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The relationship between women's hormonal state and their neural and behavioral responses to natural rewards

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The relationship between women's hormonal state and their neural and behavioral responses to natural rewards

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B.A., Knox College, 2011

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An abstract of
A dissertation submitted to the Faculty of the
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Abstract

Women's interest in and behavioral responses to food and sex change across their menstrual cycle. Food intake is lowest around the time of ovulation and highest in the post-ovulatory luteal phase of the cycle, whereas sexual behavior and desire follow the opposite pattern, peaking near ovulation and reaching a nadir in the luteal phase. The mechanisms by which women's hormonal state modulates their food intake and sexual behavior remain largely unknown. The goal of this dissertation was to inform our understanding of the relationship between women's hormonal state and their responses to food and sexual stimuli. In the first manuscript, we review the literature to show that there is striking consistency across species in cyclic patterns of food intake and sexual behavior, and we detail the evidence that cyclic shifts in motivation for food and sex are mediated by the ovarian steroids estradiol (E2) and progesterone (P4). In the following two empirical manuscripts, we ask the questions of whether women's hormonal state modulates: a) how much they desire food and sexual stimuli and/or b) how much they like them. We addressed these questions in a sample of 59 women: 30 naturally cycling (NC) women and 29 women regularly taking a monophasic oral contraceptive (OC), who participated in two test sessions at distinct hormonal times. At test session one, half of the NC women (n = 15) were near ovulation and half (n = 15) were in the luteal phase. Half of the OC women (n = 15) were in the pill-free week of their pill cycles and the other half (n = 14) were in the third week of their pill-cycles. We found that women's hormonal state was related to how motivated they were to view sexual stimuli, how much they liked sexual stimuli, and their neural response to sexual stimuli. Conversely, we did not find evidence for a relationship between women's hormonal state and their motivation for, liking of, or neural response to food stimuli. Together, these data shed light on the biological and psychological factors that contribute to women's motivated behaviors.

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Manuscript 1

Hormonal modulation of motivation for natural rewards in women and nonhuman females

Kaytlin J. Renfro & Kim Wallen, Ph.D.

Abstract

Ovarian steroids have been proposed to act as motivational switches, dynamically shifting priorities between motivation for food and sex. Here, we review the literature on ovarian steroid modulation of consummatory and appetitive feeding and sexual behaviors in nonhuman females and women, with a focus on the roles of estradiol (E2) and progesterone (P4). Collectively, work indicates that across rats, monkeys, and humans, E2 inhibits motivation for food and promotes motivation for sexual behavior. Findings with P4 are relatively more mixed and vary by species. P4 effects on feeding behavior are inconclusive, with some studies showing no effect and others showing facilitation of feeding via antagonism of E2's anorectic effects. Although P4 is required for expression of sexual behavior in rats, it is negatively related to sexual behavior and desire in nonhuman primates and women. We provide a brief overview of contextual factors that modulate hormonal effects and show that hormonal effects on motivation to engage in behavior are more subject to modulation by context than are those that affect ability to engage in behavior. For example, women and nonhuman primates are – unlike rats – physically able to engage in sexual behavior regardless of hormonal state, and context thus has greater importance in determining the occurrence of sexual behavior in women and nonhuman primates than it does in rats. The review concludes with a brief discussion of ovarian modulation of motivation for drugs of abuse, highlighting that ovarian steroids modulate drug seeking in a manner similar to their modulation of sexual behavior. Although there is striking consistency in the pattern of ovarian effects on motivation for food and sex across nonhuman species, substantial work remains to determine whether the biological and behavioral mechanisms that underlie hormonal modulation of motivation for food and sex in nonhuman animals apply to women.

Philosophers, behaviorists, and neuroscientists alike have long considered the question of why we act — of what motivates us as individuals to behave. Perhaps no individual's conceptions of the causes of behavior have been so broadly and enduringly influential as Charles Darwin's. From a Darwinian perspective, there are two main reasons to act: a) to survive), and b) to reproduce (Darwin, 1888). There are many proximate mechanisms in place to ensure that individuals are sufficiently incentivized to work to survive and reproduce (as discussed in LeDoux, 2012). Two primary hedonic motivators for action are fear and reward, which respectively trigger aversive motivation and appetitive motivation (Bradley & Lang, 2000). For the purposes of this review, we focus on appetitive motivation, and specifically on the seeking of the two natural rewards that map onto the Darwinian imperatives of survival and reproduction: food and sex (Berridge & Kringelbach, 2008).

It has been argued that food and sex are the fundamental rewards for which neural reward systems evolved (as discussed in Schultz, 2000; Kelly & Berridge, 2002). The rewarding properties of food and sex are attested to in part by individuals' willingness to work for them—to expend cognitive, physical, and temporal resources to gain access to them (Berridge, 1996; Pfaus et al., 2012). Beyond motivational value, Berridge and Robinson (2003) propose that the rewarding nature of a stimulus is also derived from its hedonic impact–how much it is liked–and the quality of one's implicit and explicit memories of previous interactions with the stimulus. There is strong support for the notion that food and sex are, to varying degrees and dependent on context, not only wanted, but also liked and remembered (Berridge, 1996; Paredes, 2009; Pfaus et al., 2012). Broadly, the cognitions and behaviors that correspond to wanting, liking, and learning about a food stimulus are quite similar to those that correspond to wanting, liking, and

learning about a sexual stimulus (see Figure 1 for a depiction of the behavioral reward cycles for food and sex) (Georgiadis & Kringelbach, 2012).

Despite, or perhaps because of, the substantial degree of overlap in behavioral and psychological mechanisms, food and sex are rarely pursued simultaneously – it is often the case that one is prioritized over the other (as reviewed in Schneider, Wise, Benton, Brozek, & Keen-Rhinehart, 2013). In some animals, this motivational tradeoff is pronounced, such as in species that exclusively forage and accumulate weight for months of the year and then fast completely during the mating season (Le Boeuf & Laws, 1994; Baker, Fowler, & Antonelis, 1994). Less extreme examples of shifts in priority between food and sex are evident in day-to-day human and nonhuman behavior, such as the changes in the prioritization of food that occur across a diurnal cycle.

But what mechanisms drive shifts in motivational priorities between food and sex? It is clear that motivation for one over the other is dynamically modulated by an interaction between internal state and external features of the motivating item (see Figure 1 for examples of internal and external factors that modulate motivational value) (Schneider et al., 2013). Of identified factors modulating motivation, we focus here on ovarian steroids, which have emerged as prime candidates for switching motivation between food and sex and for more generally modulating motivational processes and reward seeking in nonhuman animals and women (Roney, 2016; Yoest, Cummings, & Becker, 2014; Schneider et al., 2013; Anker & Carroll, 2010).

Below, we review the nonhuman and human literature on the relationship between ovarian steroids (with primary focus on estradiol [E2]) and progesterone [P4]) and female motivation for food and sex. Our review focuses on the relationship between cyclic fluctuations in gonadal steroids and motivation and behavior. Because males experience relatively constant

levels of gonadal steroids, we have limited our discussion to females. In including discussions of females in both the nonhuman and human literature, we hope to highlight the conservation of hormonal mechanisms across species, as well as to use the inconsistencies across the literatures to inform our understanding of translation of methodologies across species and of the differential role of hormones in nonhuman females versus women.

Models of hormonal effects in nonhuman animals and women

There are two primary ways in which the relationship between ovarian steroids and motivated behaviors is studied in nonhuman animals: a) via tracking behavior across estrus or ovarian cycles and correlating it with endogenous steroid levels, and b) by removing the animals' ovaries, administering the steroid(s) of interest, and measuring behavior (Schneider at al., 2013; Carroll & Anker, 2010; Wallen, 1990). In studies that take the former approach, researchers often compare behavioral and/or neural endpoints between the fertile phase of the animal's cycle and the nonfertile phase of the cycle. In the case of rats, this is the estrus phase as compared to the metestrus and/or diestrus phase. In primate work, this is the periovulatory phase as compared to the luteal phase. Both the estrus phase and the periovulatory phase are characterized by a preceding sharp spike in E2, leading researchers to frequently draw equivalences between the two. There are, however, notable differences between estrus and the periovulatory phase. For example, in rats, there is spike in P4 that occurs concurrently with the pre-estrus peak in E2, which is absent in nonhuman primate periovulatory phases (Figure 2a) (Hoff, Quigley, & Yenn, 1983). Because rats do not experience a post-ovulatory luteal phase as nonhuman primates do, it is similarly difficult to make parallel the nonfertile phases of rat and primate cycles. By removing the animals' ovaries (i.e., performing an ovariectomy [OVX]) and administering

steroids of interest, one is able both to draw clearer connections across species and, of course, to move beyond correlation and make causal inferences about steroid effects on behavior.

Experimental manipulation of hormones in women poses obvious consent and health issues and is used much less frequently than in nonhuman animal work. The favored approach in studies of women is to track women's changes in interest in food and sex across their menstrual cycles. Women's ovarian cycles mirror those of nonhuman primates, in that E2 levels rise throughout the first half of their cycles ("follicular phase"), and peak just prior to ovulation ("periovulatory phase") (Stricker et al., 2006). After ovulation, E2 declines, and P4 rises substantially and remains high for the final 14 days of their cycles ("luteal phase") (Stricker et al., 2006) (Figure 2). Of note is that because the periovulatory phase in women is short (i.e., 24 – 48 hrs) and its timing is not straightforwardly predictable (Dirieto, Bailly, Mariani, & Ecochard, 2013), few studies are designed to specifically test women in a hormonally-confirmed periovulatory phase. What is more often the case is that women are tested in the mid-follicular phase, and women's responses in the follicular phase are compared to responses in the mid-luteal phase (e.g., Jones et al., 2018). A not insubstantial amount of inconsistency between studies on hormonal state effects is thus likely partially attributable to the variability of the timing in "fertile" phase test sessions.

In women taking HCs, ovarian function is inhibited via hormonal negative feedback and endogenous E2 and P4 are kept at constant low levels (Speroff & Darney, 2010). The most common form of HC is the combination birth control pill (i.e., combination oral contraceptives [OCs]) (Mosher & Jones, 2010). A combination OC consists of a synthetic estrogen (in the majority of cases this is ethinyl estradiol) and a synthetic progestin (the exact progestin used varies much more widely than does the estrogen used, but commonly-used ones include

levenorgestrel, norgestimate, norethindrone acetate, and drosperinone). The synthetic estrogen and progestin in the pill suppress natural fluctuations in E2 and P4 by inhibiting the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH), thereby preventing follicular development, ovarian steroid production, and ovum release (Speroff & Darney, 2010). The resulting hormonal state from OC use is thus low constant levels of estrogens (EE and E2) and high stable levels of a synthetic progestin (Figure 2). Because OC users do not ovulate and have a unique hormonal profile, they provide an opportunity to test which midcycle effects identified in NC women are due to ovulation itself, as well as to identify the impact of synthetic steroids on motivated behavior. More broadly, because the overwhelming majority of U.S. women will use an OC at some point in their lives (Mosher & Jones, 2010), it is increasingly important to characterize the neural and behavioral effects of an OC hormonal state.

Ovarian hormonal modulation of food intake and motivation: Nonhuman females

Work in rodents and nonhuman primates shows that food intake decreases around the time of ovulation. Correlational studies indicate that increased E2 levels predict the periovulatory nadir in food consumption, and experimental work supports the notion that E2 is not only related to, but critical for, periovulatory appetite suppression (Wade & Zucker, 1970; Czaja & Goy, 1975; Rosenblatt, Dyrenfurth, Ferin, & Wiele, 1980; Kemnitz et al., 1989; Asarian & Geary, 2002). Specifically, rats, hamsters, guinea pigs, and rhesus monkeys all show a marked increase in food intake and weight gain following ovariectomy, and this effect is reversed by administration of doses of E2 that produce physiological levels (Wade & Zucker, 1970; Czaja & Goy, 1975; Morin & Fleming, 1978; Kemnitz et al., 1989; Asarian & Geary, 2002; Richard, Lopez-Ferreras, Anderberg, Olandersson, & Skibicka, 2017). E2 appears to exert its anorectic effects via estrogen receptor alpha (ERalpha) as indicated by work showing that ERalpha

knockout produces an obese phenotype that is not reversed by exogenous E2 administration (Musatov, et al., 2007). The importance of ERalpha to appetite suppression is further evidenced by work showing that ERalpha-specific agonists suppress food intake, whereas ERbeta agonists are without effect on food consumption (Roesch, 2006).

