Hormone-based models for comparing menstrual cycle and hormonal contraceptive effects on human resting-state functional connectivity

Kathleen V. Casto, Timothy Jordan, Nicole Petersen

Social Sciences Division, New College of Florida, 5800 Bay Shore Road, Sarasota, FL 34243, USA

Department of Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, CA 90095, USA

Abstract

Oral contraceptives (OCs) are widely used yet understudied given their potential for public health consequences. Emerging investigations scaling from single-subject, dense-sampling neuroimaging studies to population-level metrics have linked OCs to altered brain structure and function. Modeling the hypogonadal, hypergonadal, or mixed state effects of OCs in terms of their impact on hormone action in the brain is a valuable approach to synthesizing results across neuroimaging studies and comparing OC effects to companion findings from research on menstrual cycle phase effects on brain anatomy and function. Resting-state functional connectivity studies provide a powerful tool to evaluate the role of OCs on the intrinsic network connectivity that underlies multiple behavioral domains. The preponderance (but not consensus) of the current literature indicates that (1) as the menstrual cycle proceeds from a low to high progesterone state, prefrontal connectivity increases and parietal connectivity decreases; (2) OCs tend to mimic this connectivity pattern; therefore (3) OCs may produce a hyperprogestogenic state in the brain, in spite of overall reductions in endogenous steroid hormone levels. Alternative models are also considered.

Keywords

Neuroendocrinology; Menstrual cycle; Estradiol; Progesterone; Resting state; Functional connectivity; Neuroimaging; Oral contraceptives; Hormonal contraceptives; fMRI

1. Introduction

1.1. Overview

Hormonal contraceptives, composed of synthetic ovarian hormones, are a broad class of pharmaceuticals that prevent pregnancy by interfering with the hormonal processes.
governing ovulation as well as the mechanics of implantation and sperm mobility (Frye, 2006; Rivera et al., 1999). Types of hormonal contraceptives include slow/continuous-release methods such as an adhesive external patch, subcutaneous implant, injection, intrauterine device, the vaginal ring, and the fast-release daily pill. The synthetic hormone formula may contain a relatively small dose of estrogens (e.g., ethinyl estradiol), but is often characterized by the more dominant dose of progestin (e.g., levonorgestrel). Combined oral contraceptives (OCs) are a commonly used form of hormonal contraceptive that contain both a progestin and synthetic estrogen. For comprehensive review of the basic characteristics, mechanisms of action, formulas and types, and interaction with neuroendocrine systems, see (Hampson, 2020) and in this issue, Hilz (2022).

Emerging evidence suggests that OCs could influence mental health outcomes (Edwards et al., 2020; Pérez-López et al., 2020; Skovlund et al., 2018) as well as emotion, cognition and social behavior (for reviews, see Arthur et al., 2022; Beltz & Moser, 2020; Jentsch et al., 2022; Lewis et al., 2019; Pletzer & Kerschbaum, 2014). Neuroimaging studies also point to systematic changes in neurobiology as a result of OC use. Electroencephalography studies have shown effects of OCs on brain function for 50 years (Brötzner et al., 2014; Velasco et al., 1972). Recent systematic review of OC use effects on brain structure and function (Brønnick et al., 2020) tentatively concluded that the prior research is complex, but shows early indication for systematic effects of OCs on brain structure and function involved in emotion and cognitive processing. Structural studies, employing methods such as MRI and DTI, have found volumetric and connectivity differences between OC users and non-users in areas such as the amygdala, anterior cingulate cortex, hippocampus, fornix, and salience/attention networks (see also, Heller et al., 2022, in this issue). However, structural studies show notable inconsistency in the regions of interest making it difficult to determine both replicability of these findings and impact on functioning. Studies that focused on neural activity (measured by fMRI), in the context of emotional or cognitive tasks, have found that OC users compared to nonusers show a variety of differences in patterns of activity in prefrontal and insular areas, the amygdala, and fusiform face region during facial and emotion processing, particularly fear response and learning (Gingnell et al., 2013).

However, drawing general or translational conclusions from this research is difficult for a number of reasons including the lack of overarching endocrine models for understanding and testing mechanistic explanations for how OCs affect the brain. The hormone cocktail of OCs both interferes with endogenous menstrual cycle-related patterns of production of these same hormones, and replaces them with a relatively steady-state level of the synthetic versions. Thus, approaches to studying OC effects on the brain should be centered on models of ovarian hormone exposure or deprivation – i.e., to what extent do synthetic hormones in OCs mimic or block the same effects in the brain as their endogenous counterparts? Comparing how ovarian hormone levels across the cycle phases produce results similar or different than OC effects, can help categorize the ovarian-hormone-model of OC effects on brain neuroanatomy. Thus, studies that account for the menstrual cycle phases in naturally-cycling individuals as comparators provide added benefit for uncovering mechanistically how OCs affect the brain.
In the sections that follow, we introduce several models of OC effects on hormone action in the brain and how menstrual cycle phase comparisons inform these models. We then introduce one key area of research that is particularly well suited for analysis using this approach: studies exploring resting state functional connectivity (rsFC) by menstrual cycle phase and OC use. To demonstrate a model-based analysis, we first review and evaluate the research on menstrual phase effects on rsFC. Then, we assess the extent with which prior research has shown 1) evidence that resting-state networks are different in OC users and naturally-cycling individuals and 2) the extent with which OCs mimic menstrual phase rsFC fluctuations. We attempt to synthesize these findings in terms of how the evidence speaks to broad models on OC effects on the brain: hypogonadal, hypergonadal, or mixed state. With this framing, we hope to model a research approach that bridges the gap between the larger-scale network analysis common in neuroimaging research and the more cellular or pharmacologic focus on steroid/ovarian hormone interaction with neurotransmitter mechanisms.

1.2. Modeling OC effects on ovarian hormone modifications

The hypothesis that OCs could alter typical neuroanatomy and function is premised on evidence that ovarian hormones are essential modulators of neural activity (Toffoletto et al., 2014) and produce well-documented changes to dendritic spine density (Gould et al., 1990; Woolley & McEwen, 1992; 1993) and synaptogenesis (Haraguchi et al., 2012; McEwen & Woolley, 1994). Both within and outside of menstrual pattern regulation, the production, secretion, and action of neuroactive estrogens and progestogens have far-reaching effects on neural activity, network structure and function (Porcu et al., 2016). With their function generally being neurotrophic and neuroprotective, and their critical role in modulation of receptor action and neural circuitry involved in memory, emotion, and reward, estrogens and progestogens play an essential role in basic cognition, brain health, and mental illness etiology (Galea et al., 2017; Sharma et al., 2021). Therefore, suppressing naturally occurring, endogenous production and patterns of fluctuation could alter these processes. Yet, there is little understanding regarding if or how the replacement with synthetic hormone formulas in the OCs mitigate the “loss” of their naturally occurring counterparts. Although there is increasing evidence for group-level differences between OC users and naturally-cycling nonusers in various outcomes of interest (neural, cognitive, emotional, behavioral), the literature is generally lacking in functional models for testing the underlying mechanism – what are the causes of these observed effects? Recent research on animal models of hormonal contraceptive action in the brain have and will continue to be essential to uncovering these mechanisms (for review, Porcu et al., 2019; this issue: Hilz, 2022; Lacasse et al., 2022; Tronson & Schuh, 2022).

