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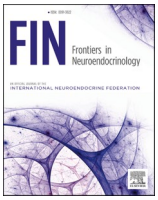

Hormonal contraceptives, stress, and the brain: The critical need for animal models

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ABSTRACT

Hormonal contraceptives are among the most important health and economic developments in the 20th Century, providing unprecedented reproductive control and a range of health benefits including decreased premenstrual symptoms and protections against various cancers. Hormonal contraceptives modulate neural function and stress responsivity. These changes are usually innocuous or even beneficial, including their effects on mood. However, in approximately 4–10% of users, or up to 30 million people at any given time, hormonal contraceptives trigger depression or anxiety symptoms. How hormonal contraceptives contribute to these responses and who is at risk for adverse outcomes remain unknown. In this paper, we discuss studies of hormonal contraceptive use in humans and describe the ways in which laboratory animal models of contraceptive hormone exposure will be an essential tool for expanding findings to understand the precise mechanisms by which hormonal contraceptives influence the brain, stress responses, and depression risk.

1. Hormonal contraceptives. What we know

Hormonal contraceptives (HCs) are one of the most important health and economic developments in the 20th century, used by at least 85% of women in western countries for 5 or more years at some point in their lives. Of all HCs – including oral contraceptives or "The Pill", implants (e.g., Norplant), cervical rings, injections (e.g., Depo-Provera), and some intrauterine devices (IUDs, e.g., Mirena) – oral contraceptives remain the most accessible and commonly used. Approximately 15% of married women and 26% of unmarried menstruators of reproductive age use oral contraceptives (United Nations, 2019), translating to more than 151 million people worldwide using oral contraceptives, 74 million injectables, 23 million implants, and 159 million IUDs (either hormonal or copper) at any given time. This makes HCs one of the most widely used classes of drugs worldwide (Chadwick et al., 2012). By allowing unprecedented control over reproduction, HCs have resulted in health benefits that extend well beyond family planning and expanded financial independence for individuals and families. Common health benefits include menstruation-related, alleviating premenstrual symptoms and premenstrual dysphoric disorder (PMDD), dysmenorrhea, endometriosis, and polycystic ovarian syndrome (PCOS) (Chadwick et al., 2012; Wong et al., 2009; Brown et al., 2018; Hewitt and Cromer, 2000). HCs also substantially reduce the risk of some forms of cancer including ovarian, endometrial, and colon cancers by up to 50% (Chadwick et al., 2012; Murphy et al., 2017; Luan et al., 2015; Havrilesky et al., 2013; Michels et al., 2018; Iversen et al., 2017). In addition, regulatory effects of HCs are the primary reason for many individuals being on HCs, especially during adolescence: these include regulating periods, decreasing acne, and alleviating premenstrual symptoms (Hewitt and Cromer, 2000; Lahoti et al., 2021).

HCs also broadly benefit mental health. Most individuals using HCs experience either improved mood and decreased risk for depression and panic disorder (Keyes et al., 2013; Cheslack-Postava et al., 2015), or have no noticeable impact on mood or depression (Scheuringer et al., 2020). Nevertheless, for a subset of individuals – approximately 4–10% of users – HCs come with serious side effects including increased risk for depression and suicidality (Porcu et al., 2019; Poromaa and Segebladh, 2012; Skovlund et al., 2016; Skovlund et al., 2018; Edwards et al., 2020; Schaffir et al., 2016; Worly et al., 2018; Anderl et al., 2021; Anderl et al., 2020). This equates to around 30 million people worldwide that experience anxiety or depression as a consequence of HC use at any given time.

Balancing known risks with known benefits for HCs is widely practiced when prescribing HCs. For example, HCs increase risk of blood clots and cardiovascular disease in patients that smoke (Petitti, 2003; Frye, 2006); and there is a small, temporarily increased risk of breast

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and cervical cancers with increasing duration of use (Mørch et al., 2017; Appleby et al., 2007). For most individuals, these risks are balanced against long-term reduction of other cancers, including ovarian and colorectal cancers (Chadwick et al., 2012; Murphy et al., 2017; Luan et al., 2015; Havrilesky et al., 2013; Michels et al., 2018; Iversen et al., 2017). Androgenic formulations of HCs are preferentially prescribed to adolescents for their beneficial effects on bone development (Hewitt and Cromer, 2000; Lahoti et al., 2021; Frye, 2006). Predicting who will benefit from HCs and who is at risk of deleterious side effects, and delineating strategies to optimize outcomes for all HC users is an important factor in reproductive health medicine. To extend this consideration to mental health benefits for HCs, we first need to understand how HCs impact the brain (Pletzer and Kerschbaum, 2014; Taylor et al., 2021) and psychological processes (Cobey and Buunk, 2012) and identify specific risk factors for adverse mood effects.

In this review, we make a case for the need for well-designed rodent models of HC-exposure, in concert with studies of human HC users, to understand the mechanisms by which HCs interact with a variety of biological and environmental factors to modify mental health. Animal models are uniquely suited to begin to address this gap in knowledge. Well-designed experiments will provide a basis to understand the molecular, circuit, and systems level impacts of HC formulations on stress-responsiveness, and on a range of psychological processes including depression-like behaviors, reward, motivation, and anxiety. By understanding the processes modulated by HCs and how they interact with individual risk factors, we can begin to apply a personalized medicine approach in which we aim to identify individuals that will benefit from specific HC formulations or strategies.

2. Why we need animal models

Studying HCs in the people that use them is essential for identifying the impact on people's life, mood, brains, and general health. To date, this work has defined various ways, reviewed below, by which HCs influence the brain. And yet individual differences in experience, genetics, stress exposure, age, and duration of HC use, as well as vulnerability to mood and other psychiatric disorders, make studying specific effects of HCs on neural mechanisms and psychological processes extremely difficult in human-subjects research. This is particularly problematic when these side effects occur in only a subpopulation of HC users. When data is collapsed into averages, and we assume the results represent "the average user", important effects that occur in a relatively small proportion of people are often obscured (Foster and Beltz, 2018).

A number of approaches have been used to reduce inter-individual variability and understand the impact of HCs on mental health. One effective approach has been to recruit people who have previously experienced adversemood symptoms (e.g, Poromaa and Segebladh, 2012; Petersen et al., 2021; Gingnell et al., 2013); another focuses on younger people using HCs for the first time (e.g. Skovlund et al., 2016; Skovlund et al., 2018); and a third uses sophisticated, daily behavioral assessments and repeated imaging to assess HC effects on individuals' mood and cognition over time (Foster and Beltz, 2018; Beltz and Moser, 2020; Kelly et al., 2020). These approaches have demonstrated more consistent results, yet it remains difficult to assess how different factors, including age, duration of use, and prior stress contribute to vulnerability to adverse consequences of HCs, and under what circumstances HCs confer protection against mood disturbances.

A second sticking point for understanding the effects of HCs in the brain and on mental health is that we do not yet know which mechanisms of HCs mediate these effects. HCs cause direct effects in the brain *via* high-affinity synthetic hormones that mimic increased levels of estradiol or progesterone and, conversely, chronic suppression of circulating estradiol, progesterone, and testosterone (Porcu et al., 2019; Graham and Milad, 2013; Graham et al., 2018; Porcu et al., 2012; Simone et al., 2015; Fleischman et al., 2010). HCs also exert "off-target" effects including androgenicity or anti-androgenicity (Fuhrmann et al., 1996; Sitruk-Ware and Nath, 2010; Schindler et al., 2003; Fedotcheva, 2021; Africander et al., 2011; Phillips et al., 1990) of synthetic progestins, regulation of the HPA axis and stress responses (e.g., Hertel et al., 2017; Kirschbaum et al., 1995) as well as interactions with glucocorticoid and mineralocorticoid receptors (GR, MR, respectively) (Fuhrmann et al., 1996; Sitruk-Ware and Nath, 2010; Africander et al., 2011; Carr, 1998) (See Table 1). Because HC users have access to a wide variety of HC types, doses, and formulations, and many people have used several types or formulations to find what works best for them and their particular circumstances, most studies of HC use also reflect this heterogeneity. This means that most studies include multiple types of HCs, formulations, and doses; albeit with a bias towards oral contraceptives, as the most commonly used HC type. This heterogeneity in many studies further complicates interpretation of what mechanisms are exerting which effects on brain and behavior.