Food intake increases following ovulation, and in animals with a post-ovulatory luteal phase, food consumption remains high until menstruation (Czaja & Goy, 1975; Rosenblatt, Dyrenfurth, Ferin, & Wiele, 1980). Although the post-ovulatory increase in food intake correlates with the luteal rise in P4, data in rodents and nonhuman primates indicate that P4 itself does not stimulate appetite (Wade, 1975; Czaja, 1978). Rather, the main effect of P4—when detected—appears to be via antagonism of the anorectic effects of E2. In OVX females, P4 alone does not lead to greater food consumption or substantial weight change (Wade, 1975; Czaja, 1978). P4 does, however, increase food intake when given on a background of E2 or administered to intact females who are experiencing moderate-high E2 (Wade, 1975).

Data indicate that E2 primarily (and some argue exclusively) works to decrease calorie consumption via decreasing meal size (Eckel, 2011; Butera, 2010). Based on these findings, Butera (2010) proposed that E2's anorectic effects are largely due to changes in satiety that are the result of E2 modulation of satiety hormones and peptides, such as cholecystokinin (CCK), ghrelin, and neuropeptide Y (NPY). This model of ovarian hormonal modulation of feeding, however, overlooks the important role of reward in feeding behaviors and discounts the growing literature on steroid modulation of motivation for food in addition to effects on food consumption (as reviewed in Schneider et al., 2013). That is, recent work shows that E2 modulates not only consummatory feeding behavior (i.e., food intake), but also appetitive feeding behaviors, which are behaviors that bring the animal into contact with food and facilitate

later consumption but do not correspond to intake in the moment (Klingerman et al., 2010; Schneider et al., 2013; Richard et al., 2017). A commonly measured appetitive feeding behavior in rodents is food hoarding, in which the animal forages for food and brings it back to its home area. Notably, the pattern of ovarian steroid modulation for food hoarding in rats and Syrian hamsters mirrors that for food intake, with E2 suppressing food hoarding, and P4 antagonizing the effects of E2 but having no effect alone (as reviewed in Bartness, Keen-Rhinehart, Dailey, & Teubner, 2011; Klingerman et al., 2010; Coling & Herberg, 1982). Beyond study of species-specific appetitive feeding behaviors, operant paradigms are commonly used in a variety of species to measure food motivation. Richard and colleagues (2017) employed a classic operant paradigm, in which rats were trained to press a lever for a sucrose pellet, to show that lever presses increased following ovariectomy, and that this increase was reversed with E2 administration. The authors further reported that specific micro-injections of E2 into the ventral tegmental area (VTA), a region commonly indicated in reward processing, was sufficient to attenuate OVX-increased lever pressing, suggesting that E2 is modulating feeding behavior at least in part via modulating neural reward circuitry (Richard et al., 2017).

Ovarian hormonal modulation of food intake and motivation: Considerations for translation to women

Despite remarkable consistency across studies and species, a number of contextual factors modulate E2 and P4 effects of food seeking and intake, and these factors are of particular importance when considering translation of this model to women. Previous work indicates that hormonal effects on feeding behaviors may be subject to modulation by food availability and quality. Specifically, research in rodents shows that hormonal effects on appetitive feeding behavior is masked when animals are fed ad libitum, and emerges only when the animals are

moderately food restricted (Klingerman et al., 2010; phenomenon reviewed in Schneider et al., 2013). Hormonal effects are similarly masked in nonhuman primates when animals are given access to a high-caloric diet, and become evident only when given access to a relatively low-caloric (i.e., chow-only) diet (Johnson et al., 2013). Both of these findings pose potential concern in work with humans given that most female participants in research studies live in a food-abundant environment and are inundated with an ever-growing number of calorically-dense foods and food stimuli (e.g, images). Because research in women largely precludes the possibility of strictly controlling participants' caloric intake, it seems likely that hormonal effects may be harder to detect than in women than in nonhuman females.

Ovarian hormonal modulation of food intake and motivation: Women

Although the findings are not as robust or coherent as in nonhumans, the literature on steroid modulation of food intake in women collectively indicates a similar pattern. That is, work shows that women's overall food intake is lowest around the periovulatory phase of their menstrual cycles and highest in the luteal phase (Dye & Blundell, 1997; Asarian & Geary, 2006; Hirschberg, 2012). In a meta-analysis, Buffenstein and colleagues (1995) found that overall calorie consumption decreases by an average of 250kcal per day during the periovulatory phase, and that caloric intake is consistently greater in the luteal phase as compared to the follicular phase. Potential concerns regarding Buffenstein and colleagues' conclusion arise from evaluation of the studies included in the analysis, of which many relied on self-report of calories consumed and estimation of cycle phase via counting methods (e.g., using the first and last day of menstruation to estimate cycle phase rather than using hormonal measures)—both of which introduce substantial error. These findings are, however, corroborated by work in which food consumption was directly measured and serum and/or salivary levels of hormones were assayed

(Lissner, Stevens, Levitsky, Rasmussen, & Strupp, 1988; Lyons, Truswell, Mira, Vizzard, & Abraham, 1989; Gong, Garrel, & Calloway, 1989; Roney & Simmons, 2017). As in nonhuman animals, work on continuous relationships between ovarian steroids and food intake in women shows that E2 is a negative predictor of food consumption, whereas P4 is a positive predictor (Roney & Simmons, 2017). It is, however, difficult to tease apart in NC women whether the positive relationship between P4 and food intake is due to appetite-stimulant effects of P4 in women, or if as is the case in nonhuman primates and rodents, P4 merely opposes E2's effects.

Whether the same patterns of hormonal modulation extend to appetitive aspects of feeding behavior in women remains largely untested and marks a notable gap in the literature. Some have cited cyclic shifts in food cravings and incidences of binge-eating episodes as support for the notion that the relationship between appetitive aspects of feeding and ovarian hormones is similar to that of the relationship between steroids and food intake (Rivera & Stincic, 2017). Women report both more frequent and more intense food cravings in the luteal phase of their cycles than they do in the follicular or periovulatory phase (Cohen, Sherwin, Fleming, 1987; Bancroft, Cook, & Williamson, 1988; Metcalf, Livesay, Hudson, & Wells, 1989; as reviewed in Buffenstein et al., 1995). In both nonclinical and clinical samples of women, binge eating episodes occur more frequently in the midluteal phase, and their incidence is negatively predicted by E2 and positively predicted by P4 (Edler, Lipson, & Keel, 2006; Klump, Keel, Culbert, & Edler, 2008; Klump et al., 2013).

Such fluctuations in food interest and intake are not seen in NC women with anovulatory cycles, and overall findings with women whose cycles are suppressed by OC use are mixed (Barr, Janelle, Prior, 1995). OCs inhibit endogenous E2 and deliver high and consistent doses of progestins, yielding a hormonal state somewhat akin to the NC women's luteal phase (Speroff &

Darney, 2010; Stricker et al., 2006). Given the luteal peak in food consumption, one might expect OC use to be associated with increased food intake. In keeping with this prediction, one of the most commonly reported side-effects and cited reasons for discontinuing OC use is weight gain (e.g., Rosenberg & Waugh, 1998). Despite sound theoretical grounds and consistent user reports, the empirical data on weight gain and food intake changes as a consequence of OC use are far from conclusive. Although a subset of studies show OC use to be predictive of increased food intake, the majority find no relationship between OC use and weight gain or total food consumption (Eck et al., 1997; Proctor-Gray et al., 2008; Tucci, Murphy, Boyland, Dye, & Halford, 2010). Of note is that more consistent relationships are found between weight gain and the progestin-only injectable contraceptive, medroxyprogesterone acetate (MPA) (more commonly known by its clinical name, "Depo-Provera") (Risser, Gefter, Barratt, & Risser, 1999; Espey, Steinhart, Ogburn, & Quals, 2000; Bahamondes et al., 2001; Bonny et al., 2006; Berenson & Rahman, 2009) Two notable differences between MPA and commonly used OCs are: a) OCs contain a low dose of ethinyl estradiol (EE) in addition to the synthetic progestin, and b) typical OC regimens are three weeks of active steroids followed by an OC-free week, during which women's endogenous E2 levels rise and their hormonal state more closely approximates that of NC women in the follicular phase of their cycles (Warner Chilcott, 2006; van Heusden & Fauser, 2002). Because it takes several days for OC progestins to accumulate in the blood (Warner Chilcott, 2006), it is possible that food intake drops during women's OC-free week and does not increase substantially until the second week of their pill-cycles when blood levels of progestins reach sufficiently high levels to oppose E2 and EE effects. If this were the case, OC use would yield only two weeks of increased food intake, which would be equivalent to NC women's luteal increase (and result in no group difference between NC and OC women).

Whether OC women's food intake drops during their OC-free week, however, remains to be tested, as women in their pill-free week are rarely included in studies.

Ovarian hormonal modulation of sexual behavior and motivation: Nonhuman females

In almost all females studied, sexual behavior and motivation follow the opposite pattern of that of food-related behavior and motivation. That is, sexual behavior and desire peak around the time of ovulation and decline post-ovulation (as discussed in Wallen, 2013). The periovoulatory peak in sexual behavior is predicted by the pre-ovulatory E2 surge. In rats, E2 makes sexual behavior possible by working synergistically with P4 to trigger a cascade of physiological effects that lead to the release of the spinal reflex: lordosis (i.e., the characteristic arching of the back that facilitates male mounting and intromissions) (Pfaff, Diakow, Zigmond, & Kow, 1974). Work with OVX rats shows that although E2 alone can produce partial sexual receptivity, E2 and P4 in sequence are necessary for full expression of receptive sexual behaviors such as lordosis (Boling & Blandau, 1939; Whalen, 1974). Because sexual capacity and behavior are under tight hormonal control, it was assumed by some that female sexual motivation is subject to the same hormonal mechanisms (as discussed in Wallen, 1990). This is indeed what has been found – researchers have shown via a variety of methods, such as effort tasks, pacing paradigms wherein the female controls the incidence of sexual behavior, and counts of behaviors that indicate female sexual interest, such as ear wiggling, that female sexual motivation in rats also peaks at ovulation (Erskine, 1989; Zipse, Brandling-Bennett, & Clark, 2000). As with incidence of sexual behavior, sexual motivation is also abolished with OVX, & female-initiated sexual contact is reinstated with the same regimen that produces full lordosis: E2 + P4 (McDonald & Meyerson, 1973; Pfaus, Smith, Coopersmith, 1999; Zipse, Brandling-Benett, & Clark, 2000; Corona et al., 2011).

Mating ability is not under direct hormonal control in nonhuman primates as it is in rats, and is thus not temporally restricted to ovulation. Rather, nonhuman primates are physically capable of mating at any point in their ovarian cycles. Although the ability to mate has been liberated from hormonal control, ovarian steroids remain critically important for primate sexual behavior (Wallen, 1990; Wallen, 2001). Specifically, E2 and P4 modulate the likelihood of mating occurrence via affecting female sexual motivation (Wallen, 1990). A commonly-used index of female sexual motivation is female initiation of sexual behavior (i.e., "proceptive" sexual behaviors). In rhesus monkeys, endogenous E2 levels predict female sexual behaviors directed toward a male conspecific, such as approach, follow, and initiation of proximity (Wallen, Winston, Gaventa, Davis-DaSilva, & Collins, 1984). Exogenous administration of E2 to OVX females dramatically increases female-initiated sexual behaviors in rhesus monkeys (Zeher, Mastripieri, & Wallen, 1998). P4 does not facilitate sexual behavior occurrence or motivation in nonhuman primates as it does in rats; rather, P4 has been shown to negatively predict sexual motivation in both semi-naturalistic and experimental contexts (Bonsall et al., 1978; Kendrick & Dixson, 1985; Wallen et al., 1984). In a study of females trained to press a lever for access to a male, Bonsall and colleagues (1978) showed that E2 levels predicted the time to male access, with higher E2 leading to shorter access times (i.e., faster pressing). Conversely, P4 positively predicted access time, such that higher P4 levels were related to longer times to male access. Kendrick and Dixson (1985) showed similar results in a series of pair tests with OVX marmosettes, where they found that E2 treatment increased proceptive sexual behavior, whereas P4 treatment dramatically reduced and almost completely eliminated female-initiated sexual behaviors. Findings with synthetic progestins treatments such as MPA provide additional support for the notion of progestin inhibition of sexual interest in nonhuman primates,

as work in rhesus monkeys shows that MPA (which binds approximately three times stronger to the P4 receptor than does P4) inhibits female-initiated sexual behavior more markedly than does P4 itself (Sitruk-Ware, 2006; Pazol, Wilson, & Wallen, 2004).