In their landmark review and call to action, Pletzer and Kerschbaum (2014) presented an early conceptual model for OC effects: A “feminizing” hypothesis whereby synthetic ovarian hormones enhance female-specific sexual dimorphisms in the brain and an opposing “masculinizing” hypothesis whereby synthetic ovarian hormones reduce these dimorphisms. Indeed, because progestin formulas can be androgenic or antiandrogenic depending on whether they facilitate or suppress androgen action, it makes sense to focus on how OC formulas affect sexually dimorphic regions. However, it is now known that both anti-
androgenic (i.e., blocks androgen receptor binding/action) and androgenic (i.e., facilitates androgen receptor binding/action) progestins suppress overall testosterone bioavailability (Hilz, 2022; Porcu et al., 2019). Further, sexually dimorphic regions are not well-defined in humans and further, animal findings on sexual dimorphisms in the brain may not generalize to humans (de Lacy et al., 2019). There remains a need for testable models of the mechanistic effects of OCs on ovarian hormone action in the brain beyond their intended mechanism of action (i.e., negative feedback on the hypogondal-pituitary signaling and GnRH production).

1.2.1. Hypogonadal state—One general model of OC effects on the brain is that they induce a state of chronic under-exposure to endogenous ovarian hormones (and their neuroactive metabolites). The main mechanism of action for OCs is synthetic steroid binding at the hypothalamus to restrict hypothalamic-pituitary-ovarian regulation of ovarian reproductive events and new endogenous hormone production (Baird and Glasier, 1993; Frye, 2006; Rivera et al., 1999). This mechanism “takes advantage” of the negative feedback system of the hypothalamic-pituitary-ovarian axis. As a result, OC use significantly inhibits hypothalamic-pituitary-ovarian activity, effectively reducing overall serum levels of endogenous progesterone and estradiol (Porcu et al., 2019; Rapkin et al., 2006; Sitruk-Ware & Nath, 2013). Thus, a key component of the hypogonadal state model would be to establish that the synthetic hormone versions do not have the same action in the brain or cannot be fully converted to their neuro-active metabolites (Giatti et al., 2020, 2016; Jayaraman and Pike, 2014; Porcu et al., 2012).

Reduced production, and thus, circulating levels of progesterone limits the ability of this hormone to carry out any dependent or interacting physiological processes (for recent review, Sundström-Poromaa et al., 2020). Progesterone action in the brain is highly complex, upregulating and downregulating various other neurotransmitter actions (serotonergic, dopaminergic, and GABAergic), interacting with other steroid hormones (Bäckström et al., 2011; Nguyen et al., 2017), and acting as a neuroprotective agent (Cai et al., 2008; Guennoun, 2020; Schumacher et al., 2016; Singh & Su, 2013). However, this latter class of effects is likely due to progesterone that is synthesized within the brain, independent of circulating concentrations (Micevych & Sinchak, 2008). Whether or not OC use impacts direct neuro-progesterone production and action is not known. Progestins generally bind with high affinity to progesterone receptors in the brain and some progestin formulas appear to have the same neuroprotective properties as endogenous progesterone (Schumacher et al., 2014; Sitruk-Ware et al., 2021). However, some progestins that have been targeted for their therapeutic potential for neuroprotection can only be delivered in a long-acting implant (i.e., they are not available as an OC) and do not appear to have the same functional effects as endogenous progesterone (Kumar et al., 2017). For recent comprehensive review of progestin effects on the brain, see Griksiene et al. (2022) in this issue.

Many of progesterone’s effects in the brain are due to actions of its metabolites. Progestins are enzymatically converted to a variety of different metabolites of differential affinity to steroid hormone receptors (Bick et al., 2021; Stanczyk, 2003; Stanczyk et al., 2013). Although information is limited, it is generally understood that metabolites of progestin do not have the exact same effectiveness at target tissues including brain areas involved
in mood, emotion, and cognition as the endogenous form of progesterone, particularly its anxiolytic neuromodulator, allopregnanolone (De Nicola et al., 2018; Jayaraman & Pike, 2014; Lenzi et al., 2008; Porcu et al., 2012). Indeed, OC use appears to reduce circulating levels of allopregnanolone (Rapkin et al., 2006). In a rodent model, hormonal contraceptives also significantly reduce levels of allopregnanolone in the brain and this appears to have adverse effects on social and sexual behavior (Porcu et al., 2012; Santoru et al., 2014). Thus, current evidence suggests that the OC use produces a hypo-progestogenic state in terms of the brain’s prolonged under-exposure to neuroactive progesterone metabolites, an effect that could have important consequences for brain anatomy and function. However, these conclusions are based limited evidence in rodent models using only a narrow sample of OC-like hormone formulas.

Less is known about how OCs interact with endogenous estrogen production and action in the brain (for review, Porcu et al., 2019). Most formulas of OCs contain a low dose of synthetic estrogen. Although the concentration is low, the exposure to the brain is more continual (less drastically fluctuating) than is typical of a naturally-occurring menstrual cycle. Some studies have shown that OC use significantly reduces circulating endogenous estradiol levels (Rapkin et al., 2006), while other evidence has shown that the mid-cycle estradiol peak, and even some follicular development, are not entirely suppressed even for formulas that contain synthetic estrogens (van Heusden & Fauser, 2002), an effect that may depend on body mass index (Edelman et al., 2009, 2014) and ethinyl estradiol (EE) dose (Baerwald & Pierson, 2004). Although EE has been shown to have higher binding affinity for estrogen receptors than its natural form, synthetic estrogen metabolites are distinct in form, function, pharmacodynamics (e.g., Coelingh Bennink, 2004; Prokai-Tatrai & Prokai, 2005).

In any case, the extent to which low doses of synthetic estrogens in modern formulas alter neural processes differently than natural estrogens is not currently well-understood (e.g., Hiroi et al., 2016). In the body, physiological symptoms of a metabolically-induced hypoestrogenic state in young women, e.g., bone density loss, are improved through OC use, particularly at higher doses of EE and with longer-term exposure (Gersten et al., 2016; Huhmann, 2020). However, cyclic low dose exposure to EE through many modern OC formulas could still produce a hypo-estrogenic state – synthetic and endogenous combined – in comparison to the total exposure that occurs in naturally-cycling individual. Thus, an estrogenic state is dependent on both the concentrations and specific chemical formulas of estrogen and, due to progestin dose-dependent suppression of EE (Endrikat et al., 2011), the type and dose of the progestogen with which it is paired.

1.2.2. **Hypergonadal state**—An alternative to the hypogonadal model is that structural and functional effects of OC use on the brain are a result of chronic over-exposure to exogenous ovarian hormones (and their neuroactive metabolites). Outside of pregnancy, circulating progestogen levels are only sustained at the level in OCs for a period of several days across the menstrual cycle (i.e., the luteal phase peak). As reviewed above, progestogens interact with neurotransmission and affect overall brain functioning, but the consequence of continual exposure is not well-understood and may depend on individual differences in progestogen sensitivity (Sundström-Poromaa et al., 2020). Assuming the
synthetic compounds function relatively similar in some capacities, the use of OCs results in a more continual brain exposure to overall progestogenic activity. Indeed, some brands of OCs involve a consistent daily dose for upwards of 3 months (Anderson & Hait, 2003; Dinger et al., 2011). Thus, a hyper-progestogenic state model could explain OC effects on brain anatomy and function.