To understand the complex interactions between HCs, stress, and precise systems, circuit, cellular, and molecular mechanisms by which HCs confer increased vulnerability – or resilience – to depression, we need to be able to experimentally control and manipulate more variables. Due to ethicality and individual variability, this is incredibly difficult in human subjects' research. Instead, we need complementary laboratory animal models of contraceptive hormone exposure that mimic the beneficial and adverse effects observed in people to identify how HCs affect the brain, determine risk factors for adverse effects, and predict which HC formulations are most beneficial for individuals.

Rat and mouse models are essential for identifying detailed molecular, cellular, and circuit-level mechanisms of hormonal action on the brain and behavior (Anker and Carroll, 2011; Oberlander and Woolley, 2016; McEwen and Milner, 2017; Song et al., 2018). In laboratory animals, we can systematically vary history of stress exposure, age of onset of HC exposure, interactions of stress during HC use, and HC formulations. Specific genotypes, including different strains and transgenic animals can identify the role of individual differences in stress or hormone responsivity (McKenna and Simon, 1993; Brinks et al., 2007; Cazares et al., 2019). Behavioral models of anxiety- and depression-like behavior (e.g., anhedonia (Planchez et al., 2019; Heinzmann et al., 2014)) and cognitive functions (e.g., memory and visuospatial navigation (Tronson and Keiser, 2019)) allow us to examine the impact of HCs on psychological processes. In laboratory animals, we can also directly measure stress hormone levels (Porcu et al., 2019), and conduct pharmacological manipulations, invasive surgical, molecular and imaging techniques to determine the precise causal mechanisms by which HCs affect the brain. Animal models of HC exposure can thus provide a way to determine which effects of HCs – direct effects on estrogen and progesterone receptors, indirect effects of reduced hormone levels, or off-target effects of synthetic hormones – mediate the various changes in affective, cognitive, and stress-related functions.

Importantly, animal models of HC exposure are not a replacement for human studies. Rather, animal models are "reverse-translational" extension of this research, whereby we design models to mimic known human states, answer questions arising from human subjects' research, and develop new hypotheses to be tested in human HC users. Animal models, when well-integrated with data from human studies, will be essential for filling-in gaps in knowledge, advancing our understanding of how HCs affect the brain, and will be instrumental in maximizing benefits and minimizing mental health risks of HCs in healthcare settings.

In this review, we will outline what we know about HC effects on the brain and define the questions arising from human studies that animal models can answer. We will end by describing existing models, discussing future directions and alternative models moving forward.

3. How hormonal contraceptives Work: A primer

HCs are usually comprised of one or two active components: either a synthetic progestin alone (e.g., progestin only pill, IUD with progestin),

Table 1
Progestin effects and binding affinities.

	OG	2nd Generation	3rd Generation		4th Generation
	Progesterone	Levonorgestrel	Norgestimate	Gestodene	Drospirenone
Progestogenicity (binding affinity)	High (50)	High (150)	Medium (15)	Very High (90)	High (25)
GR efficacy (binding affinity)	High (10)	- (1)	- (1)	Low (27)	- (6)
Anti-MR efficacy (binding affinity)	High (100)	- (75)	- (0)	High (290)	High (230)
Androgenicity (binding affinity)	Anti (0)	High (45)	Medium (0)	High (85)	Anti (2)

(Fuhrmann et al., 1996; Schindler et al., 2003; Phillips et al., 1990; Kuhl, 2005) GR: glucocorticoid receptor. MR: mineralocorticoid receptor.
Note: binding affinity does not always correspond to efficacy.

or a synthetic progestin in combination with a synthetic estrogen - typically ethinyl estrogen (e.g., Combined oral contraceptives; vaginal ring). HCs act *via* both local, uterine/ovarian level and in the brain, *via* hypothalamic-pituitary-ovarian level. Locally, progestins alter the consistency of cervical mucus, leading to a barrier less penetrable to sperm and hostile to sperm motility and survival, and changes the local hormonal dynamics to partially suppress ovulation (Rivera et al., 1999). For some HCs (e.g., IUD) these are the primary routes of action. For HCs that have substantial circulating levels of hormone (e.g., implant, OCs, vaginal ring), the primary action is *via* a negative feedback loop in the brain. Specifically, HCs prevent elevations in gonadotropin releasing hormone (GnRH) production in the hypothalamus required for pituitary production of luteinizing hormone (LH) and follicle stimulating hormone (FSH), in turn suppressing follicular development and ovarian production of progesterone and estrogens. This negative feedback loop also results in lower production and levels of endogenous progesterone and estrogen and more consistent day-to-day hormone levels than during natural cycling (Petitti, 2003; Frye, 2006; Fleischman et al., 2010; Rivera et al., 1999; Hampson, 2020) (Fig. 1).

Side effects of HCs may be due to either direct effects of high-affinity synthetic estrogens and progestins on endocrine receptors in the brain, or somewhat counter-intuitively, due to a chronic decrease in circulating hormone levels that may persist even after cessation of use (Chan et al., 2008). Importantly, whereas the estradiol component of combined hormonal contraceptives is fairly consistent (ethinyl estradiol, EE), the progestin component of contraceptives varies across several kinds and classes of progestin, each with its own specific profile of pharmacological efficacy, kinetics, and off-target effects (Fleischman et al., 2010; Fuhrmann et al., 1996; Sitruk-Ware and Nath, 2010; Schindler et al., 2003; Fedotcheva, 2021; Africander et al., 2011; Phillips et al., 1990; Kuhl, 2005; Giatti et al., 2016). Thus, HCs exert off-target effects *via* other neurotransmitter systems including GABA (Porcu et al., 2012) and dopamine (Algeri et al., 1976), and *via* the binding of exogenous hormones on other receptors including GR, MR, and androgen receptors (AR) (Fleischman et al., 2010; Fuhrmann et al., 1996; Sitruk-Ware and Nath, 2010; Schindler et al., 2003; Fedotcheva, 2021; Africander et al., 2011; Phillips et al., 1990; Kuhl, 2005; Giatti et al., 2016).

The precise off-target effects of the various synthetic progestins differ depending on their derivation. In contrast to progesterone, second-generation synthetic progestins derived from testosterone, including levonorgestrel, have no MR or GR effects and stronger androgenic efficacy; and fourth-generation, spironolactone-derived progestins, such as drospirenone, have fewer GR effects than endogenous progesterone, together with anti-MR, and anti-androgenic efficacy (Table 1). These differential effects likely incur very different short- and long-term changes on stress-related responding. Given the central role of stress and HPA-axis signaling in cognition, emotion, and psychiatric disorders (Merz and Wolf, 2017; Horst et al., 2011; Lupien et al., 2009; Tafet and Nemeroff, 2016; Bangasser and Valentino, 2014; Grillon et al., 1996; Chattarji et al., 2015; Riboni and Belzung, 2017), the modulation of stress responses by HCs is of high interest as a potential contributor to adverse effects on mood.

4. Hormonal effects on the brain

The fact that HCs affect the brain is clear – at the very least, the primary effect of circulating progestins is *via* hypothalamic suppression of pituitary production of LH and FSH. In addition, HCs exert notable effects on plasticity, structure, and function in various brain regions. This is not surprising as gonadal hormones are well known to be highly neuroactive and dynamically influence the neurons, plasticity, mood, and behavior.

There is extensive evidence for the physiological impact of estrogens and progesterone on the brain, beyond sexual behaviors, from studies of freely cycling female rodents and women and of exogenous manipulations (gonadectomy, hormone administration). Across the estrous cycle, in rats and mice, there is substantial hormone-dependent regulation of chromatin and gene expression (Jaric et al., 2019; Duclot and Kabbaj, 2015), dendritic spines and plasticity (Woolley and McEwen, 1993; Woolley et al., 1990), as well as cognitive functions including memory and behaviors such as motivation, anxiety, fear, and impulsivity (Zhuang et al., 2020; Jaric et al., 2019; Milad et al., 2006). In humans, the menstrual cycle similarly modifies prefrontal and hippocampal activity (Barth et al., 2016; Arélin et al., 2015) as well as affective states including anxiety (Gonda et al., 2008) and tasks including fear extinction. Therefore, the observation that hormonal fluctuations influence a variety of measures is consistent across the rodent estrous cycle and in humans across the menstrual cycle, sometimes in the same studies (e.g., Lebron-Milad et al., 2012), supporting the validity of animal models for studying mechanisms of hormonal (including HC) effects on the brain.