Ovarian hormonal modulation of sexual behavior and motivation: Considerations for translation to women

Comparison between work in rodents and that in nonhuman primates makes it clear that when capacity to mate is no longer dependent on hormones, contextual factors are important predictors of sexual behavior. Contextual factors that modulate hormonal effects in nonhuman primates include variables such as the monkey's rank in the group hierarchy, the time of year, and the relative stability of their social groups (Wallen, 1990; Wallen & Schneider, 2000). Context becomes substantially more important when consideration extends from nonhuman primate to human sexuality. In humans, compared with other animals, there are many more reasons both to engage and not to engage in sexual behavior. Meston and Buss (2007) asked a sample of 444 individuals to list reasons for engaging in sexual behavior, and participants collectively provided 237 unique reasons. Cited reasons included but were not limited to those motivated by pleasure seeking, stress reduction, goal attainment, and spirituality. The importance of context in the understanding of human sexual behavior is further highlighted by work showing that the occurrence of the weekend, which is a societal construct, is a strong and consistent predictor of the incidence of sexual behavior (Wilcox et al., 2004; Roney & Simmons, 2013). Societal expectations and constraints also dictate why sex is unlikely to occur, such the expectation that one not engage in sexual behavior in public venues. There are thus many (indeed, the majority) of cases in which cultural and/or interpersonal factors bear a much greater influence on one's decision to engage in sexual behavior than does one's hormonal state. This

characteristic of human sexuality makes taking contextual and social factors into consideration when assessing the impact of hormones on women's sexuality all-the-more important.

Ovarian hormonal modulation of sexual behavior and motivation: Women

Given the contextual complexity of human sexual interactions and women's physical ability to engage in sexual behavior regardless of hormonal state, it is perhaps not surprising that there has been little consistency in findings of hormonal modulation of paired sexual behaviors in humans. Although some authors report no relationship between women's hormonal state and reported incidence of paired sexual events, a relationship has been identified in a subset of cases in which contextual factors were accounted for and hormonal state was measured directly rather than estimated (Harvey, 1987; Roney & Simmons, 2013; Udry & Morris, 1968; Adams, Gold, & Burt, 1978; Stainslaw & Rice, 1988; Matteo & Rissman, 1984; Wilcox et al., 2004; as reviewed in Cappelletti & Wallen, 2016 and Motta-Mena & Putts, 2017). For example, an oft-discussed concern in studying hormonal modulation of intercourse occurrence is that couples might avoid midcycle sexual behavior if they are trying to avoid pregnancy (e.g., Stainslaw & Rice, 1988). Credence for this concern is lent by work in which pregnancy was not possible, such as in a study by Matteo and Rissman (1984) where they measured sexual behaviors between same-sex couples, and in work by Wilcox and colleagues (2004) where they tested only couples who were using a highly reliable form of contraception (e.g., tubal ligation). Both studies reported a clear midcycle peak in paired sexual behavior. Such a midcycle peak was not found by Harvey (1987), who tested women in sexually active heterosexual relationships who did not report using a consistent form of contraception. Harvey attributed the lack of midcycle increase in paired sexual behavior to pregnancy avoidance rather than to a lack of change in sexual motivation, supporting this interpretation with data showing that women reported a midcycle increase in autosexual

behavior, such as masturbation. To Harvey's point, because autosexual behaviors are subject to relatively fewer external factors, such as contraceptive concerns and/or the presence of a partner, many consider them to be a better metric of internal sexual motivation than is paired sexual behavior.

Autosexual behavior, female-initiated sexual behavior, and reported sexual desire track more consistently with cyclic changes in hormones than does overall incidence of paired sexual behaviors (Adams, Gold, & Burt, 1978; Harvey, 1987; Stainslaw & Rice, 1988; Bullivant et al., 2004; Roney & Simmons, 2013). That is, a number of studies show a periovulatory peak in women's reported autosexual behaviors and sexual desire, and a post-ovulatory decline in behavior and desire (Adams, Gold, & Burt, 1978; Harvey, 1987; Stainslaw & Rice, 1988; Bullivant et al., 2004; Roney & Simmons, 2013). Cyclic fluctuations in sexual desire have been documented both in the field and laboratory. In daily journal-based studies, women report greater sexual desire, greater incidence of sexual fantasies, and more arousal derived from sexual fantasies around ovulation (Roney & Simmons, 2013; Dawson, Suschinsky, & Lalumiere, 2012). In the laboratory, periovulatory women show more interest in visual sexual stimuli (VSS), and they also show greater genital arousal to VSS than do luteal women (Wallen & Rupp, 2010; Slob, et al., 1991). Despite the well-replicated finding that sexual desire peaks around ovulation, few researchers have tested which ovarian steroids predict sexual desire. Although E2 is a consistent predictor of sexual behavior and desire in nonhuman females, many authors have long contended that women differ from nonhuman primates and rodents, and that in human females, testosterone (T) is the key modulator of sexual desire (as discussed in Wallen, 2013 and reviewed in Cappelletti & Wallen, 2016). Work thus far, however, indicates that E2 modulates women's sexual desire as it does nonhuman animals. Roney and Simmons (2013) completed the

only study to date to measure women's daily levels of E2, P4, and T and correlate them with women's reported sexual desire. The authors found E2 positively predicted sexual desire, and P4 negatively predicted sexual desire, but T provided no predictive power of women's sexual desire. Of note is that the E2 levels two days prior to the reported sexual desire was a stronger predictor than day-of E2. Given that E2 peaks approximately two days prior to ovulation, these data align with the model of E2 promotion of ovulatory increases in sexual desire. Another important takeaway from Roney and Simmon's (2013) study is that the strongest hormonal predictor of those measured was day-of P4, which negatively predicted sexual desire.

Further evidence of progestin suppression of sexual desire in women is seen in work with women on OCs, who experience high levels of synthetic progestins for the duration of their pill-cycles (Speroff & Darney, 2010; Warner Chilcott, 2006). Such studies indicate that OC use is related to decreased sexual desire. Sanders and colleagues (2001) completed one of the only longitudinal studies on OC use and behavioral effects to date, and the authors found that 47% of women discontinued OC use within the first year, and the best predictor for discontinuation was adverse sexual/emotional side effects. Recent work by Mark, Leistner, & Garcia (2016) extended these findings to show that OC-using women report lower solitary sexual desire than do women using nonhormonal contraceptives. These findings are complemented by laboratory work, which shows that OC-using women, as compared to NC women, are less sensitive to, interested in, and rate less positively a range of sexual stimuli (Renfro & Hoffmann, 2013; Wallen & Rupp, 2010; Renfro, Rupp, & Wallen, 2015).

Although the data collectively indicate a negative relationship between OC use and sexual desire, not all studies support this phenomenon. Mixed findings regarding OC use and sexual desire outcomes may be related to factors such as the hormonal composition of OCs in the

study, the phase of the pill cycle during which the women were tested, how recently women had started using OCs, and the metrics of sexual desire used (e.g., whether the researchers assessed autosexual behavior/solitary sexual desire or paired behavior/dyadic desire [Mark, Leistner, & Garcia, 2016]). Possibly most importantly, one must also consider the potential positive effects on sexual desire resulting from removal of the fear of pregnancy. Placebo-controlled trials are ideal to account for these additional factors. Though placebo-controlled studies of OC use are quite rare, one of the only ones to test potential behavioral side effects recently showed that OC users, as compared to placebo controls, experienced decreased sexual desire, arousal, and pleasure after beginning use of OCs (Zethraeus et al., 2016), strongly supporting the idea that the hormones in OCs pharmacologically inhibit sexual motivation.

Application of findings to our understanding of motivation for drugs of abuse

It has been suggested that research on the neurobiology of motivation for natural rewards, such as food and sex, also holds promise for shedding light on the neurobiology of drugs of abuse (Kelly & Berridge, 2002; Nestler, 2005). The broad rationale underlying this perspective is that the neural reward and motivational circuits evolved to mediate seeking of and response to natural rewards, and drugs of abuse co-opt these neural pathways to produce their effects. Some argue that then what is neurobiologically the case for natural rewards should also be the case for drugs of abuse (Berridge & Kringelbach, 2015). Because ovarian steroids modulate motivation for food and sex, they may thus also modulate motivation for drugs of abuse. Given that ovarian steroids differentially modulate seeking of food and sex, the question arises: if ovarian steroids do indeed modulate drug motivation, then which pattern will the modulation follow—that of food, or that of sex?

The overwhelming evidence in both nonhuman females and women indicates that ovarian steroids modulate motivation for drugs of abuse in a manner similar to how they modulate sexual motivation, but dissimilar to how they modulate motivation for food (Becker & Hu, 2008; Becker & Koob, 2016; Carroll & Anker, 2010). That is, E2 promotes drug-seeking, whereas P4 antagonizes E2's effects and attenuates drug-seeking. Work in rats shows that acquisition, maintenance, and escalation of drug use are all potentiated in the estrus phase as compared to other phases of the ovarian cycle (Becker & Cha, 1989; Lynch, Arizzi, & Carroll, 2000; Carroll & Anker, 2010). Research in OVX female rats shows that E2 administration increases drug-seeking behaviors, and P4, as well as its metabolite allopregnanolone (ALLO) decrease these behaviors (Larson, Anker, Gliddon, Fons, & Carroll, 2007; Anker, Holtz, Zlebnik, & Carroll, 2009; Segarra et al., 2010). Data in women reveal a pattern similar to that in nonhuman animals; however, in the majority of human studies, researchers have compared women in the follicular phase to those in the luteal phase, thus largely focusing on the relationship of drug responses to P4 rather than to E2. Across a number of studies and range of psychostimulants, researchers find that women's physiological responses are greater and subjective responses more favorable to drugs in the follicular phase than they are in the luteal phase (White, Justice, & de Wit, 2002; Evans, Haney, & Foltin, 2002; Anker & Carroll, 2010). These findings have been followed up by work that shows that administration of oral micronized P4 attenuates the positivity of subjective responses to both cocaine and nicotine, leading researchers to speculate about the utility of P4 in the treatment of drug-addicted individuals (Evans & Foltin, 2006; Evans, 2007; Reed, Evans, Bedi, Rubin, & Foltin, 2011).

That the effects of ovarian steroids on motivation for and responsiveness to drugs of abuse more closely mirror ovarian steroidal effects on sex than on food raises the question of

whether sexual behavior is a better model of mechanisms underlying drug addiction than is feeding behavior. Richard and colleagues (2017) recently proposed this to be the case, suggesting that perhaps mechanisms of drug seeking more closely align with mechanisms of sexual behavior than with those of feeding behavior because drug seeking taps into systems geared toward energy expenditure (e.g., sexual behavior) rather than those biased toward energy accrual (e.g., food intake).

Concluding thoughts, implications, and future directions

When taken together, the literature on ovarian-cyclic shifts in feeding and sexual behavior in females tells a consistent story: food intake is lowest at ovulation and highest after ovulation, and sexual behavior follows the opposite pattern, and peaks at ovulation and declines after ovulation. Work collectively and convincingly indicates that E2 and P4 mediate changes in feeding and sexual behavior across the cycle; however, the relative role and importance of these hormones to the expression of feeding and sexual behaviors varies across species. It is clear that when behaviors are liberated from direct hormonal control, such as the incidence of sexual behavior is in nonhuman primates and women, that hormones serve primarily to bias motivation for engaging in the behavior, and that hormonal effects on motivation to engage in behavior are more subject to modulation by context than are those that affect ability to engage in behavior.