Different progestin compounds found in certain brands/formulas of OCs (e.g., Norgestimate) are known to interact with estrogen receptors in a way that is estrogenic in that they upregulate estrogen-binding activity and effectiveness. This, in effect, could create a hypergonadal state that is both hyper-progestogenic and estrogenic (Hilz, 2022; Griksiene et al. 2022, this issue). However, an estrogenic effect is not apparent for all progestins; a hyper-estrogenic model would be unique to specific formulations of OC. However, the estrogenic effects of progestogens suggests that any singular-hormone view of OC effects on brain anatomy and function would likely discount important interconnectedness of the steroid hormone pathway and, various agonistic and antagonistic steroid receptor binding dynamics.

1.2.3. Mixed state—Rather than a simple under (hypo-gonadal) or over-exposure (hypergonadal) effect, the complex behavior of synthetic progestins and estrogens could collectively alter or disturb ovarian hormone-neurotransmitter action in way that reflects a combination of these two patterns (Blaustein, 2004; McEwen, 1992; Turgeon et al., 2006). Further, some formulas of OCs could create an internal milieu that is abnormally low in one hormone and high in the other, e.g., both hypo-estrogenic and hyperprogestogenic. Thus, a third general model is that the emergent property of OCs on the brain is a “mixed” state. Inevitably, the complexity of hormone signaling in the brain produces a preponderance of subtle to drastic, genomic and non-genomic, facilitatory and inhibitory, and short and long-term actions that could simply make OC users neural wiring “different” than the natural state (Africander et al., 2011; Cano-Nicolau et al., 2016; Giatti et al., 2016; Mani & Portillo, 2010; Vaillant et al., 2020).

1.2.4. Androgen interactions—OC use significantly reduces serum testosterone (Louw-du Toit et al., 2017; Wiegratz et al., 2003; Zimmerman et al., 2014), effectively creating a hypo-androgenic state in terms of total circulating levels. Further, the type of progestin used in some formulas is “anti-androgenic” in that it can effectively reduce androgen signaling at the androgen receptor (Bullock & Bardin, 1977). Other types of progestin can be androgenic, upregulating androgen efficacy in binding and action. Thus, depending on the formula, hypo-/hyper-estrogenic and progestogenic effects could be conflated with their indirect effects on androgen action in the brain. However, androgens appear to play a less pronounced role in neuromodulation in females compared to males at least for some brain processes in certain brain areas (Giatti et al., 2020). Future research that compares brain anatomy and function by the androgenicity of specific formulas will be essential to establishing whether or not this unique property of progestins is a causal factor in producing, for example, differences in brain connectivity between users and nonusers.
1.3. Menstrual cycle phases in naturally cycling individuals as comparison groups for model-building evidence

The typical menstrual cycle in human females is characterized by systematic fluctuation in endogenous estradiol and progesterone on a roughly 28-day repeating pattern, beginning at menarche and ending at menopause (for review, Hampson, 2020). This pattern consists of several distinct endocrine states in consecutive order: 1) a broad 7 to 10-day window of hormonal quiescence when ovarian hormones are relatively low, 2) a brief estradiol peak ~ 14 days after menstruation onset (necessary for ovulation), 3) a subsequent broad 7 to 10 + day, more tempered rise and fall of mostly progesterone and some estradiol (necessary for facilitating implantation). However, there is substantial intra- and inter-individual variability in cycle length, which is largely dependent on the follicular phase processes, i.e., the time from menses to ovulation (Jasienska & Jasienski, 2008; Stern et al., 2022). Further, anovulatory cycles are common, particularly early in adolescence (Seidman et al., 2018). Despite these sources of variability, menstrual cycle phases in naturally-cycling individuals could serve as informative comparison conditions in providing evidence for endocrine models of OC effects on brain neuroanatomy.

Neuroimaging evidence suggests that menstrual-cycle phases and their underlying hormone shifts appear to produce some distinct and reliable structural and functional differences (for meta-analysis and discussion, Dubol et al., 2021). For example, the luteal window of peak progesterone (in combination with some estradiol) is sufficient to produce structural changes in certain areas of the brain (i.e., hippocampus, Taylor et al., 2020) and, levels of estradiol and progesterone appear to correlate with identifiable properties of neural network connectivity (Fitzgerald et al., 2020; Pritschet et al., 2020). Comparing OC-use conditions or groups to naturally cycling conditions or groups could implicate the hormone, or absence of a hormone, that is causing OC effects. For example, if OC vs placebo effects on structural anatomy in the brain are similar to mid-luteal vs mid-follicular effects, then this would suggest that OC effects could be due to a hypergonadal state induced by heightened exposure to progestins or estrogens. We expand on this kind of analysis in the sections that follow.

1.3.1. Cycle-phase determination and methodological challenges—One key caveat is that reproducible menstrual phase research can be difficult due to the methodological challenges inherent in observational studies of a temporally dynamic system that varies between and within individuals. Specifically, methods of determining menstrual cycle phase that are common in prior research (e.g., calendar day counting methods) have shown poor accuracy in coordinating with biochemical markers of ovulation (e.g., luteinizing hormone (LH) tests) (Blake et al., 2016; Gangestad et al., 2016). These problems and their solutions have been addressed in detail in manuscripts with recommendations to improve rigor (Allen et al., 2016; Janse de Jonge et al., 2019; Schmalenberger et al., 2021). Such recommendations include (but are not limited to) within-subject designs, measuring and accounting for individual differences in typical menstrual cycle characteristics of the participant sample, biochemical, body-temperature, or sonographic verification of cycle phase (in combination with counting methods), and hypothesis-driven cycle phase selection.
Hormonal assay of estradiol and progesterone levels in serum or saliva is one particularly important aspect of study designs for endocrine modeling of menstrual phase and contraceptive effects on brain neuroanatomy. Direct hormone measurement enables the statistical assessment of hormone levels as mediators of phase or OC effects, i.e., direct statistical tests of causal and explanatory relationships between brain anatomy and the hormones that are the basis of the menstrual cycle phases and OC effects. However, valid measurement of estradiol and progesterone is also challenging, and may be particularly prone to error in saliva and when salivary concentrations are relatively low (Dielen et al., 2017; Sakkas et al., 2022; Shirtcliff et al., 2000; Sun et al., 2019). Further, research designs should be careful in considering the limits of absolute hormone levels, that individual differences are often too broad to use any single measure for cross-sectional or between-subject comparisons. Within-subject sampling at multiple time points is ideal for most study designs and essential for using hormone levels as a way of “validating” other phase estimation methods.

2. Effects of OCs on resting state functional connectivity

2.1. Overview

One area within neuroimaging research that has a particular density of studies on the effects of menstrual cycle phase and OC use on the brain are studies exploring resting state functional connectivity (rsFC). This method, which generally employs fMRI, quantifies relationships between time-series of spontaneous low-frequency fluctuations of blood flow in spatially distinct brain regions, from which it is inferred that temporally correlated activity represents functionally related activity (Biswal, 2012; Damoiseaux et al., 2006; Smith et al., 2013; Smitha et al., 2017). Functional connectivity in rsFC studies can be determined using different approaches, e.g., seed based analysis or independent components analysis (ICA), which has created some discrepancies when synthesizing across studies. Research on rsFC has contributed to a growing understanding of functional networks within the brain – temporally correlated activation between spatially distinct cortical and subcortical regions – which appear to be implicated in a wide range of clinical and mental health conditions (Fox & Greicius, 2010; Woodward & Cascio, 2015), and are associated with behavioral domains (Smith et al., 2009).