For example, dendritic spines – the tiny projections that make contact, or synapses, with other neurons – increase during high-estradiol phases of the cycle (proestrus through estrus) and decline through the remainder of the cycle (Woolley and McEwen, 1993; Frankfurt and Luine, 2015). These changes have been observed across species and brain regions (see Sheppard et al., 2019 for review). In humans, changes in structure, function, and connectivity are also broadly observed across the menstrual cycle in many brain regions and circuits, including hippocampus, amygdala, and prefrontal cortex (Dubol et al., 2021). Consistent with literature from rodents, human hippocampus increases volume and activation during the follicular phase of the menstrual cycle, when estrogen is increasing and progesterone levels are low (Dubol et al., 2021).

Acute estradiol is known to play a direct role in modulating plasticity, both regulation of dendritic spines *via* a slow, genomic pathway, and regulation of synaptic plasticity *via* rapid effects on receptor, signaling, and transcriptional regulation (Hojo et al., 2011; Sellers et al., 2015; Woolley and McEwen, 1994; Luine and Frankfurt, 2012; Murphy and Segal, 1997). Indeed, administration of estradiol enhances spatial memory and synaptic plasticity in both males and females (Gresack and Frick, 2006; Jacome et al., 2016; Taxier et al., 2020), albeit *via* different mechanisms (Taxier et al., 2020; Koss et al., 2018). For example, recent

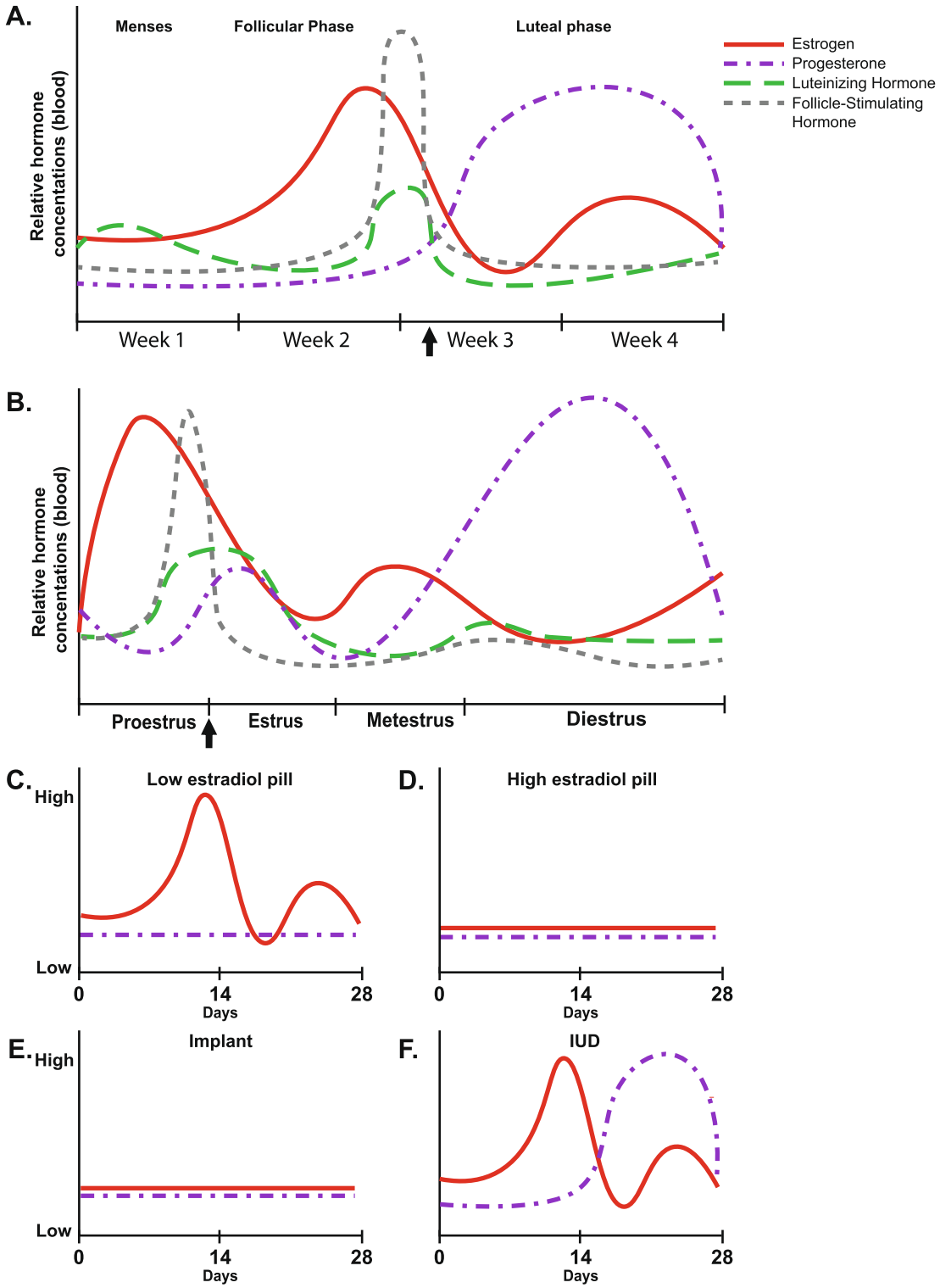

Fig. 1. Schematic of endogenous hormone levels across cycles. (A,B) Hormone levels across the menstrual cycle and estrous cycle (adapted from (Hong and Choi, 2018)). (A) The menstrual cycle consists of four phases: menses, follicular, ovulation, and luteal phase. (B) The estrous cycle in rodents consists of 4 phases: proestrus, estrus, metestrus, and diestrus. Arrows indicate time of ovulation. (C-F) Predicted endogenous estrogen and progesterone levels throughout the menstrual cycle while on different forms of HCs (Porcu et al., 2019; Pritschet et al., 2020). (C) Low estradiol oral contraceptives; (D) high estradiol oral contraceptives; (E) implant; and (F) levonorgestrel-containing IUD.

data suggests that estradiol levels affect spatial memory in women, with high estradiol correlated with better long-term memory for a spatial task, but no differences in learning or spatial working memory (Patel et al., 2022). Similarly, in rodents, estradiol biases towards hippocampal-dependent strategies for spatial tasks (Korol and Pisani, 2015); although, these effects also depend on whether progesterone co-occurs (Lacasse et al., 2022). Estradiol levels also enhance extinction of fear-related memories, with rodents and women in high-estrogen cycle phases showing faster extinction than low-estradiol phases (Graham et al., 2018; Milad et al., 2006; Rey et al., 2014; Maeng et al., 2017).

Changing hormone levels across menstrual and estrous cycles also modulate affective-related behaviors. For example, high estrogen phases are associated with greater exploratory behaviors and less anxiety in rodents across a variety of standard anxiety tests (Jaric et al., 2019; Mora et al., 1996). Consistent with these findings, in humans, the follicular phase of the menstrual cycle is related to less stress-induced negative affect compared with low-estradiol luteal phase (Albert et al., 2015). Similarly, there are substantial sex differences in reward-related processes, pathways, and behaviors, and reward-related behaviors, motivational processes, and neural circuits, are regulated by gonadal hormones in a complex way (Song et al., 2018; Becker and Chartoff, 2019). High estrogen levels during proestrus triggers increased motivation toward reward-related stimuli, and more subtly, changes in the kinds of outcomes that are preferred. For example, during proestrus mice show increased preference to mate access over food, enhanced motivation for cocaine, and decreased food or sugar pellet intake (Yoest et al., 2019; Perry et al., 2015; Datta et al., 2017; Kohtz et al., 2022). Physiological changes in estradiol across hormonal cycles are therefore essential for regulation of cognitive and affective processes.

The vast majority of studies have focused on estradiol; however, progesterone also exerts regulatory effects on the brain and behavior. Progesterone acts both directly (Lacasse et al., 2022; Toffoletto et al., 2014; González et al., 2020) and *via* neuroactive metabolites including allopregnanolone and 5α- dihydroxyprogesterone (5α-DHP), with strong positive modulation of $GABA_A$ (González et al., 2020; Belelli and Lambert, 2005). Co-ordinated estrogen and progesterone surges also modulate serotonergic activity throughout the brain, as well as dopaminergic signaling, and oxytocinergic modulation (Barth et al., 2015; Theis and Theiss, 2019). In contrast to estrogens role in increasing motivation, progesterone decreases reward-related processes. Accordingly, reward-related activation in the mesolimbic system and responses to rewarding stimuli, together with subjective 'liking' of cocaine, is higher during the late-follicular phase (high estrogen, low progesterone), compared with the mid-luteal phase when progesterone levels peak (Dreher et al., 2007; Terner and de Wit, 2006; Sofuoglu et al., 1999). When both estrogen and progesterone are high, rewarding effects and likelihood of relapse are diminished in both women and rodents (Franklin et al., 2004; Justice and de Wit, 1999; Hudson and Stamp, 2011; Evans et al., 2002). This effect is mirrored with exogenous progesterone treatments, which reduce rewarding effects of drugs of abuse including alcohol, cocaine, and nicotine across sex (Peltier and Sofuoglu, 2018; Sofuoglu et al., 2011). Nevertheless, use of nicotine and alcohol increase during pre-menstrual and menstrual phases (low levels of both estrogen and progesterone), although whether this is due to hormonal-driven changes in motivation, self-medication for premenstrual symptoms, or increased withdrawal symptomatology is less clear (Joyce et al., 2021; Carpenter et al., 2006). Progesterone, therefore, has a complex regulatory role on reward-related processes.

