distribution of receptors for E and P is primarily based on animal studies, which show receptors in the amygdala, hippocampus, hypothalamus, and cerebral cortex [10,11,103]. It is unclear to what extent this distribution overlaps with that of humans. Local actions of E and P on these areas could be important in social-emotional effects; however, there are multiple other pathways by which ovarian hormones can act on brain and behavior.

Ovarian E and P can interact with neurotransmitter systems and other hormonal systems that have important roles in mood, emotional, social, and motivational behaviors. Although a complete overview of all the possible mechanisms of E, P, and OCs is beyond the scope of this review, there are several mechanisms that might be relevant for the behavioral evidence reviewed here.

P can have anxiogenic or anxiolytic effects via the actions of its metabolites pregnenolone and ALLO on γ-aminobutyric acid (GABA) [10,17,104–107]. Anxiolytic effects are observed when P levels are high and anxiogenic effects are seen when P levels are low [107]. P also interacts with the HPA stress system [106]. Thus, P appears to influence the neurobiological mechanisms for anxiety and stress, which is important in shaping the behavioral effects of OCs.

Interactions of E with dopaminergic [108] and serotonergic [109] systems are particularly relevant for effects on reward behaviors and mood. Especially relevant for social behaviors, such as pair bonding and partner preferences, is that E enhances the function of oxytocin, a neuropeptide involved in attachment and bonding [13].

OCs decrease endogenous E, P, and testosterone levels, so they potentially suppress any behavior or neurobiological mechanism (e.g., interaction with a neurotransmitter system) that is regulated by these hormones. For example, suppression of E in OC users could lead to decreased sensitivity to the effects of oxytocin on social-reward processing [91]. Additionally, animal research has suggested that a reduction in the metabolite ALLO as a result of long-term exposure to synthetic E and P could also be involved in reduced sexual behavior and motivation [110]. OC use further increases levels of corticoid-binding globulin (CBG), which leads to lower cortisol levels in users [38]. Important to note is that, in OC users, P and E are administered simultaneously and P and E interact with each other [8]; thus, any effect of E can be influenced by P and vice versa. At present, it is unclear which neurobiological mechanisms have a role in the behavioral effects of OCs, and if these differ between long- and short-term treatment; thus, this is an important topic for future research.

with naturally cycling women with high E levels, neural correlates of fear conditioning and fear extinction were suppressed [21]. The menstrual phase of the control group likely has a role in these contrasting findings (Box 4); nonetheless, these findings strongly suggest that neural mechanisms for fear processing are altered in OC users. The resting brain of OC users further shows decreased functional connectivity between ACC and frontal nodes of the executive network, implicating consequences for emotion regulation abilities [35]. Emotion regulation is

Box 4. Methodological Approaches in OC Research

Most studies on OC use a between-subject design, comparing a group of OC users with a control group comprising naturally cycling women. While this type of design offers practical advantages, it can be subject to confounding factors, such as differences in relationship status, sexual activity, personality features; that is, all factors that might be particularly important in social behaviors. These factors should be controlled for in between-subject designs. Although placebo-controlled, double-blind, randomized, between-subject designs with pre- and post-treatment measurements are important for progress in the field because they provide causal insights into the effects of OC treatment, they are the exception [45,111].

An important methodological consideration in all designs is the menstrual phase of the control group because the low endogenous hormone profile seen during the follicular phase resembles that of OC users. By contrast, women during the luteal phase of their cycle may display higher endogenous levels of E and P compared with women taking OCs. It has been argued that comparing OC users to women during the follicular phase of their cycle is more informative for disentangling the effects of exogenous hormones since differences in endogenous hormones between the two groups are minimized [34,45]. An alternative approach could be to contrast the effects of single and multiple OC administration, to dissociate the acute, nongenomic effects of exogenous hormones from the slow, genomic (i.e., gene-mediated) effects of E and P [7,9,10] (Box 3).

important not only for mood, but also for the maintenance of social relations [36,37]; hence, this is an important avenue for future studies.