Importantly, manipulation of endogenous hormone levels with a gonadotropin-releasing hormone agonist induced changes in rsFC which mediated changes in mood scores (Fisher et al., 2017), suggesting that the interaction between neuroactive hormones and rsFC may underlie some hormone-sensitive mood disturbances. Thus, the benefit of understanding neuroendocrine impacts on rsFC is that connectivity across clinically relevant large-scale networks has the potential to (1) provide a mechanistic understanding of how ovarian hormonal fluctuations and alterations via OC use affects cognitive, emotional, and behavioral outcomes; (2) remove a source of uncontrolled variance in rsFC studies; and (3) in the future, potentially uncover biomarkers for hormone sensitivity, effectively identifying who may be adversely impacted by OCs use.

In order to investigate the effect of OCs on resting-state functional connectivity (rsFC), consistent parameters for studying the research question are needed. First, it is necessary
to establish the baseline condition to which OC use-linked rsFC will be compared – i.e., functional connectivity in naturally-cycling (NC) individuals not using OCs. Here, evidence is reviewed that in premenopausal women, rsFC fluctuates over the course of the menstrual cycle. Thus, comparing OC use effects to naturally-cycling conditions or groups creates a fluctuating baseline that can be parsed into varying numbers of phases. Using coarse measurements, menstrual phase can be subdivided into the follicular and luteal phases; using finer-grained measurements, it can be further subdivided into early follicular (also termed “menstrual” or “menses”), mid-follicular, late follicular (also termed “periovulatory” or “preovulatory”), ovulation, early luteal, mid-luteal, and late luteal (also termed “premenstrual”) phases. Although accurate determination of these more granular phase distinctions is problematic, they are highly relevant to the underlying rising and falling patterns of ovarian hormone exposure. Nonetheless, variation between studies in the use of different menstrual phase categories makes it challenging to synthesize and compare across studies. Some investigators have avoided the problem of menstrual phase category by directly evaluating the relationship between rsFC and 17β-estradiol or progesterone. This approach of direct hormone measurement benefits from the added power of continuous measurements when correlating to connectivity estimates. However, doing so assumes linear, time-independent relationships between hormone levels and connectivity measurements – i.e., linear regression models assume that hormones have the same relationship with rsFC measurements at each stage of the cycle, which does not appear to be the case (Syan et al., 2017). Correlations between hormones (estradiol, progesterone, and others) and rsFC measurements have been found to be different in each menstrual phase assessed.

Second, varying rsFC measurement approaches present challenges. All measurements of rsFC are derived from the relationships between time-series of spontaneous, low-frequency fluctuations of blood flow in different voxels in the brain (van den Heuvel & Hulshoff Pol, 2010). These can be simple Pearson correlations between the time-series in a priori selected voxels, as is the case in seed-based connectivity analyses. Alternatively, rsFC determination can be entirely data-driven, as is the case in independent components analysis. Or finally, measurements can be increasingly complex, as in time-varying functional connectivity approaches (e.g., sliding-window measurements) that describe changes in connectivity that take place during the brain imaging epoch (for review and discussion, see (Cohen, 2018; Eichenbaum et al., 2021; Lurie et al., 2020; Lv et al., 2018). Different teams have assessed rsFC fluctuations over the menstrual cycle using independent components analysis (ICA), seed-based connectivity approaches, eigenvector centrality, regional homogeneity, graph analyses, and effective connectivity approaches, among others. To further complicate the matter, motion correction strategies vary between research groups and may produce differing results when applied to the same data (Parkes et al., 2018). The field has not converged on a single best data cleaning technique or methodological approach; with respect to the latter, each provides different information about temporal dynamics and functional organization of the brain.

Given these limitations, some general observations about the baseline condition – i.e., resting-state networks in a naturally-cycling individual – with reference to OC use can be made. First, although contradictory evidence with small samples (Ns < 20) exists (De Bondt et al., 2015; Hjelmervik et al., 2014), the preponderance of evidence suggests that rsFC
does indeed change over the course of the menstrual cycle. For parsimony, evidence is briefly reviewed comparing the broadest categories of menstrual phases – connectivity in the follicular (including early, mid, and late) vs luteal (including early, mid, and late) phases (Table 1). Ovulation represents a particularly impactful epoch in each cycle (Pritschet et al., 2020), but is especially challenging to measure accurately, and the number of investigations with reliable measurements is small. Thus, the focus of this review will be comparing follicular and luteal phase patterns of rsFC. This is not to imply that ovulation is irrelevant to rsFC; rather, more investigations that prospectively follow individuals across the menstrual cycle to accurately capture ovulation are needed. Even comparisons of follicular- and luteal-phase may be limited by unknown error in cycle-phase estimation procedures within this body of research; thus, overall conclusions are tentative.

2.2. **Evaluating menstrual phase effects via seed-based connectivity analyses**

Seed-based connectivity analyses can theoretically produce millions of comparisons. In only a few seed regions has connectivity been evaluated by > 1 independent research groups, and in no region have connectivity changes over the menstrual cycle been evaluated by > 2 independent groups. One finding has been replicated across groups – that of higher connectivity between the dACC and prefrontal cortex during the luteal compared to follicular phase (Engman et al., 2018; Wetherill et al., 2016). The prefrontal area in which this connectivity difference was observed appears to be roughly overlapping between the two studies in spite of their substantial methodological differences (e.g., women who all smoke vs women who may or may not; pCASL vs BOLD; different preprocessing pipelines). Similarly, in two studies, thalamic connectivity was higher during the luteal phase compared to the follicular; in one case this was found using a putamen seed (Hidalgo-Lopez et al., 2020) and in another, a temporal cortical seed (Wang et al., 2020).

Outside of studies examining the luteal vs follicular phases, three studies have examined changes within the follicular phase, from early to late follicular (Hidalgo-Lopez et al., 2020; Lisofsky et al., 2015; Wu et al., 2016). In all studies, late follicular showed higher connectivity compared to early follicular. The studies found that late follicular had altered connectivity between right caudate and right MFG (Hidalgo-Lopez et al., 2020) left vmPFC and SMA (Wu et al., 2016), and the hippocampus and superior parietal lobe (Lisofsky et al., 2015).

Considering all analyses, a number of null results were reported, but these are difficult to interpret with small groups and rigorous multiple comparison corrections, because small sample sizes can lead to false negatives, which are indistinguishable from true negatives. Therefore, when small sample sizes report a null finding, readers must have low confidence in that reported null finding. As a general pattern, it was more commonly observed that seed-based connectivity was higher in the luteal vs follicular phase, rather than higher in the follicular vs luteal phase (see Table 1). This was especially true when evaluating seeds connected to frontal regions; higher prefrontal connectivity in the luteal phase was reported in three separate studies (Engman et al., 2018; Meeker et al., 2020; Wetherill et al., 2016) using three different seeds (amygdala, dACC, parietal cortex).
Higher connectivity during the follicular vs luteal phase was found using an amygdala seed in one study (Petersen et al., 2019), with the opposite finding in another (Engman et al., 2018), and no effect reported in a third (Syan et al., 2017). Higher connectivity during the follicular vs luteal phase was also found using a hippocampal seed in one study (Lisofsky et al., 2015) but not another (Hidalgo-Lopez et al., 2020). Interestingly, both studies reporting lower luteal rsFC found that effect in connectivity between a medial temporal lobe seed (amygdala and hippocampus) and parietal cortex. In a study focused exclusively on estradiol levels (assayed from blood) rather than phase estimation (sample was median split into low and high groups), those with low estradiol showed higher connectivity between basolateral amygdala and both the cerebellum and ACC; the low estradiol group also showed higher centromedial amygdala-cerebellum connectivity. In contrast, the high estradiol group showed higher connectivity between the basolateral amygdala and inferior frontal gyrus, precentral gyrus, supramarginal gyrus, and superior temporal gyrus; the high estradiol group also showed higher centromedial amygdala connectivity with the cuneus, fusiform cortex, occipital cortex, and temporal cortex (Engman et al., 2016).