Progesterone also influences dynamic memory systems. In contrast to the bias towards hippocampal-dependent "place" strategies with high estradiol, administration of progesterone, even with estradiol, shifted animals to a striatal-dependent response-based strategy, similar to that of low estradiol animals (Lacasse et al., 2022). This is consistent with previous work demonstrating an opposing effect of progesterone on estradiol-mediated memory enhancement (Bimonte-Nelson et al., 2006; Warren and Juraska, 1997). Thus progesterone, like estradiol, has important neuromodulatory effects, and the roles of estrogens and progesterone need to be considered in concert.

Gonadal hormones also indirectly regulate key neuronal processes via central and peripheral effects on the hypothalamic–pituitaryadrenal (HPA) axis. Specifically, progesterone, glucocorticoid, and mineralocorticoid receptors are members of the same subfamily, and progesterone binds to all three (Sitruk-Ware and Nath, 2010; Baker and Katsu, 2020; Wirth et al., 2007). Indeed, both progesterone and estrogens interact with the HPA-axis and stress responsiveness. Progesterone increases parasympathetic activity, thereby dampening the stress response and producing an anxiolytic effect (Frye, 2007; Söderpalm et al., 2004). Similarly, during high estradiol phases of the menstrual cycle, the cortisol response to stress decreases as estradiol also inhibits effects on the HPA axis (Albert et al., 2015; Young et al., 2001; Albert and Newhouse, 2019). Once again, it is possible that changes in stress responsiveness and basal cortisol levels are due to direct effects of HC hormones on receptors, indirect effects *via* suppression of circulating gonadal hormones, or off-target effects of the synthetic hormones, particularly on GRs and MRs. Here, differences among synthetic progestins in HC formations, and between synthetic and endogenous progesterone on affinity for and regulation of stress-related receptors in the periphery and in the brain are particularly interesting. The balance between GR and MRs is critical for precise regulation of HPA-axis activation, where MRs are involved in activating and increasing the stress response, and GRs are required for the negative feedback termination of the stress response (Hartmann et al., 2021). Either decreased MR activation or increased GR activation may therefore mediate the suppression of acute stress response observed in HC users (de Kloet et al., 2016).

Given the overwhelming data on modulation of neuronal structure and function by estradiol, progesterone, and the combination, the idea that HCs modulate brain and behavior is neither surprising, nor alarming. Rather, HC effects on the brain are an extension of the normal biological processes that mediate changes across physiological hormonal fluctuations. Understanding what these changes are and the underlying mechanisms mediating such changes is critical for predicting who is likely to be vulnerable to adverse consequences and thus tailoring reproductive healthcare, including HCs, appropriately for each individual. Moving forward, the use of animal models in understanding specific hormone-mediated effects on the brain provides a template for future models of contraceptive hormone exposure in mice.

5. HC effects on mood, anxiety, and depression

There is substantial conflict in the literature about whether modern HCs contribute to changes in mood and increase risks for, or rates of, anxiety, panic, or depression. On the one hand, the vast majority of individuals report no change in rates or risk for these disorders, and if anything, many people experience improved mood with HCs, particularly around menstruation (Keyes et al., 2013; Cheslack-Postava et al., 2015; Scheuringer et al., 2020; Lopez et al., 2012; Coffee et al., 2006). And yet, adverse emotion and mood-related effects are reported to be the main reason discontinuation of HC use (Sanders et al., 2001; Lewis et al., 2019). For some, HCs have serious affective side effects including depression and suicidality (Porcu et al., 2019; Poromaa and Segebladh, 2012; Skovlund et al., 2016; Skovlund et al., 2018; Edwards et al., 2020; Schaffir et al., 2016; Worly et al., 2018).

Understanding how HCs exert these effects on mood, anxiety, and depression, and identifying who will experience beneficial effects *versus* who is at risk for deleterious side effects from HCs is critical for increasing standards of care. One emerging risk factor is adolescence, which seems to be a particularly vulnerable period for HC-associated depression (Skovlund et al., 2016; Skovlund et al., 2018), both during adolescence, and for years following cessation of use (Anderl et al., 2021; Anderl et al., 2020). Nevertheless, there are limited studies on adolescent HC use and the existing studies rely on self-report from individuals that self-select to go on HCs. Without the option of randomization, it is difficult to rule out additional, HC-independent effects on depression risk in this subpopulation of HC users.

Previous experience of mood-related side effects of HCs is another risk for future adverse reactions. There is a growing body of literature that exploits this difference and focuses on individuals in this group to understand HC-mediated changes that correlate with increased risk. These studies demonstrate that individuals who have previously experienced emotion-related side effects are more likely to show structural and functional changes during HC use (Petersen et al., 2021; Gingnell et al., 2013). The prefrontal cortex shows some thinning, and there are

altered activation patterns of emotion-related brain regions including amygdala and insular cortex in these individuals (Petersen et al., 2021; Gingnell et al., 2013). Nevertheless, interpreting these structural findings is more complex since, first, these changes do not necessarily correlate with mood symptoms or other behavioral changes, and because HC use also exerts long-lasting influences on cortical volume (Pletzer and Kerschbaum, 2014; Petersen et al., 2021; Pletzer et al., 2014), raising the questions of what is causal, what is correlational, and what are long-lasting changes after HC use.

People with prior diagnoses of depression, independent of HC use, are also at higher risk for HC-triggered or compounded depression (Bengtsdotter et al., 2018). This may be dependent on HC formulation, for example, in major depressive disorder, progestin-only contraceptives were associated with more depression compared with natural cycling, and in contrast to a decreased risk of depression with combined oral contraceptives (Young et al., 2007). Notably, this risk profile is reversed in the post-partum period with a decreased risk of depression with progestin-only contraceptives (pill or IUD) (Ti and Curtis, 2019). These findings highlight the potential role of progestins in mood-related side effects. Indeed, whereas the estradiol component of HCs modulates some of the cognitive changes (Beltz et al., 2015), progestins have been more strongly implicated in mood-related effects (Schaffir et al., 2016; Worly et al., 2018). These findings also emphasize the importance of taking basal hormonal state into account – and suggests that adolescence, young adult, post-partum, multiparous, and *peri*-menopausal states might have very different benefit/risk profiles for different formulations of HCs.

These studies, and ongoing research, provide critically important new data for potential risk factors – including adolescence, or initiating HC use during adolescence, and the role of progestins in mood-related side effects. And yet, understanding the causal relationships between HCs and risk for depression is extremely difficult in human studies. Animal models will be essential for understanding questions of the mechanisms underlying HC effects on mood, and the causality of HC effects observed in human studies. These models are especially suited to addressing difficult-to-answer questions including: what are the effects of HCs during adolescence, how androgenic *vs* anti-androgenic progestins differentially affect risk for depression-like behaviors, and how known risk factors for depression, including prior stress exposure, modifies risk for depression while using HCs.

5.1. HC effects on reward and motivational processes

Given the robust regulatory effects of ovarian hormones on reward and motivational processes, it is not surprising that HCs may also modulate these processes. Yet the research on endogenous hormones, such as changes in reward across the menstrual or estrous cycle (Dreher et al., 2007; Justice and de Wit, 1999; Hudson and Stamp, 2011), is not sufficient to make firm conclusions about the effects of HCs on reward related processes. HC-modulation of motivation, reward, and hedonic processes is particularly important for the role of HCs in risk for depression. Because stress and motivational systems are highly interactive, and decreased motivation and the related construct, anhedonia, are hallmarks of depression (Planchez et al., 2019; Slattery and Cryan, 2017). Gonadal hormones have important modulatory effects on motivational processes (Song et al., 2018). In studies of human HC users, the impact of HCs on motivated and reward-related behaviors is dependent on the specific task and whether the task uses money, food, or social rewards. For example, HCs decrease the oxytocin-induced effects on ratings of partner attractiveness (Scheele et al., 2016), and decrease activation of insula activation during subtle sexual cues (Abler et al., 2013). Conversely, HCs show increased activation of insula and lateral prefrontal cortex in a monetary reward task (Bonenberger et al., 2013). Other effects depend on progestin levels. During smoking, for example, low exogenous progestin levels predicted higher satisfaction and overall greater negative affect during abstinence (Hinderaker et al., 2015).