Work also indicates that the impact of context on expression and detection of hormonal effects is greater in women than in other females. Although the literature as a whole suggests that ovarian steroids modulate feeding and sexual behavior in women much as they do in nonhuman animals, results are more mixed than are those in the rodent and nonhuman primate literatures. The greater inconsistency among findings in women likely reflects not only the influence of context, but also lack of precision in measurement of women's hormonal state. That is, the

majority of studies in women do not confirm where women are in their cycles via a direct hormonal measurement. This methodological issue extends to work with women taking OCs, in that very rarely is it reported or considered where women were in the pill-cycles at time of test.

Given the methodological limitations and added contextual factors, it is perhaps all-the-more striking that findings in of ovarian-cyclic shifts in motivation in nonhuman animals translate as well as they do to women. That said, there is still substantial work ahead to assess whether the biological and behavioral mechanisms that drive cyclic changes in motivation for food and sex in nonhuman animals map onto women.

The current thesis

In the following two papers, we seek to address a subset of the issues and open questions raised here about the relationship between women's hormonal state and their cyclic changes in feeding and sexual behavior. In paper one, we directly test whether the motivational value of food or sexual stimuli differs by and changes across women's menstrual cycles or OC pill-cycles. In paper two, we ask whether women's hormonal state is related to their neural response to and hedonic evaluations of food or sexual stimuli. To address past issues of imprecision in hormonal group assignment in women, we test NC women in a hormonally-confirmed periovulatory state, and to better characterize the potential effects of OCs on response, we test OC users both while actively taking OCs and during their pill-free week. Together, these data offer insight into the behavioral and cognitive mechanisms underlying ovarian-cyclic shifts in feeding and sexual behavior.

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Figure 1.

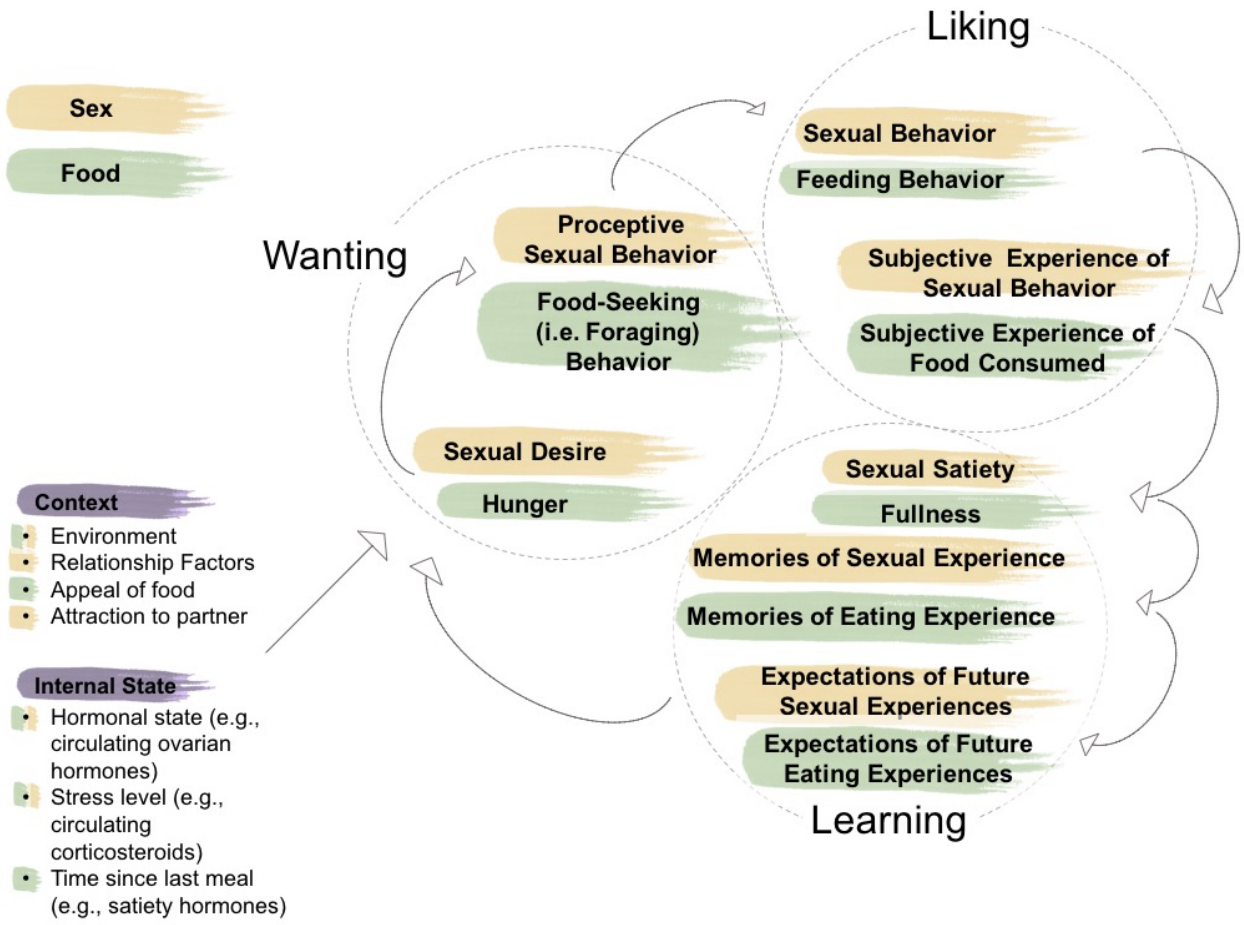

Figure 1. Behavioral and cognitive cycles of feeding and sexual behavior, as divided by Berridge & Robinson's (2003) tripartite model of reward, which includes distinction between "wanting," "liking," and "learning."

Figure 2.

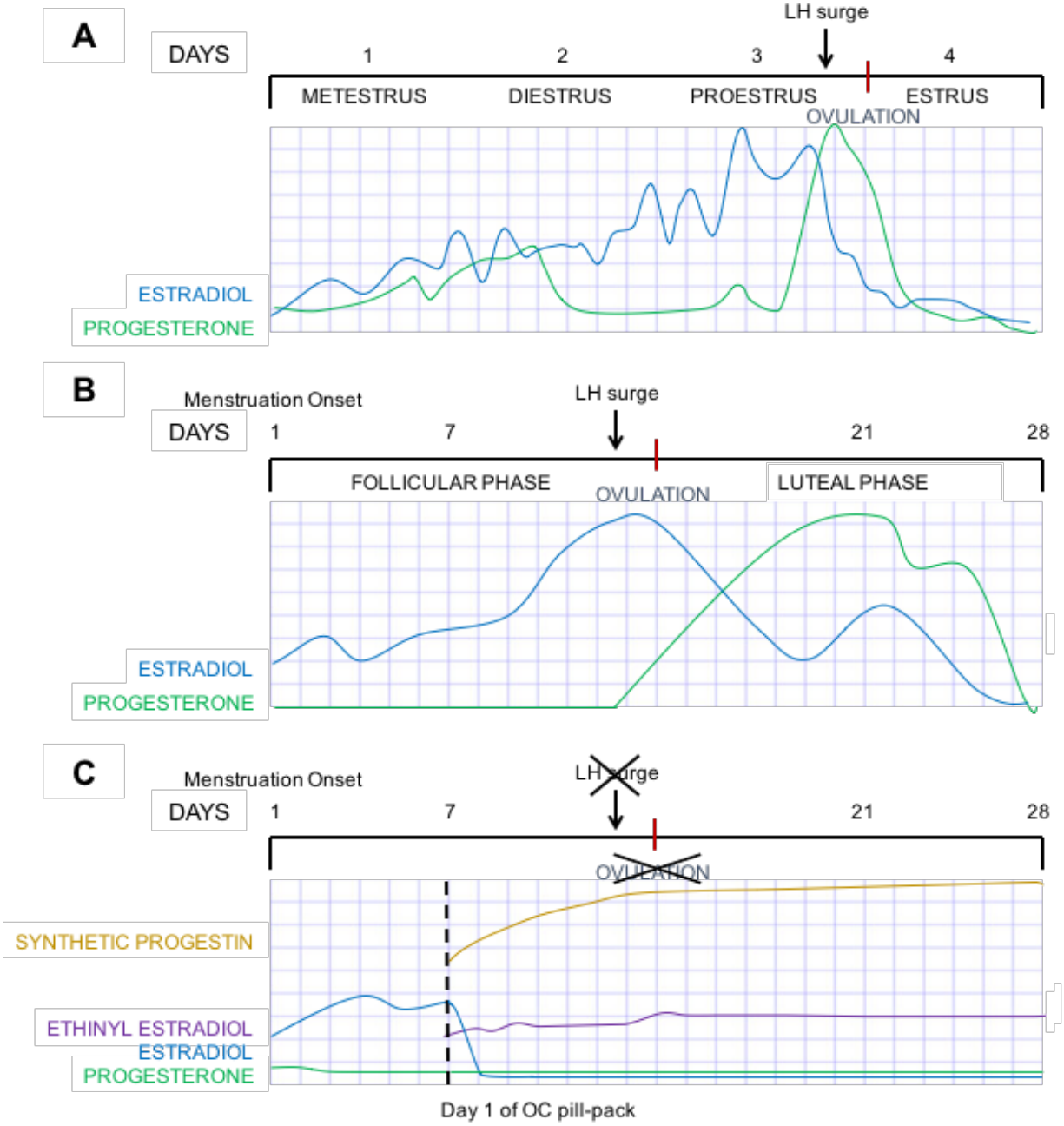

Figure 2. Depiction of ovarian cycles in the: a) rat, b) rhesus monkey and naturally cycling woman, and c) woman taking oral contraceptives (OCs) (Data in figures a and b modeled off of data presented in Fillingim & Ness, 2000).

Manuscript 2

The relationship between women's hormonal state and their motivation to view images of food or sex

Kaytlin J. Renfro & Kim Wallen, Ph.D.

Abstract

Women's food intake and sexual desire change inversely across their ovarian cycles: food intake decreases near ovulation and peaks in the luteal phase, whereas sexual desire peaks near ovulation and decreases in the luteal phase. Such data have been interpreted as indicating that ovarian steroids dynamically shift motivational priorities between food and sex. It is, however, unknown whether the motivational value of food or sexual stimuli changes as a function of a woman's hormonal state. We tested this possibility by investigating whether women's motivation to view images of food or sex varied with their menstrual cycle phase or with oral contraceptive (OC) use. We recruited naturally cycling (NC) women in the periovulatory phase (n = 15), NC women in the luteal phase (n = 15), OC women in the pill-free week of their pill-cycle (OC_0; n = 15) and OC women in the third week of their pill-cycles (OC_3; n = 14). Women attended two test sessions timed one week apart. We assessed motivation with a task in which participants key-pressed to increase or decrease viewing time of computer-displayed images. Each test consisted of 80 images: 20 images of male-female couples engaged in active but non-emotive tasks, 20 of male-female couples engaged in explicit sexual behavior, 20 of high-caloric, palatable food, and 20 of low-caloric, bland food. Women's hormonal state at session 1 predicted their motivation to view sexual but not food stimuli. Specifically, periovulatory women showed greater motivation to view sexual stimuli than did luteal or OC_3 women, but not more than did OC_0 women. Consistent with previous work, we found a woman's hormonal state when she first visited the laboratory predicted her response at both session 1 and session 2. Taken together, our data indicate that a woman's hormonal state modulates the motivational value of sexual stimuli, and that the initial hormonally-modulated value may persist across time, even after her hormonal state changes.