Prefrontal (dIPFC) and sensorimotor connectivity over the menstrual cycle were rigorously investigated in an innovative study that imaged a single woman every few days day over an entire menstrual cycle (Arélin et al., 2015), obviating the need to define and assign menstrual phases. Progesterone was positively related to connectivity in this evaluation, broadly consistent with the finding described above – higher prefrontal connectivity during the luteal phase, when progesterone is high.

### 2.3. Evaluating menstrual phase effects via independent components analysis

The most commonly used approach to evaluate resting-state network dynamics over the menstrual cycle has been comparing networks defined by ICA during the follicular and luteal phases. Two investigations (Hjelmervik et al., 2014; Syan et al., 2017) report no differences in network connectivity between the follicular and luteal phases. One study, de Bondt et al. (2015), reported only a small cluster in the cuneus of higher connectivity in the luteal vs follicular phase that did not survive false-detection rate correction. Pletzer et al. (2016) reported mixed higher and lower connectivity in a luteal vs follicular phase comparison. Specifically, higher connectivity was found during the luteal phase between the default mode network (DMN) and cuneus, and also between a frontoparietal network with the medial prefrontal cortex and the basal ganglia. Lower connectivity was found during the luteal phase between a frontoparietal network and sensorimotor cortex, between the same network and also opercular cortex, and also between a mesolimbic network and the precuneus and basal ganglia. Petersen et al. (2014) reports uniformly lower connectivity in the luteal compared to the follicular phase, specifically lower anterior cingulate cortex (ACC)-executive control network (ECN) connectivity, and lower DMN-angular gyrus connectivity. Notably, Hidalgo-Lopez et al. (2020) replicated the latter finding in an independent sample, albeit in the right rather than left hemisphere. These four areas of lower parietal connectivity during the luteal phase are depicted side-by-side in Fig. 1. This replication tentatively suggests that studies finding no effect may have been subject to a type II error, as small sample sizes continue to pose power problems for neuroimaging research (Button et al., 2013; Carter et al., 2016; Lieberman & Cunningham, 2009; Poldrack et
al., 2017) or overzealous data cleaning procedures, as the most stringent motion-correction procedures necessarily carry increased signal loss (Parkes et al., 2018). This finding also provides a notable parallel to what has been reported in seed-based connectivity studies, with both seed-based and ICA approaches finding lower parietal connectivity during the luteal vs follicular phase.

However, there could be important variability within the follicular phase that should be explored in future research. For example, one ICA comparison found primarily lower connectivity during late follicular compared to early follicular phase (Pletzer et al., 2016), with decreased connectivity in the basal ganglia, calcarine, and superior parietal lobe. The late follicular phase was only found to have higher connectivity in the left temporal cortex compared to early follicular. Thus, converging evidence suggests a connection between menstrual phases marked by higher ovarian levels and reduced parietal connectivity relative to phases marked by lower ovarian levels; but this effect might depend on greater specificity of the connectivity patterns within each phase. Specifically, future research that accounts for the late follicular phase could provide insight on whether the cycle-phase effects on connectivity are likely due to estradiol (late follicular) or the combination of estradiol and progesterone (mid-luteal).

2.4. Evaluating menstrual phase effects via complex network approaches

In contrast to seed-based connectivity analyses, which provide focused information about specific brain regions, complex network approaches may characterize network information on a whole-brain level. Pritschet et al. (2020) measured ovarian hormones daily throughout an entire menstrual cycle and correlated these with rsFC. Rather than using time-series per se to measure rsFC as in other approaches, time-series were entered into a coherence equation, which was in turn entered into a matrix correlating each of 415 nodes with each other. The relationship between these rsFC measurements and ovarian hormones were then evaluated using vector autoregression, a system of equations that quantifies changes in two or more fluctuating variables – in this case, (1) ovarian hormone levels and (2) rsFC spectral coherence measurements. This analysis showed that progesterone was associated with negative connectivity across various rsFC networks, with no networks showing higher progesterone-related connectivity, suggesting broadly lower connectivity during the luteal compared to follicular phase.

The same data was analyzed using a different complex network approach, dynamic community detection, which measures network topology – specifically, how tightly nodes within a network cluster together and also how flexibly they reorganize, moving from one cluster to another. This quantifies the modularity of the network, or the extent to which a network can be broken down into sub-components, and how reliably those sub-components group together. These mesoscale network dynamics (i.e., above the structure of individual nodes but below the structure of the entire network) were found to be relatively stable,

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1 “Node” throughout this review refers to the fundamental element of a graph that cannot be further divided into smaller subunits. The smallest detectable node in a neuroimaging study is a single voxel, or volume element (Sporns, 2018); in the study described here, voxels were grouped together into parcellations.
fluctuating a great deal during ovulation and returning to a similar topology during the luteal phase to that observed in the follicular phase (Mueller et al., 2021).

A third complex network analysis was also applied to the same data (De Filippi et al., 2021), this time evaluating turbulent brain dynamics, a novel approach derived from fluid dynamics. In fluid dynamics, turbulence refers to rapid, chaotic (irregular), and diffuse changes in fluid pressure and velocity. The same equations that describe turbulent dynamics in fluids can be applied to rsFC time series, and produce significantly higher measurements of amplitude turbulence when applied to these data vs randomly-generated noise (Deco and Kringelbach, 2020). Amplitude turbulence and two measurements of information transmission (information cascade and information transfer) were found to be higher during the luteal phase vs follicular (De Filippi et al., 2021). Importantly, the information transmission measurements do not refer to any measurements of cognitive or behavioral information transmission; these refer to the dynamics of coupled oscillators.

In a relatively larger set of women (N = 60), participants were imaged once each during the early follicular, late follicular, and luteal phases, and regions of interest (ROIs) were placed in the hippocampus, caudate, and putamen. Eigenvector centrality was calculated, which reflects how connected a node is to other nodes; high eigenvector centrality scores indicate that a node is highly connected (or highly central) to other nodes. Higher eigenvector centrality was found during the luteal phase in the hippocampal ROI only (no phase effect in putamen or caudate nodes); this only survived false detection rate correction when compared to late follicular eigenvector centrality (Hidalgo-Lopez et al., 2021). This is compatible with a previous finding that whole-brain eigenvector centrality is positively correlated with progesterone levels (Arélin et al., 2015). However, another study of global centrality, which is related to eigenvector centrality, reported fewer global hubs during the luteal phase (Donishi et al., 2018). Using magnetoencephalography, one study found higher betweenness centrality and lower leaf fraction and tree hierarchy in the posterior cingulate during the periovulatory phase vs follicular or luteal (Liparoti et al., 2021).