Consistent with these observations, HCs modulate structural and functional measures in regions associated with salience, reward, and motivation. Importantly, this also depends on age of onset of HC use. For example, HC users show changes in resting state connectivity in salience and reward networks, and adolescent-onset HC use showed altered resting state functional connectivity in salience network, over and above that observed in adult-onset users (Sharma et al., 2020). Moreover, HC use is associated with decreased cortical thickness in lateral orbitofrontal cortex, a region critical for responding to rewarding stimuli (Petersen et al., 2021).

Given the important role of gonadal hormones in regulating reward and motivation, it is somewhat surprising that there are not more studies on HCs and motivation/reward processes. As noted earlier, rodent models continue to be critical for characterizing the neural systems and complexities of hormonal contributions to these processes. This supports the idea that animal models of HC exposure will be an essential step for understanding the modulatory roles on specific reward- and motivation-related processes, and the intersections between motivation, reward, anhedonia, and depression in HC users.

5.2. Hormone contraceptives and cognition

Sex hormones also modulate cognitive strategies, with circulating estrogen levels implicated in verbal memory, fear extinction, and spatial strategies (Beltz and Moser, 2020; Graham and Milad, 2013; Milad et al., 2006; Sherwin, 2012; Mordecai et al., 2008) and testosterone implicated in visuospatial memory (Aleman et al., 2004; Cherrier et al., 2001). Similarly, we should expect that HCs modulate molecular-, circuit-, and systems-level activities triggered by cognitive tasks, thereby affecting performance and strategy. Of the cognitive processes so far examined, there are contradictory effects of HCs, suggesting that here too HC effects may be due to direct effects on hormone receptors, off-target effects, or overall suppression of endogenous estrogen and progesterone.

Although we often automatically code “changes in cognition” as problematic, there is a growing understanding that many tasks have multiple strategies for effectively completing them. This is certainly true for our growing understanding of sex differences in cognition and memory, where cognitive strategies and behavioral responses vary across males and females (Tronson and Keiser, 2019; Tronson, 2018), some of which are driven by gonadal hormones (Taxier et al., 2020; Luine, 2014). Perhaps the best-known example of this is spatial cognition, where women and female rodents show a bias towards local, landmark cues, and men and male rodents are biased towards distal, directional information (Chai and Jacobs, 2010). This effect is, at least in part, dependent on gonadal hormones, with high circulating estradiol levels associated with a bias towards landmark information (Harris et al., 2022; Scheuringer and Pletzer, 2017), towards categorical information over metric cues (Holden and Hampson, 2021), and towards place over spatial strategies (Korol and Wang, 2018; Korol et al., 2004; Korol and Kolo, 2002). This is also true for behavioral responses, for example, fear-related responses in females are more likely to show an active, darting response together with an immobile, freezing response (Gruene et al., 2015), and faster extinction of fear conditioning (Lebron-Milad et al., 2012; Lebron-Milad et al., 2012). These factors are also modulated by levels of circulating estrogens, with higher circulating levels of estrogens in females resulting in faster extinction (Milad et al., 2006; Rey et al., 2014; Maeng et al., 2017; Bierwirth et al., 2021), at least across some behavioral measures (Tang and Graham, 2019; White and Graham, 2016).

With this in mind, HCs, like naturally occurring hormones, do modulate strategies and performance of some cognitive processes and affective learning, even in the absence of mood symptoms. Indeed, the composite score on cognitive performance as a whole is somewhat higher in people on oral contraceptives and in early follicular (high circulating estrogen and progesterone) compared with those in the mid-luteal (low estrogen and low progesterone) phase of cycle (Gogos,

2013). Similarly, patterns of cognitive processes in the active phase of HCs most resemble those at menstrual phases when levels of estrogen are highest (Beltz et al., 2015; Hampson, 2018). This is a transient effect, where cognitive function during inactive pill phases most resembles that during the menstrual phase (i.e., low hormone levels). This suggests that despite suppression of estrogens and progesterone, HC modulation of cognition is, in large part, due to their direct effects at hormone receptors (Beltz et al., 2015; Hampson, 2018; Stanczyk et al., 2013).

Not all modulatory effects on cognition are due to estrogenic and progestogenic effects directly, and there are contradictory observations from specific cognitive tasks. In visuospatial cognitive tasks, for example, this pattern of better performance in HC and high estradiol/progesterone levels was true for delayed memory and attentional subtasks, with no differences between groups in visuospatial memory, an effect replicated in other studies (Pletzer et al., 2014; Wharton et al., 2008). In contrast, other studies have observed marked effects on visuospatial cognition, with the direction of the effect dependent on progestin androgenicity. Here, HC formulations with androgenic progestins enhance visuospatial tasks, whereas those with anti-androgenic progestins decrease performance (Pletzer and Kerschbaum, 2014; Wharton et al., 2008; Gurvich et al., 2020). Curiously, there is also some evidence for long-term effects of HCs on visuospatial tasks. In midlife, individuals that had previously used HCs show enhanced visuospatial performance compared with menstruators who had never used them, and this effect was strongest for individuals with more than 15 years of HC use (Egan and Gleason, 2002). Not all modulatory effects on cognition are due to estrogenic and progestogenic effects directly, and there is contradictory observations from specific cognitive tasks. In visuospatial cognitive tasks, for example, this pattern of better performance in HC and high estradiol/progesterone levels was true for delayed memory and attentional subtasks; with no differences between groups in visuospatial memory, an effect replicated in other studies (Pletzer et al., 2014; Wharton et al., 2008).

Verbal processes are also modulated by HCs, although how it is affected is somewhat inconsistent. Verbal fluency was decreased in HC-using compared to naturally cycling individuals (Griksiene and Ruksenas, 2011). Yet other studies have observed no differences in verbal fluency with HCs, but improved verbal memory (Mordecai et al., 2008). The discrepancy in verbal fluency may be due, in part, to different effects of progestin androgenicity across studies. When broken down by HC formulation, androgenic HCs were more likely to decrease verbal fluency than anti-androgenic progestins (Griksiene and Ruksenas, 2011). Although opposite in direction to visuospatial tasks, the role of androgenicity here is consistent with a shift towards a more “male-like” pattern of cognitive function.

Other learning and memory tasks are modulated by HCs in accordance with low circulating hormones. Fear extinction, for example, is slow, consistent with menstrual phases with low levels of estradiol (Graham and Milad, 2013). In other tasks, memory modulation is more consistent with direct effects of exogenous hormones. For example, eyeblink conditioning, a cerebellar mediated learning task, is enhanced beyond the hormone-dependent accelerated acquisition of eyeblink conditioning in women compared with men (Beck et al., 2008; Holloway et al., 2011).

Not all cognitive processes are modulated by HCs. Studies of attentional processes and inhibitory processes have observed no difference in performance in HC *vs* freely cycling individuals (Scheuringer et al., 2020; Mordecai et al., 2008; Gingnell et al., 2016). And yet, imaging studies have observed that HCs do modulate attentional networks. Specifically, attentional network activation in HC users resemble those in the follicular phase (Cohen et al., 2022), suggesting that here, any effects may be mostly driven by the hormone-suppressing effects of HCs. Congruent with this mechanism of action, progesterone specifically plays an important role in modulating correlations of neural activity between different attentional tasks, and patterns of activation in HC-users are consistent with those in low-progesterone states (Schultheiss et al., 2012).

Perhaps the most important take-away for effects of HCs on cognition and cognitive function is that different mechanisms of HC function likely contribute to different effects of HCs on cognition. Estrogenic effects and androgenic effects, suppression of hormone levels, and off-target effects of HCs can all influence cognitive function, sometimes in contradictory ways. Animal models will be valuable for identifying the precise mechanisms by which HCs impact cognitive processes and, specifically, the roles of direct HC effects on hormone receptors, the effects of chronic decreased circulating hormone levels, and of off target effects of HCs on systems including, stress-related responses.