Introduction

In women and a variety of females of other species, behavioral responses to food and sexual stimuli change across the ovarian cycle (Buffenstein, Poppitt, McDevitt, & Prentice, 1995; Asarian & Geary, 2006; Schneider, Wise, Benton, Brozek, & Keen-Rhinehart, 2013; Roney & Simmons, 2013; Roney & Simmons, 2017). Food intake is typically lowest around the time of ovulation and highest in the post-ovulatory luteal phase of the cycle, whereas sexual behavior and desire follow the opposite pattern, peaking near ovulation and reaching a nadir in the luteal phase (Buffenstein et al., 1995; Asarian & Geary, 2006; Schneider et al., 2013; Roney & Simmons, 2013; Roney & Simmons, 2017). Work in nonhuman females has convincingly shown that ovarian-cycle shifts in motivation for food and sex are mediated by the steroids estradiol (E2) and progesterone (P4). In rats and rhesus monkeys, ovariectomy (OVX) leads to increased food intake and decreased sexual behavior (Boling & Blandau, 1939; Cjaza & Goy, 1975; Zehr, Maestripieri, & Wallen, 1998). OVX effects are reversed in both species with administration of E2, which suppresses feeding and increases sexual motivation (Erskine, 1989; Cjaza & Goy, 1975; Zehr, Maestripieri, & Wallen, 1998). In rats, P4 attenuates the anorectic effects of E2, and in monkeys, P4 opposes E2's facilitation of sexual behavior (Wade, 1975; Kendrick & Dixson, 1985). Together, these results have been interpreted as indicating that ovarian steroids modulate motivational priorities, dynamically determining when food or sex are pursued (Shneider et al., 2013; Roney, 2016).

Roney and Simmons (2017) recently provided data suggesting that E2 and P4 modulate food intake and sexual desire in women as they do in nonhuman animals. In a study of naturally cycling (NC) women across their menstrual cycles, the authors identified a midcycle drop in food intake and a corresponding spike in reported sexual desire, both of which were predicted by

the midcycle, pre-ovulatory peak in E2. Reported food intake subsequently increased in the luteal phase of the women's cycles, whereas sexual behavior decreased, and these changes corresponded to the luteal increase in P4. The authors interpreted their data as indicating that hormonal mechanisms of motivation are conserved across species, and that these mechanisms function adaptively. The authors argued that E2 and P4 work together to increase motivation for sex at the expense of motivation for food during the fertile time of a woman's ovarian cycle (i.e., ovulation), thereby prioritizing sexual behavior when conception is possible (Roney & Simmons, 2017).

The proximate mechanisms by which a woman's hormonal state modulates food intake and sexual desire remain largely unaddressed and unclear. The stated assumption is that women's hormonal state modulates the motivational salience of food and sex (Roney & Simmons, 2017; Fessler, 2003). However, whether the motivational value of food and/or sexual cues change(s) across a woman's cycle has not been directly tested. The first aim in this study was to address this gap in the literature by comparing motivation to view images of food or sex between women in distinct hormonal states. We compared responses between NC periovulatory (high E2, low P4) women and NC luteal (high P4, moderate E2) women, with the expectation that NC periovulatory women would show more motivation to view sexually explicit images than would luteal women, but that luteal women would show more motivation to view images of food than would periovulatory women. Because the majority of U.S. women suppress natural ovarian cycles at some point in time with oral contraceptives (OCs) (Mosher & Jones, 2010), we also sought to characterize the relationship between OC women's unique hormonal state and their motivation for food and sex. To this end, we compared OC women in the third week of their pill cycles (OC_3) to OC women in the pill-free week of their pill-cycles (OC_0). Given

that OC_3 women represent women in a high progestogenic state with low estrogens and OC_0 women are in a low progestogenic state with moderate E2 (van Heusden & Fauser, 2002; Warner Chilcott, 2006; Speroff & Darney, 2010), we expected OC_0 women to show greater motivation to view sexual images than would OC_3 women, and OC_3 women to show more motivation to view images of food than would OC_0 women. Similarly, we predicted that periovulatory NC women would show greater motivation for sexual stimuli than would OC_3 women and OC_3 women would show greater motivation for food stimuli than would periovulatory NC women.

The second aim of this study was to determine whether the motivational value of food and sexual stimuli change dynamically as women's hormonal states change. Although work outside of the laboratory indicates that the women's interest in and motivation for hedonic stimuli, such as sexual stimuli, track with women's current hormonal state, the story is not as clear for findings from laboratory research. In within-subject laboratory studies on response to sexual stimuli where women are tested across multiples phases of their menstrual cycles, some find that a woman's hormonal state at the first test session predicts both her initial, first-test responses to the stimuli, as well as her responses at subsequent test sessions (Renfro, Rupp, & Wallen, 2015; Suschinsky, Bossio, & Chivers, 2014; Wallen & Rupp, 2010; Slob et al., 1996; Slob, Ernste, & ten Bosch, 1991). That is, laboratory studies of response to sexual stimuli appear to be subject to a "carry-over effect," wherein a woman's hormonal state when first exposed to the laboratory setting and stimuli has a lasting impact on her responses to similar stimuli later seen in that same setting, even though her hormonal state has changed. This phenomenon has now been identified across multiple laboratories and a variety of physiological, cognitive, and subjective measures, suggesting it is more than a by-product of small sample sizes and type one error (Renfro, Rupp, & Wallen, 2015; Suschinsky, Bossio, & Chivers, 2014; Wallen & Rupp,

2010; Slob et al., 1996; Slob, Ernste, & ten Bosch, 1991). To extend this work and determine whether a carry-over effect of women's hormonal state would apply to a metric of women's motivation to view stimuli, as well as to responses to a nonsexual reward (food), all women were tested again approximately one week after their initial test. In keeping with previous laboratory work, we predicted that women's hormonal state at first test would be a better predictor of her second-test responses than would her hormonal state at time of testing.

Method

Participants

59 women participated in the study (M_{age} = 24.22, SD_{age} = 4.58): 30 naturally cycling (NC) women and 29 women regularly taking an oral contraceptive (OC). Prior to enrollment, individuals completed an online screening questionnaire to determine eligibility for study participation. The screening survey included questions about demographics, sexual orientation, hormonal contraceptive use, menstrual cycle regularity, dietary restrictions, experience with sexual stimuli, as well as measures of attitudes about eating/food (The Three-Factor Eating Questionnaire-R18 [TFEQ-R18]; De Lauzon et al., 2004) and sexual behavior (Brief Sexual Attitudes Scale [BSAS]; Hendrick, Hendrick, & Reich, 2006). All NC participants reported having regular menstrual cycles and having not taken any hormonal contraceptive for at least three months prior to scheduled participation. All OC participants reported taking a monophasic combination OC for at least three months prior to participation. Because many psychotropic medications affect appetite, sexual desire, or both, women currently taking psychotropic medications were not enrolled in the study (Ahmann et al., 2001; Balon, R., 2006; Masand & Gupta, 2002). Given that the sexual stimuli in the image set depicted opposite-sex couples engaged in explicit sexual behavior, participants were only recruited if they identified as equally

to exclusively opposite-sex attracted (as indicated via a score ≥ 3 [corresponding to equally opposite-sex and same-sex attracted] on the Kinsey scale; Kinsey, Pomeroy, Martin, Gebhard, 1953) and reported prior experience with viewing sexual images. To further account for potential confounding factors, participants were also screened for dietary restrictions, and no participants enrolled indicated adhering to a meat-free, gluten-free, or otherwise substantially-restricted diet.

Hormonal Group Assignment

NC women were randomly assigned to attend their first test session in the periovulatory (n = 15) or luteal phase (n = 15) of their menstrual cycles. Expected timing of the periovulatory and luteal phase was derived from the average menstrual cycle length and the start date of their last period as provided by participants. The periovulatory phase was estimated to occur approximately 14 days prior to the estimated start date of the participant's next menstrual cycle. Luteal phase assignment corresponded to approximately seven days prior to the estimated start date of the participant's next menstrual cycle. To confirm proper group assignment, participants in the periovulatory phase took luteinizing hormone (LH) tests each morning for up to seven mornings around estimated ovulation until they received a positive result. Upon receipt of a positive LH test, participants emailed a photograph of the LH test to a secure lab email account. Once the positive result was confirmed, the participant was scheduled for her test session within the following 24 – 36 hours. The LH tests used are reported to be over 99% effective at detecting the LH surge (First Response Ovulation [Church & Dwight Co., Inc., Princeton, NJ]), and LH tests are considered to be a highly accurate (~97%) and accessible means of detecting subsequent (24 – 48 hrs later) ovulation (Su, Yi, Wei, Chang, & Cheng, 2017). Luteal women's group assignment was confirmed via report from the participant that she began her next menstrual cycle ≤ 13 days following her first test session, which all women assigned to the luteal group here

reported. These two tests reflected different hormonal states, with the periovulatory test reflecting elevated E2 and low P4, and the luteal reflecting elevated P4 and moderate E2.

OC women were randomly assigned to attend their first test session in either the pill free week of their pill-packs (n = 15; group subsequently referred to here as "OC_0") or the third week of their pill-packs (n = 14; termed "OC_3"). Session timing was determined from participants' provided start-date of their current pill-packs. OC_0 participants were scheduled at minimum three days into their pill-free week so as to afford sufficient time for the synthetic steroids to be metabolized and absent from circulation (Warner Chilcott, 2006). OC_3 women were scheduled at minimum three days into the third week of their pill-pack to capture peak concentration of synthetic hormones in women's blood (Bayer Healthcare Pharmaceuticals Inc., 2012; Warner Chilcott, 2006).

Study Design

All participants attended two test sessions spaced approximately one week apart. 15 NC women attended their first test session in the luteal phase of their menstrual cycles, and their second session in the menstrual phase of their cycles. 15 NC women attended their first session in the periovulatory phase of their cycles and their second session in the luteal phase of their cycles. 14 OC women attended their first test session in the pill-free week of their pill-pack and their second session in the first week of their pill-pack. 14 OC women attended their first session in the third week of their pill cycle and their second in the pill-free week of their pill-packs.

Procedure

At both test sessions, participant completed a keypressing paradigm (see description below) designed to measure motivation to view images of couples or food. In attempt to standardize hunger levels between hormonal groups, all participants were asked to abstain from

eating for two hours before the test session. Prior to completing the experimental task, participants rated their hunger level on a digital analog scale that ranged from 0 (not at all hungry) to 100 (extremely hungry) and completed a brief questionnaire about their current mood (mood items selected from the Positive and Negative Affect Scale; Watson, Clark, & Tellegan, 1988). Participants also reported their hunger and mood (assessed in the same manner) after participating in the experimental paradigms, and they additionally answered select questions from the Female Sexual Function Index (FSFI; Rosen et al., 2000). Behavioral testing was administered on a desktop computer in a private room, and responses were linked only with a unique subject ID and not with participants' personal identities. Participants were compensated $20 per hour for study participation (yielding a total payment of approximately $60). All procedures were approved by the Emory University Institutional Review Board.

Stimuli

Participants saw four categories of images: low-caloric foods ("LC foods"), high-caloric foods ("HC foods"), opposite-sex couples engaged in non-emotive tasks (termed here "neutral couples"), and opposite-sex couples engaged in explicit sexual activity ("sexual couples"). Images of LC foods depicted bland starch and vegetable foods, such as plain oatmeal and cucumbers. Images of HC foods depicted palatable sweet and savory foods, such as cakes and cheeseburgers. Representative neutral couple images include images of opposite-sex pairs performing an active task wherein they were not touching, such as running or walking. Sexual couple images depicted opposite-sex pairs engaged in penile-vaginal intercourse or oral sex. No food images included people and no couple images included food. All images were sized such that the aspect ratio was maintained and the longest image dimension (length in the case of vertically-oriented images and width in the case of horizontally-oriented images) was sized to

700 pixels.