Although developed over a decade ago (Friston et al., 2011), the effective connectivity technique had gone unutilized when examining the menstrual cycle, a deficit recently remedied by Hidalgo-Lopez et al. (2021). Effective connectivity analysis is a method by which not only the connection between two regions is determined, but also what direction the information between them is flowing. In their study, Hidalgo-Lopez et al. found numerous differences between menstrual cycle phases: 12 between late and early follicular phases, 6 between mid-luteal vs early follicular, and 6 between mid-luteal vs late follicular. In summary, the mid-luteal phase had overall decreased effective connectivity compared to both early and late follicular phases. Four connections peaked in either early or late follicular phases: two connections, right middle frontal gyrus to posterior cingulate cortex and right anterior insula to left supramarginal gyrus, were higher in early follicular compared to mid-luteal and late follicular; two others, left supramarginal gyrus to left middle frontal gyrus and left anterior insula to left middle frontal gyrus, were found to be higher in late follicular compared to early follicular and mid-luteal. Early follicular was also found to have one connection lower than the other two phases, left anterior insula to L SMG (Hidalgo-Lopez et al., 2021).
2.5. Summary: How does rsFC change over the menstrual cycle?

The differences in rsFC approaches employed make it challenging to draw an overall conclusion summarizing changes in rsFC over the menstrual cycle. Given both the parameterization of the independent variable, menstrual phase, and the dependent variable, rsFC analyses have been approached differently in the literature, leading to contradictory findings. Very likely, the effect of menstrual phase on rsFC depends on (1) how phase is defined, measured, and compared; (2) which region or network is being measured; (3) which dynamic (time series, turbulence, etc) within that spatial distribution is being measured; and (4) which preprocessing choices the investigators made.

Effects that have been replicated or converge across methodological approaches stand out as particularly likely to be true positives. These include (with respect to replicated results):

- Higher hippocampal eigenvector centrality during the luteal vs follicular phases
- Higher thalamic connectivity during the luteal vs follicular phases
- Higher dACC-prefrontal connectivity during the luteal vs follicular phases
- Lower parietal-DMN connectivity during the luteal vs follicular phases

The latter two conclusions are broadly similar to those reported in a recent review describing multimodal imaging findings across the menstrual cycle (Dubol et al., 2021).

The functional significance of these findings remains unclear, and the state of the field invites the question: Of the many options for rsFC analysis, which is the correct approach? Seed-based approaches are particularly helpful for guiding brain stimulation therapies, and along with ICA, EC, and regional homogenity have been correlated with behavioral domains and clinical syndromes. It is possible that more complex approaches will be developed and provide even more important mechanistic and clinical insight, but the optimal approach for each experiment will depend on the specific parameters of the data included in the study and the research question being investigated.

2.6. To what extent are resting-state networks different in OC users vs naturally-cycling individuals?

Network connectivity is influenced by (although not perfectly congruent with) features of neural architecture (Honey et al., 2010; Suárez et al., 2020) that are susceptible to influences by OCs. One tractography (diffusion tensor imaging) study reported higher mean diffusivity, a measurement affected by white matter properties, in the fornix of OC users compared to naturally-cycling (NC) women (De Bondt et al., 2013). Gray matter volumes and cortical thickness measurements have been reported to be different in OC users compared to non-users (for review, see Brønnick et al., 2020). Measurements of neurochemistry suggest serotonin 5-HT2A receptors may be unaffected by OC use (Frokjaer et al., 2009) whereas binding potential at the 5-HT4 receptor is significantly lower (Larsen et al., 2020), and prefrontal GABA measurements are lower in OC users compared to women who are ovulating, but not during other cycle phases (De Bondt et al., 2013, 2015a). Effects of OCs on other neurotransmitter systems have not been reported in humans, although preclinical
literature details effects of some contraceptive hormones on markers of dopamine signaling and glutamate signaling (for review, see Concas et al., 2022).

2.6.1. Effects of OCs evaluated using ICA—Network analyses relying on ICA have produced contradictory results (Table 2). De Bondt et al. (2015b) found no effect of OCs on DMN or ECN rsFC ($N_s = 18$ NC, 19 OC). Petersen et al. (2014) found lower connectivity in OC users taking active OCs compared to follicular women when evaluating DMN and ECN connectivity. By contrast, when collapsing across menstrual cycle groups to create a single “naturally-cycling” baseline that included early follicular, periovulatory, and mid-luteal women, Sharma et al. (2020) found no effects of OCs on DMN connectivity, but higher connectivity in OC users (vs the NC group) between the MFG and salience, executive control, and reward networks. They also reported higher angular gyrus-ECN connectivity in OC users vs NC women, contradicting Petersen et al. (2014).

2.6.2. Effects of OCs evaluated using seed-based connectivity—Seed-based analyses of OC effects on rsFC have explored seeds placed in the amygdala (Larsen et al., 2020), dACC (Engman et al., 2018), parahippocampal cortex (Nasseri et al., 2020), and putamen (Sharma et al., 2020). Engman et al. (2018) selected for women who had previously experienced negative affect while using OCs, which may produce different results than the same analysis performed in women without such sequelae. In this well-designed randomized trial, resting-state functional connectivity in OC users was compared to that of naturally-cycling women during the follicular phase, and also to a group of women assigned to a placebo, who were assigned during the luteal phase. This comparison indicated that OCs reduce amygdala connectivity with the postcentral gyrus relative to either the follicular or luteal phase, and also reduce amygdala-cuneus connectivity relative to the luteal phase only. The same group also placed seeds in bilateral dACC, and found that connectivity between the dACC and precuneus was lower in OC users relative to the luteal group, but higher relative to the follicular group.

By contrast, Nasseri et al. (2020) compared hormonal contraceptive users (OC + vaginal ring) during the active and inactive phases of pill use, and found higher amygdala connectivity with ventromedial PFC. Importantly, this was measured following a stressor, and therefore cannot be compared to Engman et al. (2018). Participants underwent a cold pressor test, a physiological stressor that elicits cortisol release and produces different patterns of functional connectivity, especially with respect to the amygdala, compared to people who have not undergone the stressor (Clewett et al., 2013). Nasseri et al. (2020) also placed a seed in the parahippocampal cortex, and found lower connectivity between this seed and the lateral occipital cortex.

Seed-based connectivity analyses present a general (but not uniform) pattern of higher connectivity with prefrontal regions during active OC use when compared to other groups (e.g., inactive OC condition or NC women in their follicular phase), and lower connectivity with parietal and occipital regions (Table 3).
2.7. **To what extent do OCs mimic menstrual phase rsFC fluctuations?**

In parallel with the finding that parietal connectivity is lower during the luteal phase vs follicular phase, and frontal connectivity is higher during the luteal phase vs follicular phase, OCs appear to produce a similar reduction in parietal and increase in frontal connectivity, although evidence is stronger for the latter than the former, and this pattern could easily be overturned by a single, well-designed study. However, the current state of the literature tentatively suggests that rather than creating a hypogonadal brain state, OCs create a hyperprogestogenic brain state, mimicking and then exaggerating the effects of endogenous hormones on rsFC. In those who experience adverse reactions, either connectivity pattern (produced by endogenous or exogenous hormones) may be different. Importantly, network-level (ICA) results are too sparse for any conclusions to be drawn.

3. **Methodological considerations and recommendations for future directions**

**Underlying differences in those who continue v. discontinue OCPs.**

Some individuals who use OCs experience negative mood effects as a result of OC use (Gingnell et al., 2013; Petersen et al., 2021), and some do not. It stands to reason that those who experience these adverse effects will discontinue using OCs, whereas the those who do not experience them continue their use, creating an inherent confound in observational studies that compare resting-state networks between these two groups. It may be the case that individuals who experience adverse effects have an underlying sensitivity to gonadal hormones that is reflected in their intrinsic connectivity networks (before ever using OCs). This has been shown in those with PMDD, who experience persistent, trait-like differences in connectivity as compared to controls without PMDD symptoms (Petersen et al., 2019), even during times of the cycle when symptoms abate. Whether those who do vs do not have adverse responses to OCs experience hormone sensitivity that is reflected in different rsFC patterns is not established empirically; rather, it presents an intriguing avenue for future investigation, and emphasizes the need for randomized-controlled trials.