6. Hormonal contraceptives and the stress response

One unifying – or perhaps confounding – intermediary in cognitive effects, mood and affective regulation, and reward and motivation is the role of HCs in regulation of stress and glucocorticoid signaling pathways. That HCs modulate the stress response is consistent with the known relationships between ovarian hormones and the HPA-axis, as discussed above. Indeed, the modulation of stress responsiveness is perhaps one of the most robust and replicated effects in studies of HC users, with most studies showing a blunted stress response (Porcu et al., 2012; Hertel et al., 2017; Kirschbaum et al., 1995; Merz and Wolf, 2017; Lewis et al., 2019; Sharma et al., 2020; Kirschbaum et al., 1999; Nielsen et al., 2013; Rohleder et al., 2003; Mordecai et al., 2017; Boisseau et al., 2013; Aleknaviciute et al., 2017; Bouma et al., 2009; Høgsted et al., 2021; Roche et al., 2013), and to a lesser extent, altered basal cortisol levels (Porcu et al., 2019; Hertel et al., 2017; Boisseau et al., 2013; Aleknaviciute et al., 2017; Meulenberg et al., 1987; Lovallo et al., 2019), providing an indirect mechanism by which HCs may modulate mood, motivation, and cognition (See Table 2). Given the importance of stress in the etiology of depression- and anxiety-related disorders (Planchez et al., 2019; Tafet and Nemeroff, 2016; Bangasser and Valentino, 2014; de Kloet et al., 2016), regulation of motivation and reward-related processes (Slattery and Cryan, 2017; Lynch et al., 2020), and modulation of cognition and memory (Merz and Wolf, 2017; Lupien et al., 2009; McGaugh, 2018; Shors, 2004), the role of HPA-axis regulation by HCs needs to be a central consideration in understanding the benefits and risks of HCs on the brain.

Changes in stress responsiveness – either exaggerated or insufficient responses – are commonly associated with risks for mood or anxiety disorders (Hartmann et al., 2021; de Kloet et al., 2016), and it is likely that changes in stress responsivity increase risk or resilience to depression and other altered affective states. For example, a chronically blunted response is a risk factor for depression and dysregulated motivational system (Carroll et al., 2017; Burke et al., 2005). Elevated baseline cortisol levels may also be indicative of a chronic stress-like phenotype, which contributes to psychiatric disorders including depression (Hertel et al., 2017; Carroll et al., 2017). Indeed, although some studies have observed blunted stress response in the absence of mood-related side effects of HCs, it may be somewhat more likely that blunted stress responses are observed in HC-users with a history of depression or other mood changes associated with HCs (Lewis et al., 2019).

In addition to psychiatric disorders, stress is a potent modulator of cognition and memory (Horst et al., 2011; Lupien et al., 2009; McGaugh, 2018). HCs demonstrably alter the relationship between emotion-related memory formation and stress responses. For example, oral contraceptive use results in decreased memory for emotion-related stimuli (Nielsen et al., 2013; Mordecai et al., 2017), potentially due to the suppression of acute stress response in individuals using HCs. In contrast, whereas increased cortisol prior to a learning task caused impairments in fear learning and retrieval during the follicular and luteal phases of the menstrual cycle, in participants on oral contraceptives, cortisol enhanced learning and had no effect on retrieval (Merz et al., 2012; Kuhlmann and Wolf, 2005). These bidirectional effects on fear

Table 2
HCs modulate stress and HPA-axis function.

ACUTE STRESS RESPONSE						
	Measured	**Tissue**	**HC formulation**	**Stress**	**Subjects**	**References**
↓	Cortisol	Saliva	LVNG-IUDs and EE + LVNG	ACTH challenge	Adult humans	(Aleknaviciute et al., 2017)
			COC	ACTH challenge		(Kirschbaum et al., 1999)
			N.R.	TSST		(Rohleder et al., 2003)
			N.R.	TSST		(Kirschbaum et al., 1995)
			COCs	TSST		(Mordecai et al., 2017)
			N.R, adolescent use	TSST		(Sharma et al., 2020)
			COC	CPS and images		(Nielsen et al., 2013)
			COC	CPS		(Nielsen et al., 2014)
			EE + gestodene	SECPT		(Merz and Wolf, 2017)
			multiple	psychosocial stressors		(Roche et al., 2013)
			multiple	GSST	Adolescents	(Bouma et al., 2009)
			EE + gestodene	Exercise	adults	(Boisseau et al., 2013)
↓ (am only)			OC or implants	public speaking and mental math		(Lovallo et al., 2019)
			COC/IUDs	Awakening		(Høgsted et al., 2021)
↓	Cort.	Plasma	EE-LVNG	Acute restraint stress	Rats	(Porcu et al., 2019)
↓	ACTH	Plasma	Estradiol injection and progesterone implants	Restraint stress	Rats	(Young et al., 2001)
↑	Cortisol	Saliva	LVNG IUDs	TSST		(Aleknaviciute et al., 2017)
			multiple	Acute cortisol		(Gaffey et al., 2014)
			multiple	CPS		(Herrera et al., 2019)
			COC or vaginal ring	CPS		(Nasseri et al., 2020)
		Plasma	COC	cortisol administration		(Gaffey et al., 2014)
	Cort.	Serum	intravaginal P4 releasing device	Social isolation	Sheep	(Freitas-de-Melo et al., 2016)
N.E.	Cortisol	Saliva	EE + LVNG	TSST	Human adults	(Aleknaviciute et al., 2017)
			N.R.	Oral presentation		(Merz and Wolf, 2015)
			N.R.	Oral presentation		(Schoofs et al., 2008)
	Cort.	Plasma	Estradiol injection and progesterone implants	Acute restraint	Rats	(Young et al., 2001)
	Tolerance to heat	Behav.	COC	Heat stressor	Humans	(Tenaglia et al., 1999)
corr. with prog.	Cortisol	Saliva	N.R.	emotion-arousing		(Wirth et al., 2007)
BASAL CORTISOL						
Measured		**Tissue**	**HC formulation**	**Stress**	**Subjects**	**References**
↑	Cortisol	Saliva	EE + gestodene		Humans	(Boisseau et al., 2013)
			EE + desogestrel	-		(Meulenberg et al., 1987)
		Urine	EE + gestodene	-		(Boisseau et al., 2013)
		Hair	LVNG-IUDs	-		(Aleknaviciute et al., 2017)
		Plasma	multiple	-		(Hertel et al., 2017)
(am only)			COC/IUD	-		(Høgsted et al., 2021; Lovallo et al., 2019)
			OC/implant			(Lovallo et al., 2019)
	Total & free Cortisol, CBG	Plasma	EE + desogestrel	-		(Meulenberg et al., 1987)
	Cort.	Plasma	EE-LVNG	–	Rats	(Porcu et al., 2012)
N.E.	Cortisol	Saliva	N.R.	-		(Kirschbaum et al., 1995)
			COC	-		(Nielsen et al., 2013)
		Hair	Oral EE + LVNG	-		(Aleknaviciute et al., 2017)

N.E: no effect. Corr: correlates; prog: progesterone level.
Cort.: corticosterone; ACTH: Adrenocorticotropic hormone; CBG: corticosteroid binding globulin.
EE: Ethinyl Estradiol; LVNG: levonorgestrel; COC: combined oral contraceptives, not specified; N.R.: not reported; IUDs intrauterine device.
TSST: Triers Social Stress Test; SECPT: socially evaluated cold-pressor test; GSST: Groningen Social Stress Test; CPS: Cold Pressor Test.

conditioning also demonstrate the delicate balance on stress responses, timing, and cognitive/affective processes that preclude simple conclusions about HCs, stress responses, and whether these are beneficial or risk factors for adverse consequences.

One regulator of stress-reactivity is the FK506 binding protein 51 (FKBP5), a chaperone protein that is increased in response to MR activation and activation of the stress response, that negatively regulates GR responses, resulting in increased basal corticosterone levels (Hartmann et al., 2021; Häusl et al., 2021). Individuals that use HCs also show increased peripheral FKBP5 levels (Hertel et al., 2017), consistent with elevations in basal cortisol levels. How peripheral FKBP5 levels in HC users relates to central levels remains an open question – and one that we are not able to address in human studies. FKBP5 is particularly interesting target for future studies on HC regulation of stress due to the linkage between FKBP5 and psychiatric disorders including depression (Lee et al., 2011; Klengel et al., 2013; Tozzi et al., 2018; Wang et al., 2018). Moreover, given the association of FKBP5 polymorphisms as a known risk factor for these disorders, it is possible that this may be a genetic factor that modifies risk for adverse mood and depression effects of HC use (Klengel et al., 2013; Wang et al., 2018; Merkulov et al., 2017; Thomas et al., 2021). Whether FKBP5, or other known regulators of stress responsiveness (e.g., corticosteroid-binding globulins (Meulenberg et al., 1987; van der Vange et al., 1990), DNA damage inducible transcript 4 (DDIT4) (Scheuringer and Pletzer, 2017); corticotropin releasing hormone (Ketchesin et al., 2017)) modifies the association between HC-triggered suppression of stress responsiveness and risk for

(or resilience to) depression and other adverse emotion-related outcomes is an exciting direction of future research.