Participants saw 80 unique images in each test session: 20 from each category, and 160 unique images in total across the two test sessions. Images were acquired from internet sources. To ensure that images were accurately reflective of the image category to which they were assigned, all test images were piloted prior to use by group of seven women who did not participate in the study. In the pilot, women were asked to view the images as long as they would like, and to rate the images on how appetizing they found them (in the case of the food) or how sexually appealing (in the case of the couples). Pilot participants rated the images on a scale from 1 – 9, with 1 indicating the lowest possible rating (corresponding to "extremely unappetizing" in the case of food and "extremely sexually unappealing" in the case of couple images), and 9 indicating the highest possible rating (corresponding to "extremely appetizing" and "extremely sexually appealing"). In total, individuals rated 618 images in the pilot (341 couple images and 244 food). Pilot participants rated the HC images subsequently selected for the image set as much more appetizing than the selected LC foods, and the mean ratings for either category did not differ across the two test sessions (Mean ± SD, Session 1: HC food = 7.19 ± 0.42, LC food = 4.72 ± 0.35; Session 2: HC food = 7.08 ± 0.38, LC food = 4.80 ± 0.45, both *p's* < 0.001 for HC vs. LC and both *p's* > 0.27 for Session 1 vs. Session 2). Pilot participants also looked longer at the selected HC foods than they did at LC foods (Mean ± SD, Session 1: HC food = 2.06 ± 0.56, LC food = 1.46 ± 0.21; Session 2: HC food = 2.06 ± 0.33, LC food = 1.49 ± 0.19, both *p's* < 0.001 for HC vs. LC and both *p's* > 0.60 for Session 1 vs. Session 2). Pilot participants rated the sexual couples included in the image set to be more sexually appealing than they did the neutral couples, and the ratings did not differ across the two sessions (Mean ± SD, Session 1: Sexual couples = 7.21 ± 0.66, Neutral couples = 4.57 ± 0.23; Session 2: Sexual couples = 7.20 ± 0.59,

Neutral couples = 4.57 ± 0.28, both *p's* < 0.001 for Sexual vs. Neutral and both *p's* > 0.96 for Session 1 vs. Session 2). Average pilot viewing time was also longer for the selected sexual couples than for the neutral couples (Mean ± SD, Session 1: Sexual couples = 3.33 ± 0.76, Neutral couples = 1.75 ± 0.41; Session 2: Sexual couples = 3.28 ± 0.89, Neutral couples = 1.76 ± 0.29, both *p's* < 0.001 for Sexual vs. Neutral and both *p's* > 0.86 for Session 1 vs. Session 2)..

Keypress paradigm

To assess motivation to view the images presented, participants were given a task wherein they were able to alter the display time of the images they saw by pressing keys on the desktop keyboard (paradigm adapted from Aharon et al., 2001; Hahn, Xiao, Sprengelmeyer, & Perrett, 2013; Wang, Hahn, Fisher, DeBruine, Jones, 2014; Hahn, DeBruine, Fisher, & Jones, 2015). As a default, each image showed for 1.5 seconds. Participants could extend the image viewing time by repeatedly pressing the "up" arrow on the keyboard. Alternatively, participants could decrease viewing time by repeatedly pressing the "down" arrow on the keyboard. Each "up" keypress added 200ms to the image viewing time and each down keypress subtracted 50ms. Keypress time was modeled after time allotted to keypresses in similar paradigms (e.g., Wang et al., 2014; Hahn et al., 2015). Time was added or subtracted only by independent keypresses—holding down the key continuously did not add or subtract time beyond the equivalent of one keypress. To keep participants informed of how much viewing time remained, a horizontal time-bar appeared below the image and its width changed in proportion to the amount of image time remaining.

Images were presented in a randomized order and in two blocks: a block of food images and a block of couples images. A fixation cross appeared in between each image, and participants were required to press the spacebar to initiate image presentation. Participants were

not provided with an explicit explanation of what the keypresses meant beyond that they were a means to change the amount of time that the image was on the screen. To safeguard against participants repeatedly pressing the down arrow to shorten the length of the experimental session, they were told that button presses affected the display-time of the image on the screen but not the overall time of the study. Although keypresses actually did affect the experimental time, the effect was on the order of seconds.

Practice trials

To give participants experience with a 1.5s presentation time and with keypressing to adjust the viewing time, all women completed a practice session of the behavioral paradigm. The practice session consisted of six images: two images of stars during which participants were instructed to do nothing and let the time elapse, two images of up arrows in which participants were instructed to briefly extend the viewing time by repeatedly pressing the "up" arrow on the keyboard, and two images of down arrows in which participants were instructed to shorten the viewing time by repeatedly pressing the "down" arrow on the keyboard. The instructional practice trials were followed by brief test trials wherein participants saw a 1.5s display of the "up" arrow and a 1.5s display of the "down" arrow, and were instructed to press the respective key as many times as possible for the duration of the image presentation. The test trials were administered to acquire a general measure of how fast participants were able to press the keys and ensure that there were no differences between the hormonal groups in overall keypress speed.

Statistical analyses.

Mixed factor Analysis of Variance (ANOVAs) were used to determine whether women's motivation to view images was related to their hormonal state, and if so, whether this effect

differed with image category. In the case of a main effect or interaction, follow-up ANOVAs and/or simple contrasts were performed.

Effect size estimates were calculated as η_p^2 for ANOVA results, Cohen's *d* for unpaired t-tests, and Cohen's d_z for paired t-tests. Results are expressed as mean ± standard deviation of the mean, unless otherwise noted. A probability value of $p < 0.05$ was considered significant.

Results

Participants

Of the 59 women tested, 55 are included in the present analyses ($M_{age} = 24.22$, $SD_{age} = 4.71$). Three NC periovulatory participants were excluded: one woman because she did not return for the second test session, one because she was taking medication for treatment of a hormonal condition at time of test, and one because she was a statistical outlier on behavioral measures (> 3 SD's above the mean). One OC_0 woman was excluded because it was later discovered that she was taking a triphasic rather than monophasic OC.

Average BMI across women was within normal range (M = 23.67 ± 3.9), and hormonal groups did not differ in BMI ($F(3,50) = 0.39$, $p = 0.76$, $\eta_p^2 = 0.02$). Hormonal groups also did not differ on frequency of pornography usage ($F(3,51) = 2.36$, $p = 0.08$, $\eta_p^2 = 0.12$) or positive ($F(3,50) = 0.50$, $p = 0.68$, $\eta_p^2 = 0.03$) or negative ($F(3,50) = 1.20$, $p = 0.32$, $\eta_p^2 = 0.03$) affect at the beginning of the test session (Table 1).

Keypress paradigm

We first sought to determine whether our paradigm worked as it should, and thus tested whether the motivational value of HC foods and sexual couples was overall greater than that of LC foods and neutral couples, respectively. To test whether participants keypressed to extend the viewing time of the HC food images and sexual couples images more than they did for those of

the LC food and neutral couples images, we performed a series of paired t-tests on the overall viewing time, which takes into account both "up" and "down" keypresses. As shown in Figure 1, participants pressed much more to extend the viewing time of the HC foods than they did for the LC foods in both Session 1 ($t(54) = 6.64$, $p < 0.001$, $d_z = 0.90$) and Session 2 ($t(54) = 6.76$, $p < 0.001$, $d_z = 0.91$). Similarly, participants pressed to increase the viewing time of the sexual couple images more than they did those of the neutral couples in both Session 1 ($t(54) = 3.09$, $p = 0.003$, $d_z = 0.42$) and Session 2 ($t(54) = 3.09$, $p = 0.003$, $d_z = 0.42$) (Figure 2).

To control for individuals' overall propensity to keypress, we calculated change scores for both the food (HC – LC) and couples (sexual – neutral) images, which are used as the dependent measures in all following analyses.

Test of hormonal state effects on viewing time in Session 1

To determine whether a woman's hormonal state predicted how much effort she would expend to view images, and whether this effect differed with image content, we conducted a 4 (hormonal state [periovulatory vs. luteal vs. OC_0 vs. OC_3]) x 2 (image category [food change score vs. couple change score]) mixed factor ANOVA. The ANOVA revealed a main effect of hormonal state ($F(1,51) = 4.04$, $p = 0.01$, $\eta_p^2 = 0.19$), no main effect of image category ($F(1,51) = 2.02$, $p = 0.16$, $\eta_p^2 = 0.04$), and an interaction between hormonal state and image category ($F(1,51) = 4.02$, $p = 0.01$, $\eta_p^2 = 0.19$). Follow-up analyses showed the interaction was such that there was no effect of hormonal state on women's viewing time for food (HC – LC) images ($F(3,51) = 1.11$, $p = 0.36$, $\eta_p^2 = 0.06$; Figure 3), but there was an effect of hormonal state on viewing time for couples (sexual – neutral) images ($F(3,51) = 5.82$, $p = 0.002$, $\eta_p^2 = 0.26$). Specifically, NC periovulatory women pressed to extend the viewing time for sexual couples images more than did NC luteal women ($p < 0.001$, $d = 1.58$) and OC_3 women ($p = 0.008$, $d =$

1.12), but not more than OC_0 women ($p = 0.14$, $d = 0.43$). OC_0 women did not differ in their viewing time of sexual images from OC_3 women ($p = 0.19$, $d = 0.47$) (Figure 4).

Test of carry-over effect of initial hormonal state on future viewing time

To test our prediction that a woman's hormonal state at the first test session (her "initial hormonal state") would predict not only her key-pressing behavior in the first session, but also her responses in the second session, we used a 4 (initial hormonal state [periovulatory vs. luteal vs. OC_0 vs. OC_3]) x 2 (session 1 vs. session 2) mixed factor ANOVA on women's couples (sexual – neutral) viewing time. The test yielded a main effect of initial hormonal state ($F(3,51) = 5.58$, $p = 0.002$, $\eta_p^2 = 0.28$), no main effect of session ($F(1,51) = 1.50$, $p = 0.23$, $\eta_p^2 = 0.029$), and no initial hormonal state by session interaction $F(1,51) = 1.19$, $p = 0.32$, $\eta_p^2 = 0.07$).

Because there were two outliers in the dataset (behavioral responses > 3 SD's from mean), we removed these participants' data and reanalyzed the dataset to determine whether the outliers were driving the results. The effects were largely unchanged. Without the outliers, initial hormonal state remained a significant predictor ($F(3,49) = 4.67$, $p = 0.006$, $\eta_p^2 = 0.22$), and there was still no main effect of session ($F(1,49) = 2.73$, $p = 0.11$, $\eta_p^2 = 0.05$). However, with outliers excluded, the effect size for the interaction between initial hormonal state and session more than doubled ($\eta_p^2 = 0.15$), though the effect was still not significant by conventional statistical standards ($F(3,49) = 2.76$, $p = 0.052$). Because of the moderate effect size, we performed follow-up post-hoc analyses on the interaction, which revealed that although initial hormonal state was a significant predictor of viewing time at session 2 ($F(3,49) = 3.30$, $p = 0.028$, $\eta_p^2 = 0.17$) as it was at session 1 ($F(3,49) = 5.62$, $p = 0.002$, $\eta_p^2 = 0.26$), the effect was relatively weaker. Women who were in the periovulatory phase at their first test session key pressed more for the images in their second session than did women who were in the luteal phase at their first session ($p = 0.006$, $d =$

1.33); however, this effect was again slightly weaker than it was at session 1, and there was no longer a statistically significant difference between their viewing time and that of OC_3 women ($p = 0.06$) even though the effect size remained large ($d = 1.09$). To further characterize the interaction, we performed a series of paired t-tests, which showed that women who were in the luteal or OC_3 phase during their first test session had longer viewing times at their second test session than they did at their their first sessions ($t(13) = 2.40$, $p = 0.03$, $d_z = 0.67$ and $t(13) = 3.28$, $p = 0.006$, $d_z = 0.88$, respectively), but women who were in the periovulatory phase or OC_0 phase at first test did not change in their viewing times from the first to second sessions ($p's > 0.37$) (Figure 5).

Given that there was no relationship between women's hormonal state and their viewing time of food images at the first session, we did not run further analyses to test for a carry-over effect of women's hormonal state on viewing time of food images in the second test session.

Discussion

We provide here evidence that a woman's hormonal state predicts the motivational value of sexual stimuli but not of food stimuli. In line with our predictions, we found in session one that NC women in the periovulatory phase of their menstrual cycles were more motivated (as measured via keypresses) to view sexual stimuli than were NC women in the luteal phase or women actively taking OCs. OC women in their pill-free week at session one did not differ from periovulatory women and, contrary to expectations, also did not differ significantly in motivation to view sexual stimuli from OC women in the third week of their pill-cycles.