OC users demonstrate blunted reactivity of the **hypothalamus–pituitary–-adrenal (HPA) stress system** [38,39]. The interaction between OC use and the HPA stress system is illustrated by a study demonstrating that OC users displayed a different neural response to cortisol administration compared with nonusers. Cortisol administration increased hippocampus activation during fear conditioning in OC users, but decreased it in men and naturally cycling women, suggesting that women taking OCs are more sensitive to emotional information during stressful situations [40]. However, in nonstressful situations, amygdala activation towards negative pictures was suppressed in OC users [41], which is in line with altered emotional memory [42], and suggests impaired processing of emotional information. Another study reported increased activity of the fusiform face area towards angry and neutral facial expressions in users, which could reflect increased attention to specific features of the face relative to emotional aspects [43]. Clearly, more research is needed to draw a definite picture of the direction of the effects of OC use on emotional reactivity.

In women who are vulnerable to the negative mood symptoms of OCs, such as irritability and depression [44], suppressing endogenous sex hormone levels might affect emotional reactivity systems differently compared with users who do not experience mood symptoms. Previous OC users that experienced negative mood symptoms showed a lack of habituation of the amygdala to emotional faces, but decreased activation of the inferior frontal gyrus and insula to affective stimuli after one OC treatment cycle [45]. Moreover, increased reactivity of anterior insula to emotional faces after pharmacological suppression of sex hormones was positively linked to negative mood symptoms [46]. These findings highlight the importance of investigating individual differences in the effects of OC treatment (Box 5). Altered emotional reactivity of the insula and amygdala in women who are susceptible to negative mood symptoms could be a neural mechanism for the association between OC use and depression [47]. The fluctuations of E over the cycle are important in regulating emotional reactivity systems, a mechanism that is dysfunctional in women with major depression [23]. Specifically, the suppression of E and its fluctuations as consequences of OC use can modify emotional reactivity systems and provide a neuroendocrine mechanism for the link between OC use and depression [47].

Box 5. The Challenges of OC Research

OC research is in its infancy and the field faces several crucial challenges. The first one is the users' age. Girls often initiate OC use during puberty [15,112], when the brain is undergoing organizational changes due to a surge of sex hormones [16]. One of the major challenges for OC research is to investigate how OC use interferes with the organizational effects of sex hormones on the brain [2] and consequently with social development during adolescence [47].

A second challenge is investigating individual differences in effects of OCs. Mood symptoms and history of mood symptoms are important to take into account because behavioral and neural effects of OC use might be different in women who are vulnerable to negative mood symptoms [45]. Disentangling how users who experience mood symptoms differ from users who do not at the neural and behavioral level is also clinically relevant. Genetic variation in hormone receptors is an important source for determining sensitivity to the effects of hormones [113], and likely also OC treatment. Genetic variation in ER [59] and the mineralocorticoid receptor for glucocorticoids, an important receptor in stress functions [62], are candidates for explaining variance in individual differences to the effects of OCs. Prospective studies must investigate other possible genetic factors, especially those genetic factors that pose a risk for developing negative mood symptoms and depression following OC use.

A final important challenge is whether effects of OC use on social-emotional behaviors and brain functions are permanent or reversible. A study suggested that the behavioral effects are reversible [18], whereas another suggested they are not [2]. Nevertheless, this discrepancy highlights that OC studies must take into account the history and duration of OC use, especially since changes in brain structure are positively predicted by duration of OC use [2]. Thus, every longitudinal study assessing brain volume or social-emotional development should consider OC use.

In summary, endogenous ovarian hormones modulate fear and stress processing, and the first studies done on this topic indicate that these processes are altered in OC users, which has implications for their vulnerability to stress, anxiety, and mood disorders (e.g., [47,48]). The relation between OC use and impaired fear extinction fits with the effects of suppressed endogenous ovarian hormones, especially low E. However, not all effects of OC treatment on emotion processing can be readily explained by such a mechanism. For example, the findings on amygdala reactivity are mixed [41,45] and call for more research. Overall, these findings also have implications for research on stress and fear in general, because OC use should be considered a possible confounding factor in study designs.