Based on the strong association of HCs and changes in stress-responsiveness in individuals that use HCs, animal models of HC exposure are well placed to identify how HCs mediate these effects, as well as the molecular mechanisms underlying these changes, both in the periphery and in the brain. Importantly, animal models are also key for understanding the HC-triggered changes in the impact of stress responses on neural signaling and on specific cognitive and behavioral processes (e.g., memory, depression-like behaviors, motivation and reward-related pathways and behaviors). By using targeted molecular and biochemical tools, as well as pharmacological and genetic manipulations, we can further identify the causal roles of changes in stress responses and individual factors that contribute to risk for depression and mood-related symptoms with HCs.

7. Animal models of hormonal contraceptives

Laboratory animal models of hormone exposure are not new, and models of HC-exposure are a variation on these studies. There are substantial differences in the structure of the estrous cycle in rodents from the menstrual cycle in humans, notably in the number of days, the reabsorption of the endothelial lining in rodents, and less complexity in rodent estrous cycle compared with the human menstrual cycle (Hong and Choi, 2018). Nevertheless, the impact of ovarian hormones on the brain and on behavior is highly translatable from rodent models to human health (Sheppard et al., 2019; Becker and Koob, 2016; Choleris et al., 2018). Thus, modeling HCs in rodent models will provide a unique platform from which to study many aspects of contraceptive hormones on the brain, HPA-axis, and behavior.

Many of the questions emerging from research on human HC users cannot be effectively or ethically studied in human subjects, but are accessible with animal models. These include: which of these effects are due to direct effects of high affinity hormones on receptors, which are due to suppressed circulating hormone levels, and what is due to off-target effects of the synthetic hormones? (See more in Table 3). Answering these questions will allow us to expand from identifying phenomenological effects of HCs, towards identifying how HCs exert these effects, and eventually to predicting which HC formulations will most benefit individuals.

7.1. Existing models and parameters to consider

Existing rodent models of contraceptive hormone administration, primarily combinations of ethinyl estradiol and levonorgestrel, recapitulate basic physiological effects of HCs. Notably, like in humans, administration of ethinyl estradiol and levonorgestrel in rats cause decreases in circulating LH (Kuhl et al., 1984), estradiol (Graham and Milad, 2013; Simone et al., 2015), and progesterone and its metabolites (Porcu et al., 2012; Santoru et al., 2014) that normalize in the weeks following cessation of administration (see also Porcu et al., 2019). In addition, there is initial evidence that, like in humans, HC-exposure causes a suppression of the acute stress response, as measured by corticosterone levels in rats (Porcu et al., 2019).

HC-like combinations also modulate cognition, memory, social behavior, and anxiety in animal models (Porcu et al., 2012; Simone et al., 2015; Lacasse et al., 2022; Santoru et al., 2014), demonstrating that similar behavioral effects of synthetic hormones are observed in rodents as in humans. Specifically, long-term ethinyl estradiol + levonorgestrel administration increases anxiety-like behavior in rats (Porcu et al., 2012; Follesa et al., 2002), as does chronic levonorgestrel, but not ethinyl estradiol treatment alone (Porcu et al., 2012). Importantly, there are important effects of dose and hormone combination, with some studies showing that ethinyl estradiol alone can increase or decrease active behaviors, depending on dose and presence of levonorgestrel (Simone et al., 2015). Ethinyl estradiol + levonorgestrel decreased

Table 3
Future questions for animal models of HCs.

Observations in Humans	Some initial questions suited for animal models of HCs
HCs modulate HPA axis, possibly *via* FKBP5	• How do HCs modulate HPA axis? What changes in the brain mediate changes in stress responsiveness? • What is the role of FKBP5 and FKBP5 polymorphisms in vulnerability to adverse effects of HCs? • What is the relationship between HPA axis modulation by HCs and mood-related changes (both adverse and beneficial)?
Individual differences in mood effects of HCs	• Do different mouse/rat strains show differences in affective regulation by HCs? • Do genetic manipulations that increase vulnerability to depression in humans increase HC-induced changes in affective processes in animal models? • Does prior experience increase (e.g., prior stress) or decrease (e.g., environmental enrichment) vulnerability to affective dysregulation by HCs? • Do individual differences factors change vulnerability to any HC formulation? Or only to some specific progestins/combinations? • How are different endophenotypes/aspects of depression-like behavior (e.g., despair, anhedonia) modified by different HC formulations? How do changes in specific aspects of affective processes map on to changes in neurotransmitter systems, stress-related signaling, and circuit/systems level activity in the brain? • How does age, duration of HC use, and hormonal milieu alter vulnerability?
Different progestins/HC formulations have different effects	• How do progestins or HC regimens differ in effects on the brain, HPA axis, cognition, affective processes and behaviors? • How does progestin androgenicity differentially affect specific physiological makers, cognitive processes, and affective tasks? • Does manipulating androgenic effects (e.g., AR inhibition/activation) block or mimic the progestin effects? • How do different MR/GR effects of progestins contribute to HPA axis modulation and affective regulation?
Greater vulnerability to depression during HC use in adolescence	• Does exposure to HCs in pubertal animals exacerbate the affective modulation compared with adult animals? Do all HCs have this effect or are some more likely to be protective? • Do risk factors for depression (e.g., early life stress) interact with HCs to trigger depression? • How do HC-induced changes in the brain during puberty compare with HC-induced changes during adulthood?
Long-lasting adverse or beneficial effects of HCs	• Does HC exposure during adolescence increase vulnerability to stress-induced depression during adulthood? Does this require ongoing exposure to HCs? • How does HC exposure (at any time) induce lasting changes to ER, PR, AR, MR, or GR levels or distribution in the brain? Are there any epigenetic (chromatin or DNA methylation, for example) that persists after HC use, and changes gene expression patterns?

(*continued on next page*)

Table 3 (*continued*)

Observations in Humans	Some initial questions suited for animal models of HCs
Broad changes in brain structure and function, and Modulation of cognitive strategies	• Do HCs modulate neurosteroid levels (including estradiol and progesterone) and does this change over time? • How does intermittent use alter long-term risks or benefits of HCs? • How do different formulations of HCs affect dendritic spine density and plasticity? Dynamic memory systems? Cognitive strategies? • How do these changes interact with individual differences (e.g., prior stress, environmental enrichment, strain differences)
How are HCs exerting effects on the brain?	• Across tasks/questions: directly test the role of estrogenic or progestogenic effects *vs* suppression of endogenous hormone levels *vs* off-target (e.g., AR, stress-related signaling) *vs* modulation of other neurotransmitter and peptidergic systems in the brain

social dominance behavior and proceptive behaviors (Santoru et al., 2014). Levonorgestrel administration also decreases extinction of fear in rats, an effect attributed to decreased circulating estrogens (Graham and Milad, 2013). Similarly, estradiol plus progesterone administration triggers response-type responses in a place-*vs*-response spatial memory task, an effect driven by progesterone (Lacasse et al., 2022), although whether synthetic progestins, particularly those with androgenic properties (e.g., levonorgestrel) have the same effect, remains unknown.

This work on rodent models of HC exposure clearly demonstrates the feasibility of HC-exposure model in rodents and provides a robust foundation for moving forward with more detailed studies. These findings also raise questions and highlight several considerations that need further study to determine the optimal parameters for models targeted to specific questions related to HC-exposure, these include (1) how to administer hormones, and (2) what doses of hormones to use. The answer to these questions depends in part on which specific hormonal contraceptive is being modeled – oral contraceptives *vs* implant *vs* IUD *vs* a once-per-month injection (e.g., Depo-Provera) – all have particular dosing regimens, formulations, and pharmacokinetics. Oral contraceptives, for example, reach a peak hormone level 1–2 h after taking a pill, and this slowly declines over at least 10 h (e.g., Alesse. [package insert]., 2017) to low levels until the next pill is ingested (Fig. 2). In contrast to these peaks and troughs, subcutaneous implants or IUDs release low and consistent levels across time, and in the case of IUDs, more localized uterine hormone release with only low levels of circulating progestin (e.g., Mirena. [package insert]., 2021). Oral contraceptives also come in a wide variety of formulations – with different progestins, different doses of hormone, as well as increases hormone doses across the three weeks of the hormone cycle (e.g., Ortho-Tricyclic) or consistent dosing across multiple months, with no hormone-free week (e.g., Seasonale).