The second aim of this study was to determine whether the motivational value of food and/or sexual stimuli as assessed in the laboratory change(s) in concert with women's hormonal state. Given the surprising but growing literature that shows that women's hormonal state at their

first laboratory test session is a better predictor of their responses at subsequent sessions than is their hormonal state at time of testing (Renfro, Rupp, & Wallen, 2015; Suschinsky, Bossio, & Chivers, 2014; Wallen & Rupp, 2010; Slob et al., 1996; Slob, Ernste, & ten Bosch, 1991), we predicted that women's hormonal state at session one (their "initial hormonal state") would also predict their responses at the second test. We found partial support for this hypothesis. That is, women who were in the periovulatory phase at their first test session continued to show more motivation for sexual stimuli at their second test session than did luteal women and OC_3 women (though the comparison with OC_3 women was no longer statistically significant, the effect remained large $d = 1.09$). Although women's initial hormonal state was a significant predictor of motivation to view sexual stimuli at both sessions, our prediction was only partially supported in that the effect of women's initial hormonal state on key-pressing behavior was relatively stronger for session one behavior than it was for session two. Our data show that the change in effect size from session one to two was due to a change in motivation across sessions in women first tested in their luteal phase or third week of their pill cycle. We found that both luteal and OC_3 women showed more motivation to view sexual stimuli at the second session than they did at the first (though both remained relatively less motivated than women who entered the study in their periovulatory phase).

Taken together, our data indicate that a woman's hormonal state modulates the motivational value of sexual stimuli, and that in a laboratory context, the initial hormonally-modulated value may persist across time and generalize to novel but similar sexual stimuli. The specific hormonal group differences identified in session one offer insight into the relative roles of E2 and P4 in modulation of motivational value of sexual stimuli. The two groups with the lowest motivation (as indicated via keypresses) to view sexual stimuli were the OC_3 women

and the luteal women. Strikingly, luteal women on average pressed more for the images of neutral couples than for the sexual couples. OC_3 and luteal women were both experiencing high levels of progestins at time of testing – luteal women via endogenous P4 and OC_3 women from high doses of synthetic progestins (Speroff & Darney, 2010; Stricker et al., 2006; Warner Chilcott, 2006). P4 has been identified as the ovarian steroid that accounts for the most variance in women's daily sexual desire (Roney & Simmons, 2013). Because P4 is specifically a negative predictor of sexual desire (Roney & Simmons, 2013), it is reasonable to infer that OC_3 and luteal women's relative lack of motivation to view sexual stimuli is due to progestin inhibition. Support for this possibility is further provided by OC_0 and periovulatory women's behavior. Periovulatory women and OC_0 women were both experiencing low levels of progestins at time of test, and both showed substantial motivation for viewing sexual stimuli. Although periovulatory women and OC_0 women were aligned in progestogenic states, they were likely experiencing quite different levels of E2 (van Heusden & Fauser, 2002; Stricker et al., 2006). Periovulatory women levels of E2 were assumedly much higher than those of OC_0 women at time of test, which we anticipated would yield more motivation for sexual stimuli, given that E2 has been shown across species to promote sexual desire and behavior (as discussed in Wallen, 2013). Although periovulatory women key pressed moderately more than did OC_0 women to view sexual stimuli (as indicated by a moderate effect size), this difference was not statistically significant. That periovulatory women did not differ in motivation from OC_0 women but did from luteal and OC_3 women suggests that in progestin inhibition had a bigger effect on motivation than did E2 promotion. These data are consistent with previous work showing that P4 accounts for more variance in women's reported sexual desire than does E2 (Roney & Simmons, 2013).

Although our findings regarding the "carry-over" effect of women's initial hormonal state on subsequent responses were expected given previous work, an open question is why the motivational value of the sexual stimuli did not update with women's hormonal state across test sessions. Data from work in nonhuman animals on cognitive incentive learning provide a possible explanation for the carry-over effect identified here. Cognitive incentive learning is a type of reward learning wherein one learns the incentive value of a stimulus and uses this knowledge to form expectations about the stimulus' future value, which then guides future motivation to access that stimulus. Much of what is known about cognitive incentive learning is derived from work by Dickinson and Balleine (1994, 1995) who performed a series of experiments that tested rats' operant responses for receiving a food pellet under different conditions of satiety. The authors found that rats trained to press the lever for the food pellet while hungry would, as one would expect, press more than would rats who were trained while sated. Oddly, when the rats that were trained while hungry were later tested on extinction trials in the same cage while sated, they continued to press the lever just as much as they had when hungry, and the same applied for those that had been trained while sated but tested while hungry. The rats thus seemed to "carry over" the initial incentive value of the food into future sessions even though their physiological state – and thus the food's value – had changed. Importantly, if the second test was done in a different environment the "carry over" effect disappeared (Dickinson & Balleine, 1994,1995), suggesting that consistency in the testing environment is crucial to maintaining the learned incentive value. Similar learning mechanisms possibly underlie the carry-over effect of women's hormonal state identified here and in others' research (e.g., Suschinsky, Bossio, & Chivers, 2014; Slob et al., 1991). Future work that changes the

environment between testing sessions could shed light on whether the carry over effect parallels Dickinson and Balleine's work on cognitive incentive learning.

Further question about the nature of the carry-over effect is raised by the finding that it did not hold equally across hormonal groups. That is, although periovulatory and OC_0 women's motivation for sexual stimuli did not update to match their hormonal state at session two, luteal and OC_3 women's did. As noted, women who were first tested in the OC_3 or luteal phase of their cycles were hormonally similar at session one in that they were both experiencing high progestins and low estrogens. It is possible that our findings reflect that release from progestin inhibition of sexual motivation is potent enough to outweigh the carry-over effect, yielding more motivation for sexual stimuli. OC_3 and luteal women were also behaviorally similar at their first test in that they showed the least motivation for the sexual stimuli of the groups tested – indeed, luteal women showed less motivation for sexual stimuli than for neutral. An alternative possibility is thus that negative motivational value does not carry over across sessions whereas positive value does.

Unlike the motivational value of sexual stimuli, the value of food stimuli did not vary predictably with women's hormonal state at either test session. When considering this null result, there are a number of potential methodological, contextual, and hormonal factors to take into account. Methodologically, it is possible that images of high-caloric food and images of sexually explicit scenes differ in that images of food are clearly a cue of a food reward whereas sexually explicit images are more than a cue, and rather constitute a sexual reward in and of themselves (Gola, Wordecha, Marchewka, & Sescousse, 2016). If this were the case, it is conceivable that the lack of hormonal effect on motivation to view food images reflects that hormones do not modulate responses to reward cues as they do to rewards. The data, however, do not bear out this

possibility. That participants expended effort to keep the HC foods on the screen indicates that they did find them to some extent rewarding, and indeed, participants overall key pressed more for the HC foods than they did for sexually explicit images. Rather than the stimuli, it is possible that contextual factors masked potential hormonal effects. This possibility is raised by work in rodents that shows that hormonal effects on appetitive feeding behavior are masked unless the animal is moderately food restricted (as reviewed in Schneider et al., 2013). Although all of our participants were asked to not eat for 2hrs prior to the session, this is likely not enough time to develop the sort of hunger that approximates moderate food restriction. It is thus possible that hormonal effects would emerge under different levels of participant satiation. A final point is that, given that the majority of work on hormonal modulation of food responses in women has focused on food intake, rather than motivation for or seeking of food, it is possible that women's hormonal state is not related to their motivation for food as it is to their consumption of food. This possibility is supported by Roth and colleagues' (2005) work in nonhuman primates that showed no ovarian cycle changes in behavior in an operant paradigm designed to tap more specifically into food motivation, despite there being ample evidence that nonhuman female primates' food intake changes across their ovarian cycles.

Limitations

Perhaps the main concern in regard to interpretation of study findings is the relatively small sample size of each hormonal group. Although a number of our effect sizes were robust, there is a concern with small sample sizes that effect sizes are inflated. To this point, we observed a rather substantial change in the effect size of the carry-over effect after eliminating two outliers from the dataset. We attempted to minimize error and enhance generalizability of the study findings by recruiting a racially diverse sample who were all screened for variables that

held potential for influencing response, such as diet, sexuality, medication usage, and experience with pornography. However, larger sample sizes would give more confidence to the reliability of the findings – particularly in the case of the carry-over effect, for which it is important to rule out the influence of chance, non-hormonal factors driving the effect.

Another limitation of the current study is that we can only infer the relationships between estrogens and progestins and women's motivation from group hormonal effects – we do not have serum or salivary levels of steroids. Measurement of circulating levels of E2 and P4 would allow the possibility to correlate steroids with the keypress behavior, which would meaningfully inform our understanding of the group effects identified. Steroid measurements would also provide additional assurance that women had been assigned to the proper hormonal group. Despite not having measures of circulating levels of steroids, we did confirm hormonal groups assignment here via indices such as LH tests and date of onset of menstruation, which is a notable improvement over a great deal of past work that uses error-prone methods such as estimation of ovulation via counting forward from the first day of menstruation.

Conclusions

The data here inform our understanding of long-identified changes in food intake and sexual behavior that occur across women's menstrual cycles. Our findings suggest that changes in sexual desire that occur across the menstrual cycle and with OC use are accompanied by corresponding changes in the motivational value of sexual stimuli. Unlike sexual stimuli, the motivational value of food stimuli do not appear to change as a function of women's hormonal state. Rather than cyclic changes in food motivation, it is possible—as has been suggested by some (Butera, 2010; Eckel, 2011)—that documented changes in food intake that occur across women's cycle are the result of changes in satiety. It would be informative in future work to

determine whether the changes in motivational value identified here directly correspond to changes in real-world behavior (e.g., are women who key press to keep the sexual images on the screen also more likely to seek out sexual images outside of the laboratory).

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Table 1.

Measure	Hormonal Group	Mean	SD
BMI	Periovulatory	23.93	3.89
	Luteal	24.33	4.30
	OC_0	22.74	2.73
	OC_3	23.59	4.58
Pornography Usage	Periovulatory	3.92	2.11
	Luteal	4	1.56
	OC_0	4.14	1.75
	OC_3	2.71	0.83
Positive Affect	Periovulatory	2.61	0.85
	Luteal	2.66	0.66
	OC_0	2.92	0.84
	OC_3	2.80	0.52
Negative Affect	Periovulatory	1.42	0.50
	Luteal	1.35	0.40
	OC_0	1.31	0.22
	OC_3	1.17	0.21

Table 1. Means and standard deviations (SDs) for BMI, pornography usage, and positive and negative affect across hormonal groups. Hormonal groups did not significantly differ on any of the measures.

Figure 1.

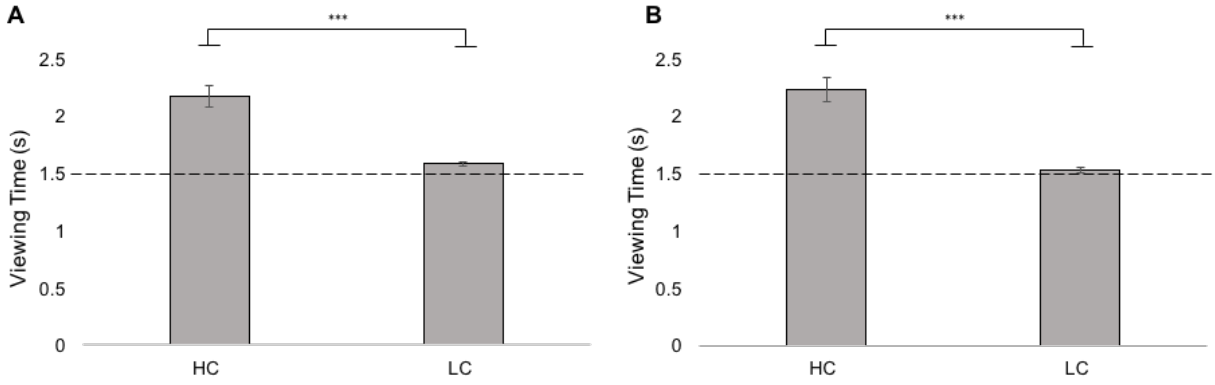

Figure 1. A) Women pressed to extend the viewing time of the HC foods more than they did for the images of LC foods (***$p < 0.001$) in Session 1. 1.5s was the default viewing time. B) Women also pressed to extend the viewing time of the HC foods more than they did for the images of LC foods (***$p < 0.001$) in Session 2.