Reward

Ovarian hormones, especially E, can regulate reward behaviors via the upregulation of dopamine (Box 3). Correlational and administration studies have illustrated the involvement of ovarian hormones in reward sensitivity towards money and drugs [49–52]. Although the relation between E and reward sensitivity might depend on the menstrual phase [50], there is a pattern of high E enhancing [49], and high P decreasing [52] the rewarding effects of drugs.

It is conceivable that OC use dampens reward processing, given that it decreases E and testosterone levels; the latter is known to stimulate the striatal reward system [53]. In line with this, a decrease in insula activation in response to monetary reward correlated with a decrease in testosterone after administration of a gonadotropin-releasing hormone agonist (GnRHa), which also suppresses E and P [54]. The same study showed that amygdala reactivity to monetary gains was also attenuated [54].

In conclusion, ovarian modulation of reward is clearly implied and it is assumable that OC users have altered reward processing, which is an important starting point for further investigation since it could reflect a mechanism that relates to depressive symptoms [47]. Altered reward sensitivity towards social and sexual stimuli in OC users is also important for social bonding processes and relationship behaviors (see the 'Partner Preference and Relationship Satisfaction' section below).

Emotion Recognition and Empathy

Does the pill influence the critical abilities needed to maneuver in our social environment, such as emotion recognition and empathy? This is an important question since such behaviors are vital to social relations; yet, this topic has only recently received interest. Correlational research indicates that ovarian hormones do indeed, as suggested by animal research, regulate social behaviors. These studies indicate that P is negatively related to emotion recognition performance but positively related to correct judgments about another individual's affective state [55,56]. The finding on emotion recognition is further corroborated by evidence from a P administration study in females displaying decreased recognition performance for faces together with reduced activation in amygdala [29]. Although no relations with E were observed in these studies, other research suggests that E is associated with social functions. E is negatively related to emotion recognition [57,58] and genetic variation in the ER is linked to social recognition [59]. In men, a single dose of E increased the autonomic response towards another person's pain response, possibly indicating increased empathic responding [60]. However, it is unknown whether these effects can be generalized to women because sex differences in the effects of E are likely. Overall, the scarcity of studies on ovarian influence on empathy and emotion recognition is remarkable and in stark contrast with the rich literature on the male hormone testosterone and its effects on social-cognitive functions [13,14].

Despite its broad relevance for women's relationships, little is known about how the pill shapes social abilities. Use of OCs might negatively impact emotion recognition [61], an effect that

depends on a woman's genetic profile [62] (Box 5). Yet, another study reported higher performance in affective judgments of other people, but unchanged emotion recognition and perspective taking in OC users versus naturally cycling women [63].

Taken together, studies on endogenous ovarian hormones do show involvement in emotion recognition and other empathy-related abilities, but the effect of OC use on these behaviors is currently unclear due to a limited number of studies that have included different types of OCs (Box 2) or use control groups with different menstrual phases (Box 4). More investigations are urgently needed since social abilities, such as empathy, are relevant for a variety of social processes; from friendships and romantic relationships to caregiving (e.g., [64,65]).

Partner Preference and Relationship Satisfaction

Given the role of female sex steroids in reproductive processes in the body, the majority of the studies on E, P, and social behavior have been conducted on reproduction-related behaviors, such as partner preferences. Overall, women have a higher preference for masculine faces [66], bodies [67], voices [68], odors [69], and behavioral displays [70] around ovulation, during the late-follicular phase, or when E and testosterone levels are high. Women's P levels have not directly been linked to mate preferences, but high P menstrual phases are associated with a preference for femininity [71], hypothetically because there is need for social support during pregnancy or when the body is preparing for pregnancy, during the luteal phase of the menstrual cycle (reviewed in [72]). Thus, there appear to be shifts in preference for sexual dimorphism over the cycle (for a critical meta-analysis, see [73]), driven by fluctuations in ovarian hormones.

At the neural level, there is evidence that high E coincides with increased reward sensitivity towards male and sexual stimuli. The E:P ratio is positively correlated to liking and OFC responses, indicating increased positive appraisal, towards male faces [74]. Furthermore, responsiveness of posterior cingulate cortex towards masculinized faces is positively predicted by E, whereas responsiveness of precentral gyrus is negatively predicted by P levels [75]. This pattern could reflect heightened attention and motivation towards masculinized faces [76], and fits with a positive relation between the E:P ratio and increased reward sensitivity towards male and sexual stimuli. Modulation of attention and reward sensitivity towards these stimuli are important for initiating social interaction, and allows for shifts in partner preference, satisfaction, and sex drive over the cycle.