There is no consensus on what an animal model of HCs must look like – indeed, any single model will have flaws and limitations. For now, the strength will be in the variety of HC administration protocols to understand the many different facets of HC effects on the brain, the body, and on behavior. The most common strategy is to model the most used contraceptives – combined oral contraceptives – *via* daily injection of ethinyl estradiol and a progestin (e.g., levonorgestrel) (Porcu et al., 2019; Porcu et al., 2012; Follesa et al., 2002). Experimentally, this is perhaps one of the most straightforward and reliable dosing strategies. However, injections can result in extremely rapid bioavailability, and fast depletion of hormone levels, and therefore may not be representative of the slower daily cycles of oral contraceptives that causes more gradual rises and gradual declines across the day after ingestion (Kuhl, 2005; Ingberg et al., 2012; Isaksson et al., 2011; Gordon et al., 1986). Because of the fast absorption and rapid decline in hormone levels, injected hormone may also require higher doses of hormones to suppress ovulation compared with oral dosing (Kuhl, 2005) (Fig. 2). As such, in rodent studies, doses of ethinyl estradiol + levonorgestrel are typically orders of magnitude higher than the human-equivalent doses, even when adjusting for rodent metabolism (Porcu et al., 2012; Simone et al., 2015; Santoru et al., 2014).

Oral dosing is another reliable administration strategy, and several studies have demonstrated that oral dosing of physiological and translationally relevant doses is feasible in mouse models. For example, oral administration of a dose of ethinyl estradiol + levonorgestrel analogous to that used in prescribed formulations is effective for suppression of ovulation and can be maintained over long periods of time (Isono et al., 2018). These studies have primarily used oral gavage of hormone

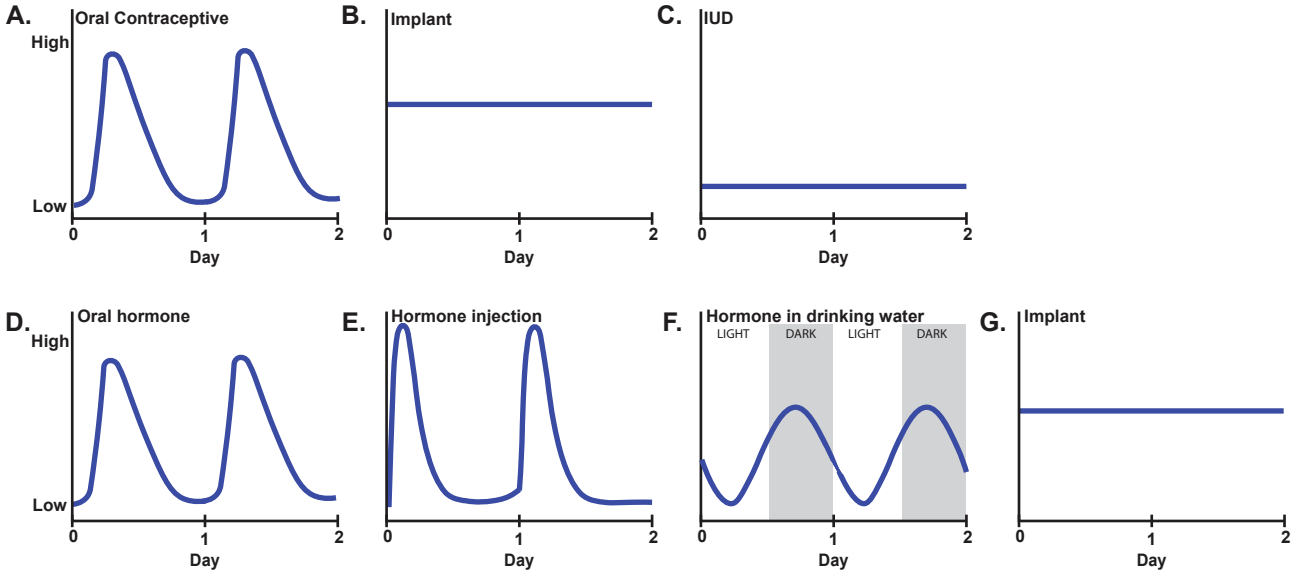

Fig. 2. Schematic of exogenous hormone levels while taking various forms of HC. (A-C) Exogenous hormone levels in humans on (A) oral contraceptives pill, (B) implant, or (C) IUD. (D-G) Hypothesized exogenous hormone levels in animal models of hormonal contraceptives. (D) Daily oral hormone administration (E) daily hormone injection; (F) continuous access to hormone in drinking water; (G) subcutaneous implant or osmotic minipump.

solution (Santoru et al., 2014; Isono et al., 2018), which is both time consuming for the experimenter and stressful for the animals, making it less sustainable long term. Delivering hormone *via* drinking water (Gordon et al., 1986) provides a more consistent level of hormone (at least during the dark cycle) without sharp peaks in concentration. Alternatively, a single daily dose of hormone, delivered in a small volume of palatable substance (e.g., sucrose) once daily is also feasible. This option has the advantages of less stress for the animal compared with daily oral gavage or injection and high face validity. However, animals must be singly housed, that may be an additional stressor for rats (Becker and Koob, 2016; Westenbroek et al., 2005), although less so for mice (Becker and Koob, 2016; Bronson, 1979; Arndt et al., 2009) (alternatively animals could be moved to individual compartments to consume the hormone), and it is less tightly controlled in terms of ensuring every animal consumes the entire dose every time. These are not the only hormone delivery methods, nor should they be. Implant, osmotic minipumps, and IUD methods of hormone delivery are extremely useful (Allaway et al., 2021; Scommegna et al., 1977; Einer-Jensen, 1980; Madularu et al., 2014), particularly for studying slow-release HC formulations (Fig. 2); although these are yet to be used to study the effects of HCs on brain and behavior. New strategies will no doubt emerge as we continue through this exciting period of interest and rapid developments in the effects of HCs on the brain.

The question here is not which is the best model to use. All these models have advantages and disadvantages. Rather, the questions are: which model or delivery system is optimal to address the specific questions under study, and how do we develop additional models that effectively address specific questions. For example, if we are looking at direct effects of contraceptive hormones on brain and behavior, then testing animals soon after an injection or acute oral dose is optimal. In contrast if we are studying persistent or chronic effects of HCs, then acute oral dosing with behavioral testing occurring some hours later, or drinking-water or subcutaneous implant might be appropriate options. What is important is that different approaches and their converging and diverging outcomes are going to provide a wealth of data on how HCs modulates the brain, cognition, social, and affective processes.

Similarly, given negative feedback control of hormone levels, different doses of HCs will provide information and allow for comparison of the direct effects of HCs on estrogen and progesterone receptors *versus* the suppression of hormone levels *versus* off-target effects. These differential effects can be explained by the U-shaped or inverted U-shaped dose response curves. For example, using very low doses that do not suppress hormone levels may demonstrate direct effects of synthetic hormones on receptors, whereas using moderate doses that effectively suppress endogenous hormone levels will yield information on the impact of low circulating hormones on brain and behavior, and using high doses that suppress hormones will also likely increase both direct and off target effects by binding with non-ER/PR receptors for which they have lower binding affinity. Comparing experiments using different doses and routes of administration will be essential for understanding all possible effects of HCs on the brain and behavior – even when some of these doses are outside the physiological/translational range.

Varying precise progestins tested and different regimens will also provide more information about how these factors change vulnerability to side effects of HCs. For example, animal studies are well-placed to identify the functional differences in anti-androgenic and androgenic progestins effects on the brain, on stress, and on mood-related side effects. As more studies and laboratories work on HC-related questions using animal models, the better able we will be to translate these findings back to the people that use HCs.

8. Conclusion

Identifying who will likely benefit from specific formulations of HCs and predicting who is likely at risk for adverse side effects will allow for more people to benefit from the economic and health benefits of HCs, with fewer people experiencing depression and other adverse mood-related side effects. To do this, we first need to understand how HCs affect the brain, the modulation of cognitive, affective, and stress-related processes. Animal models are well placed to fill the gap in how we understand these processes, where models are designed to answer questions posed by studies of HC-users, and to develop new questions to be subsequently addressed in human studies. In this way, animal models will be essential to understand risk factors, variability, and mechanisms by which HCs modulate the brain, to develop strategies for more personalized approaches to HC prescribing, and as a platform on which to study new and emerging HCs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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