**Former users vs never users.**

Structural MRI studies have indicated that discontinuing OC use may not reverse effects on cortical thickness (Pletzer et al., 2015). To understand the role that OCs play in shaping intrinsic connectivity networks, it may be informative to compare OC-naïve individuals to first-time to long-time OC users.

**Formulation comparisons.**

Hundreds of different OC formulations are now available to the healthcare marketplace, and well-controlled RCTs evaluating effects of OCs on the brain have been limited to studying a single formulation. Different effects may emerge when evaluating monophasic vs multiphasic formulations; 28-day vs longer formulations; androgenic vs antiandrogenic progestins; 1st vs 2nd vs 3rd vs 4th generation progestins; high vs low dose; and any other differences in formulations not captured here. Big data approaches as described in Taylor et al. (2020) will be necessary to successfully evaluate the contributions of these factors.
**Delivery system comparisons.**

It stands to reason that ethinyl estradiol and synthetic progestins produce the same effects on the brain regardless of mode of delivery – pill, patch, vaginal ring, injectable, or other – yet, this has not been established empirically. Route of delivery causes major differences in bioavailability of pharmaceuticals ([Rowland, 1972](#)) and influences subjective responses to drugs with abuse liability ([Gossop et al., 1992](#); [Kalman and Smith, 2005](#)). This may be an unexplored area contributing to differences in brain structure and function among people using different forms of hormonal contraceptives.

**Analytic techniques.**

Although relatively few studies of OC effects on intrinsic network connectivity have been published, a number of different analytic techniques have been applied: seed-based connectivity, independent components analysis, and several different time-varying functional connectivity approaches. Within the larger field of resting-state functional connectivity analyses, no single approach has emerged as generally superior to other approaches. Rather, the optimal approach depends on the parameters of the research problem – for instance, seed-based approaches are useful when a priori predictions can be made, and both independent component analysis and regional homogeneity are useful when a data-driven approach is called for. Although not currently clinically implementable, time-varying functional connectivity approaches show some promise for classifying brain states ([Du et al., 2018](#)).

**Statistical power considerations.**

Above, we discuss the possibility that false negative replication failures may be attributable to lack of statistical power. An alternative and very plausible explanation is that the findings that failed to replicate were false positives to begin with – a problem that is also attributable to small sample sizes. False positives have historically convoluted neuroimaging findings, leading to the very stringent multiple comparison correction methods that we suggest may have produced type II errors, potentially by swinging the pendulum too far in the other direction. The remedy for both problems – false negatives and false positives produced by low statistical power – is the same: Increased sample sizes are needed, and the field would benefit from consortium-type efforts to continue to move forward by increasing available statistical power.

**4. Summary and conclusions**

Neuroscientists now have compelling evidence that both the menstrual phase and its modulation by OCs shape human intrinsic connectivity networks. Converging evidence points to (1) higher connectivity between the medial temporal lobe and the prefrontal cortex when endogenous progesterone is relatively elevated, or when synthetic progestins delivered by OCs are present and (2) lower connectivity between the parietal cortex and the default mode network when endogenous progesterone is elevated, and possibly also between the occipitoparietal cortex and the medial temporal lobe when synthetic progestins delivered by OCs are present. Together, this suggests that OCs may produce a hyperprogestogenic state in the brain, although robust and reproducible confirmatory studies are needed before this can
be conclusively stated. A number of existing reviews have called for such studies (Pletzer and Kerschbaum, 2014; Taylor et al., 2020). Here, those calls for rigorous and reproducible RCTs are echoed, and key rsFC comparisons in need of replication are identified.

As research progresses, other key features should be kept in consideration for examination during study design. First, studies should seek to differentiate between OCs taken by participants as doses, absorption methods, and pharmaceutical formulation will alter how the individual’s hormones are specifically manipulated and therefore, how it affects the brain. Secondly, future research should examine each type of OC’s effect on rsFC in similar regions so that comparisons can be made to find commonalities in rsFC alterations in OC users. Potential candidates for consideration across studies are the amygdala and MFG as both were found in multiple studies to have altered connectivity for OC users. Likewise, OC users should be differentiated by those with and without negative effects brought on by OC use. Thirdly, the field would benefit from longitudinal studies that measure effects of OC onset and offset by studying the same individuals as they begin and end OC use. Finally, future studies may benefit from a focus on the age at which OC treatment is initiated and duration of use.

That said, understanding the impact of neuroendocrine factors on rsFC is not a clinically meaningful end unto itself, and finding effects of ovarian hormones on rsFC in the absence of behavioral correlates almost appears to be a solution in want of a problem – that is, is there any functional or clinical significance to rsFC fluctuations over the menstrual cycle, or in response to OC use? It has not yet been established empirically that changes in rsFC as a response to endogenous hormone fluctuations or due to OC use produces any clear adverse or beneficial effects. Indeed, a prospective study of individuals with PMDD showed the stability of resting-state connectivity across the cycle, which differed significantly from those of healthy controls whether symptoms were surging or abating (Petersen et al., 2019).

We propose here that an important yet missing explanatory piece is the lack of information about the relationship between gonadal hormones and endogenous neurotransmitters. It seems likely that gonadal hormones do not act on rsFCs directly, but only through their capacity to modulate classical neurotransmitter systems, which in turn are responsible for resting-state dynamics (e.g., Stagg et al., 2014). Trying to detect second-order effects of gonadotrophins on rsFC without knowledge of the first-order effects may contribute to the confusing landscape of results. Unknown first-order effects include both the effects of neurotransmitters on rsFC, and the effects of ovarian hormones on neurotransmitters.

In summary, prior research on steroid hormone action in the brain and how synthetic hormone formulas in OCs affect these processes offers a window into uncovering broader models for OCs’ mechanistic effects on the brain, cognition, and behavior; three broad models are reviewed: hypogonadal state, hyper-progestin state, and dysregulated state. Systems-level functional and structural neuroimaging studies have been able to establish differences between OC users and non-users, and in rare cases within-individual changes associated with OC use. It is proposed that incorporating competing hormone-action-alteration mechanistic models with neuroimaging designs, and retroactively with prior findings, could offer important insight into the causes and consequences of OC use, with
potential to guide future research aimed at mitigation. Perhaps essential to modeling the OC effects in future research would be the inclusion of hormonal assay protocols in studies comparing OC users and non-users, and of equal importance, taking account of menstrual cycle phases of the relative non-OC use comparison group.

As the field broadly advances on the neurochemistry supporting rsFC networks, it will become increasingly important for neuroendocrinologists to lead the field in investigating (1) the distribution and dynamics of in vivo neurohormone receptors and (2) the interactions between neurohormones and neurotransmitters. It is notable that the parietal and cortical regions where hormonal rsFC effects tended to be concentrated are not directly responsible for reproduction, and the distribution of hormone receptors in these regions (in human brains) remains unknown. With these pieces explained, scientists will be better able to identify the mechanisms of menstrual-related mood disorders, work toward prospective identification of individuals who are susceptible to adverse reactions to hormone administration, and develop new therapies to help those who are sensitive to endogenous hormone fluctuations across the lifespan.