Intriguingly, the shifts in mating preference are absent or tuned towards femininity in OC users (e.g., [66,71,77]), potentially because the natural fluctuations of E, P, and testosterone are suppressed [4,12]. In line with this hypothesis, testosterone predicts preference for masculinity in naturally cycling women but not in women taking OCs, who have lower testosterone levels [78]. The lowered endogenous levels of ovarian hormones are not only related to shifts in partner preferences, but possibly also cause blunted physiological responses [79] and altered attention towards sexual stimuli [80] in OC users. Responses from anterior insula and precentral gyrus towards erotic stimuli, which are indicated in evaluating the rewarding value of sexual stimuli and sexual arousal respectively [81], are also attenuated in women taking OCs [82]. These findings potentially reflect the neural underpinnings of decreased libido in OC users [83]. Interestingly, sensitivity to the rewarding value of infant cuteness is increased in women using OCs [84]. The co-occurrence of decreased sexual interest but increased sensitivity to infant cues is also seen under low testosterone in fathers, and could serve to enhance parenting behavior [85].

Overall, ovarian hormone fluctuations are related to partner preference, and suppressing these processes with OCs might have consequences for users' relationships. Indeed, when women terminate OC use during marriage, they are more likely to report dissatisfaction when they have a relatively unattractive partner and high satisfaction when they have a relatively attractive partner

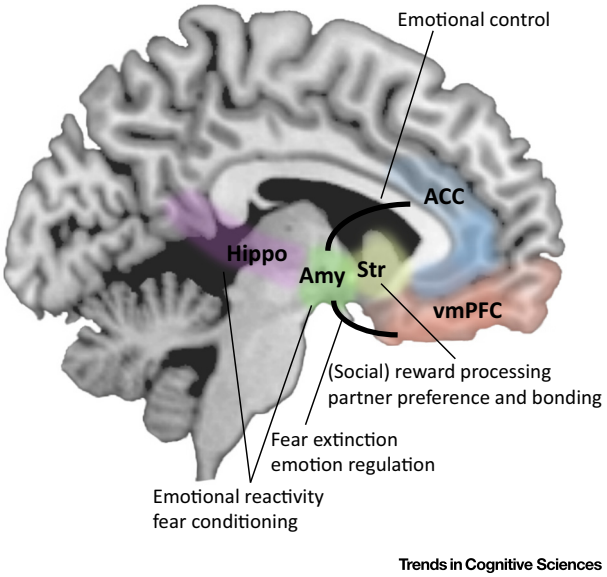

Figure 1. A Heuristic Model of Social-Emotional Behaviors and Brain Systems Affected by Oral Contraceptive (OC) Use. Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; Hippo, hippocampus; Str, striatum; vmPFC, ventromedial prefrontal cortex.

[86]. This study adds to a body of evidence implicating that OC use is associated with negative consequences for women's relationships, such as increased jealousy and mate retention behaviors [87,88], and decreased sexual satisfaction and partner attraction [89,90]. Recently, it was shown that OC users show decreased striatal sensitivity to the effects of oxytocin administration when viewing of pictures of their partners [91]. Thus, altered reward sensitivity for the partner's appearance could be a mechanism through which OC use affects relationship satisfaction, which is an interesting avenue for prospective studies.

Heuristic Model of the Social-Emotional Effects of OCs

Based upon the evidence from menstrual cycle studies and several administration studies investigating the effects of ovarian hormones on social-emotional behavior and brain function, we propose a heuristic model of the behaviors and brain mechanisms that are targeted by OC use (Figure 1).

First, on the basis of research on ovarian hormones, and demonstrated by initial OC studies, it is expected that OC use impairs fear extinction [18,20]. The exact neural mechanisms of this relation need to be investigated in future studies, but regions of interest are amygdala, hippocampus, and the amygdala-vmPFC network implied in fear conditioning and extinction [21].