Acknowledgments & disclosures

NP and TJ were supported by NIDA, R00DA045749. All authors report no conflicts of interest or financial disclosures.

Data availability

No data was used for the research described in the article.

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Fig. 1.
Four studies reported lower parietal connectivity during the luteal vs follicular phase using ICA. The location of the peak voxel reported in each study is depicted by the crosshairs in the below images.
Table 1

Seed-based connectivity analyses comparing luteal to follicular rsFC.

| Author & Year            | Sample size | Cycle phase determination method                  | Comparison reported on here | Seed region | Location of result | Direction of result relative to luteal group (reference) |
|-------------------------|-------------|---------------------------------------------------|-----------------------------|-------------|--------------------|--------------------------------------------------------|
| Syan et al, 2017        | N= 25 (within-subjects) | Calendar + serum hormone assay + LH test | Late luteal vs follicular | amygdala    | none               | =                                                     |
|                         |                          |                                    |                             | dlPFC       | none               | =                                                     |
|                         |                          |                                    |                             | insula      | none               | =                                                     |
|                         |                          |                                    |                             | PCC         | none               | =                                                     |
|                         |                          |                                    |                             | somatosensory cortex | none         | =                                                     |
|                         |                          |                                    |                             | visual cortex | none         | =                                                     |
| Hidalgo-Lopez et al., 2020 | N = 60 (within-subjects) | Calendar + salivary hormone assay + LH test | Mid-luteal vs follicular | caudate    | none               | =                                                     |
|                         |                          |                                    |                             | hippocampus | none               | =                                                     |
|                         |                          |                                    |                             | putamen     | thalamus           | ↑                                                     |
| Engman et al, 2018      | N= 17 (within-subjects) | Calendar + serum hormone assay     | Mid-luteal vs early follicular | amygdala   | cerebellum, paracentral lobule, prefrontal cortex (superior frontal gyrus, middle frontal gyrus) | ↑ |
|                         |                          |                                    |                             | dACC        | prefrontal cortex (middle frontal gyrus), superior temporal gyrus, transverse temporal gyrus, postcentral gyrus | ↑ |
| Wetherill et al, 2016   | Follicular phase N = 22 Luteal phase N = 16 | Calendar | Luteal vs early follicular | dACC       | medial prefrontal cortex into ventral striatum | ↑ |
|                         |                          |                                    |                             | OFC         | none               | =                                                     |
| Meeker et al, 2020      | N= 13 (within-subjects) | Calendar + serum hormone assay + LH test + basal body temperature | Mid-luteal vs early follicular | IPL        | medial prefrontal cortex | ↑ |
| Wang et al, 2020        | Late follicular N= 28 Mid-luteal N= 25 | Calendar | Mid-luteal vs late follicular | insula     | none               | =                                                     |
|                         |                          |                                    |                             | thalamus    | none               | =                                                     |
|                         |                          |                                    |                             | Temporal cortex | thalamus     | ↑                                                     |
| Author & Year | Sample size | Cycle phase determination method | Comparison reported on here | Seed region | Location of result | Direction of result relative to luteal group (reference) |
|--------------|-------------|----------------------------------|-------------------------------|-------------|-------------------|-----------------------------------------------------|
| Petersen et al, 2019 | N = 18 (within-subjects) | Calendar + serum hormone assay + LH test | Late luteal vs follicular | PCC | none | = |
| | | | | mPFC | none | = |
| | | | | IPL | none | = |
| Lisofsky et al, 2015 | N = 21 (within-subjects) | Calendar + serum hormone assay + LH test | Mid-luteal vs late follicular | hippocampus | superior parietal cortex | ↓ |
| | | | | amygdala | posterior cingulate, parietal cortex | ↓ |

1. Other comparisons may have been performed in the manuscript. Original manuscripts may also have used different terminology (e.g., “menstrual” in place of “early follicular” that we have altered to increase consistency between studies).
2. Where symmetrical bilateral seeds were used, these were described here as a single seed for parsimony.
Table 2
Effects of oral contraceptives on resting-state functional connectivity measured with independent components analysis.

| Author & Year            | Sample size                      | Network | Comparison          | Location of result                  | Direction of result relative to active OC group |
|--------------------------|----------------------------------|---------|---------------------|-------------------------------------|-----------------------------------------------|
| De Bondt et al., 2015b   | NC (follicular, ovulation, luteal) N= 18 | DMN     | NC vs OC            | n/a                                 | =                                             |
|                         | OC (active, inactive) N= 19       |         | Active vs inactive  | n/a                                 | =                                             |
| Petersen et al., 2014    | Follicular N = 20                 | DMN     | Active pill vs follicular | Left angular gyrus                  | Active OC < follicular                         |
|                         | Luteal N = 25                    | ECN     | Active pill vs follicular | Left middle frontal gyrus           | Active OC < inactive OC                       |
|                         | Active OC N = 24                 |         | Active pill vs inactive pill | Left middle frontal gyrus           | Active OC < follicular Active OC < inactive OC |
| Sharma et al., 2020      | Adult onset OC use N= 15         | DMN     | NC vs OC            | n/a                                 | =                                             |
|                         | Pubertal onset OC use N = 15      | ECN     | NC vs OC            | Left anterior cingulate             | Active OC > NC                                |
|                         | NC N = 48                        |         | Salience Network    | Left superior medial frontal gyrus  | Active OC > NC                                |
|                         | Pubertal vs adult onset OC use   |         |                     | Left anterior cingulate             | Active OC > NC                                |
|                         | Reward Network                   |         |                     | Left supramarginal gyrus            | Pubertal > adult                              |
|                         | Limbic Network                   |         |                     | Left inferior parietal gyrus        | Pubertal > adult                              |
|                         |                                  |         |                     | Left middle frontal gyrus           | Active OC > NC                                |
Seed-based connectivity analyses of OC effects on rsFC. Active (hormone-containing) OCs tend to be associated with higher prefrontal connectivity and lower parietal connectivity compared to inactive pills or endogenous hormone states.

| Author & Year      | Sample Size | Notable Sample Characteristics | Seed region | Comparison | Location of result | Direction of result relative to active OC group |
|--------------------|-------------|---------------------------------|-------------|------------|-------------------|-----------------------------------------------|
| Nasseri et al 2020 | N = 20       | ≥4mo monophasic HC (oral or vaginal) use prior to study | Amygdala    | Active OC vs inactive OC | vmPFC | ↑ Active OC > inactive |
|                    | (within-subjects) | | Parahippocampus | Active OC vs inactive OC | Lateral occipital cortex | ↓ Active OC < inactive |
| Sharma et al 2020  | Adult onset OC use N = 15 | Pubertal onset OC use N = 15 NC N = 48 | Putamen | Active OC vs NC | Middle frontal gyrus | ↑ Active OC > NC |
| Engman et al 2018  | NC N = 17 OC N = 15 | Previous negative affect while using OCs | Amygdala    | Active OC vs follicular Active OC vs placebo during luteal phase | Postcentral gyrus Postcentral gyrus, cuneus | ↓ Active OC < follicular ↓ Active OC < luteal |
|                    |             |                                | dACC        | Active OC vs follicular Active OC vs placebo during luteal phase | Superior frontal gyrus Precuneus | ↓ Active OC > follicular ↓ Active OC > luteal |
|                    |             |                                |             | Active OC vs placebo during luteal phase | Precuneus | ↓ Active OC < luteal |

Table 3