Our model also predicts that, because basal emotional reactivity of amygdala and hippocampus is regulated by P and E [23,24,30,31], the use of OCs modulates the responsiveness of these regions towards affective stimuli. Findings on amygdala reactivity in OC users are limited and mixed [41,45], and more research is needed to confirm the direction of this effect.

Second, our model proposes that OC use affects the regulation of, and control over, emotional responses. Actions of E and P at subcortical emotion systems or prefrontal regulation systems can also give rise to ovarian modulation of amygdala connectivity with prefrontal and ACC regions [27,30], which are important circuits for emotion regulation [92]. Therefore, a question

that needs to be addressed in future OC research is whether abilities in emotional regulation and control are affected in OC users and whether that is caused by alteration of amygdala-vmPFC and amygdala-ACC connectivity. A next question is whether dysfunctional emotion regulation abilities are implicated in the increased chance for developing mood disorders [47].

Finally, E and P regulate partner preference shifts over the menstrual cycle, and OC use inhibits these shifts in partner preference [66,77]. The neural mechanism that is responsible for these effects is currently unknown, but effects of OC treatment on social reward processing in striatum [91] is a putative mechanism. Moreover, overall decreased reward processing following OC use could provoke depressive symptoms in users [47].

In the emerging field of research on the social-emotional effects of OCs, our heuristic model puts forward several hypotheses that can serve to guide prospective research. Neurobiological mechanisms driving the effects of OCs on the social-emotional brain remain to be scrutinized, but there is a multitude of candidate mechanisms (Box 3). Different methodological approaches can dissociate the short- and long-term effects of OC use (Box 4).

Concluding Remarks and Future Perspectives

Over the past decade, research has started focusing on the ovarian modulation of social-emotional behavior and brain function, and the impact of OC use, reflecting a heightened motivation to increase knowledge of this topic. Many questions remain (see Outstanding Questions) and the field faces important challenges (Box 5); therefore, we hope that our review will stimulate future studies in the field. Our model, depicted in Figure 1, proposes that emotional processes, such as fear extinction and emotional reactivity, are influenced by use of OCs. The model also predicts that functions vital to relationships, such as social reward and emotion regulation, are targeted by OC treatment. These social functions have received the least research attention and, therefore, we want to underscore the importance of the topic of how pill use impacts the social abilities that women need in everyday social interactions and relationships (see Outstanding Questions). We outline two research domains that capture those abilities; behaviors that are important for initiating social interactions, such as social reward and approach, and behaviors that are important for maintaining social interactions and relations, such as empathy and emotion regulation. Reward processes are important for social approach [93] and relationships [94]. Empathy is important for the maintenance of romantic relationships [64], friendships [95], and parenting [65], whereas emotion regulation is implied in the quality of romantic relationships [36] and predictive of maladaptive parenting [96]. Behavioral and neuroscientific insights into how the pill affects these social abilities sheds light on why the pill changes social processes, such as relationship satisfaction [86,87,89,90] and whether OC use impacts other social relations, such as friendships and parenting.

The relevance of OC research is manifold. First and foremost, research on OCs and social-emotional behavior and brain function is relevant at the individual level, because users need to know the consequences of pill use. Given that, worldwide, over 100 million women use the pill, OC research is relevant at the societal level. Furthermore, OC research has implications for a broad scientific community, because it will show how neuroscience researchers should take OC use into consideration when planning research and analyzing data. Finally, at a clinical level, OC research is of critical importance because it will aid in better informing women to make the choice of whether, and at what age, they should start using OCs.

Outstanding Questions

What are the effects of long-term OC use in women in terms of core social behaviors, such as empathy and social reward, which are vital to partner bonding and mother–child bonding?

OC use is associated with altered relationship behaviors, but what are the other real-life consequences of OC use? Does OC use impact parental caregiving?

How do OCs change brain function in the developing female brain during puberty?

Are the neural and behavioral changes induced by OC reversible?

What are the neurobiological and neural mechanisms by which OC act on the brain, and which of these brain mechanisms drives the effects on social-emotional processes?

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