Figure 2.

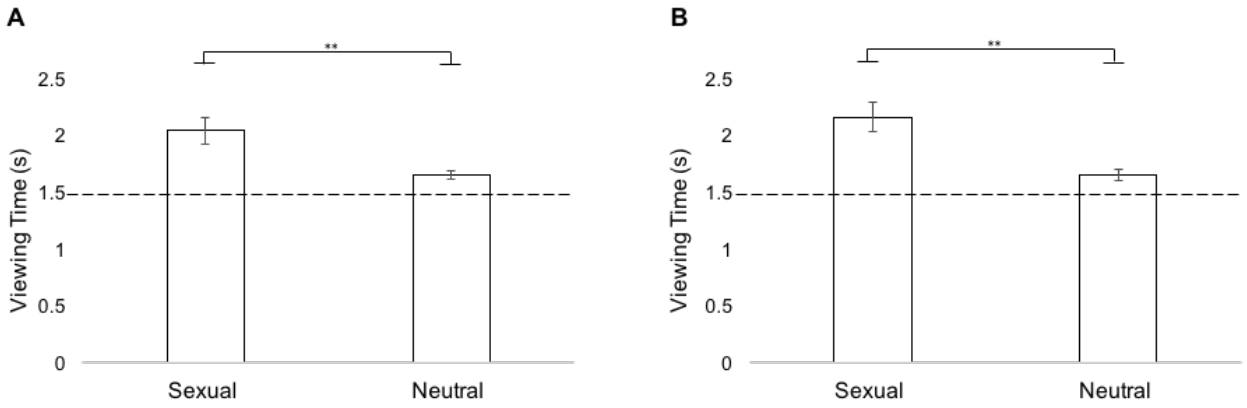

Figure 2. A) Women pressed to extend the viewing time of the sexual couples images more than they did for the images of neutral couples (**$p < 0.01$) in Session 1. 1.5s was the default viewing time. B) Women also pressed to extend the viewtime of the sexual couples images more than they did for the images of neutral (**$p < 0.01$) in Session 2.

Figure 3.

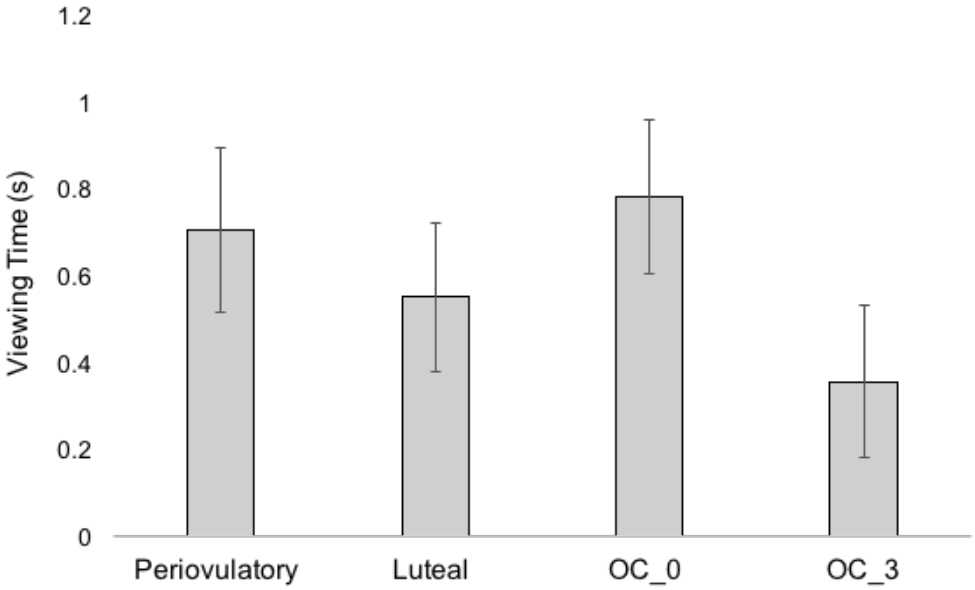

Figure 3. There was no effect of hormonal state on mean viewing time for high-caloric (- low-caloric) food images.

Figure 4.

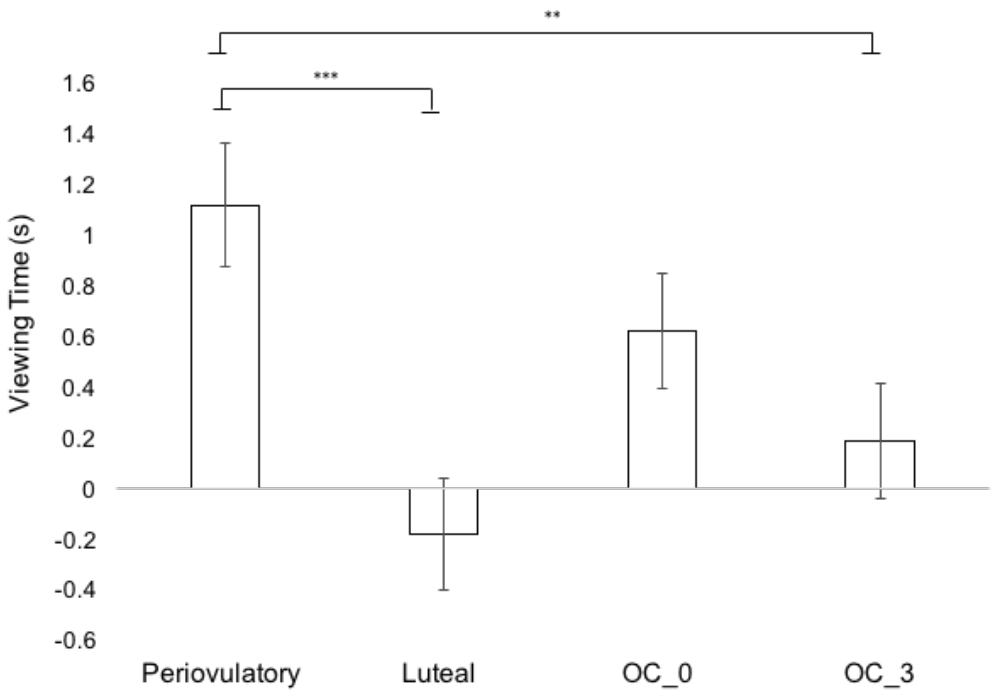

Figure 4. Mean viewing time for couples images (sexual – neutral) by hormonal state during session 1. Periovulatory women keypresses to increase the viewing time for the sexual couple images (-neutral) more than did luteal women (*** $p < 0.001$) and more than did OC_3 women (** $p < 0.01$).

Figure 5.

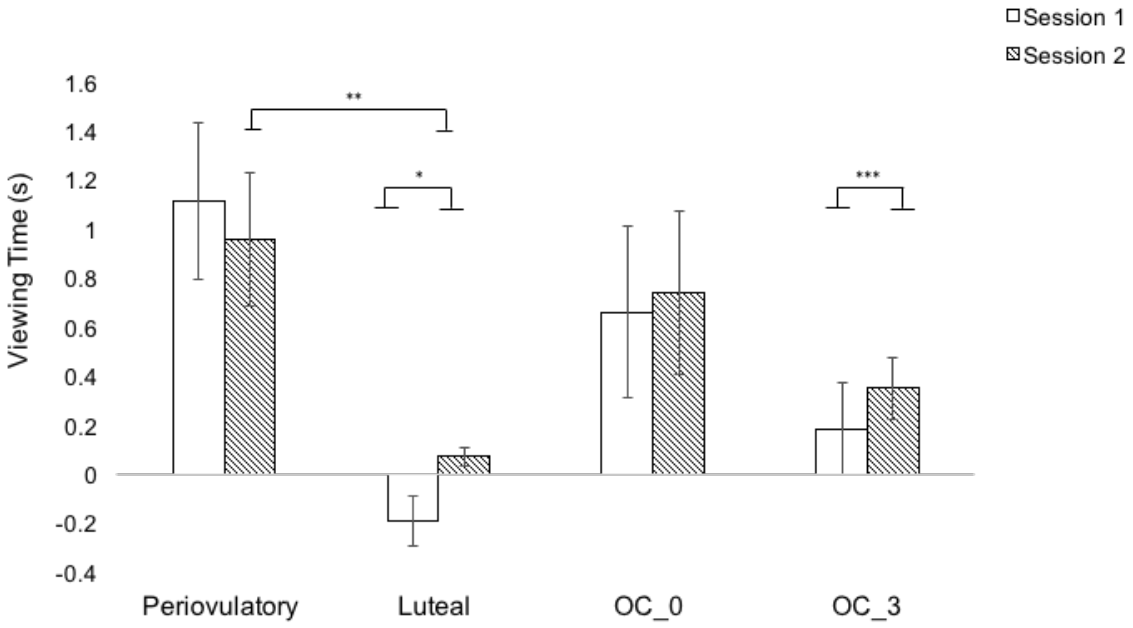

Figure 5. Mean viewing time for couples images (sexual – neutral) by hormonal state at first session ("initial hormonal state") and session number. Women who started the study in the periovulatory phase keypressed to extend the viewing time in the second session more than did women who started in the luteal phase (** $p < 0.01$). Women who started in the luteal (* $p < 0.05$) or OC_3 phase (*** $p < 0.001$) of their cycles keypressed to extend the viewing time for sexual stimuli more in the second session than they did in the first.

Manuscript 3

Women's subjective and neural responses to food or sex: Relationship to menstrual cycle phase and oral contraceptive use

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Abstract

Behavioral data indicate that women's hormonal states modulate the value of two natural rewards: food and sex. The mechanisms by which hormonal modulation of value occurs remain largely unclear. Here, we addressed this gap in the literature by testing the relationship between women's hormonal state and their hedonic evaluations of and neural responses to food and sexual stimuli. We recruited four groups of women: naturally cycling (NC) women in the periovulatory phase of their menstrual cycle (n = 15), NC women in the luteal phase of their cycle (n = 13), women taking oral contraceptives (OCs) who were in the pill-free week of their pill-cycle (OC_0) (n = 15), and OC women in the third week of their pill-cycle (OC_3) (n = 14). We used functional magnetic resonance imaging (fMRI) to measure participants' neural response to images of high-caloric (HC) foods, low-caloric (LC) foods, couples engaged in sexually explicit behavior, and couples engaged in active by non-emotive tasks. Following the neuroimaging, participants rated the images they saw in the MRI on appeal. Women's hormonal state was related to their neural and subjective response to sexual stimuli but not to food stimuli. Specifically, we found that OC_0 women showed greater activation in a region of the orbitofrontal cortex (OFC) in response to sexual stimuli than did luteal or OC_3 women, but not greater activation than did periovulatory women. We identified a similar pattern in women's subjective ratings, such that OC_0 women rated sexual stimuli to be more appealing than did luteal and OC_3 women, but not more than did periovulatory women. These data provide converging behavioral and neural evidence that hedonic evaluation of sex are sensitive to women's hormonal state, but evaluations of food are not.

Introduction

Women's interest in food and sex changes across their menstrual cycles. Women's food cravings and consumption decrease around the time of ovulation and increase in the post-ovulatory luteal phase of their cycles (Cohen, Sherwin, & Fleming, 1987; as reviewed in Buffenstein, Poppitt, McDevitt, & Prentice, 1995). Conversely, women's sexual desire and behavior peak at ovulation and decline in the luteal phase (Roney & Simmons, 2013; Adams, Gold, & Burt, 1978; Stainslaw & Rice, 1998). Similar menstrual cycle shifts are seen in women's subjective evaluations of food and sexual stimuli. For example, women rate images of high-caloric foods to be less appealing in the periovulatory phase than they do in the luteal phase, whereas they rate sexual stimuli, such as images of potential sexual partners, to be more attractive in the periovulatory phase than they do in the luteal phase (Frank, Kim, Krzemien, & Van Vugt, 2010; Junger, Kordsmeyer, Gerlach, & Penke, 2018).

Data from nonhuman animals indicate that menstrual cycle shifts in interest in food and sex are likely due to menstrual-associated changes in levels of the ovarian steroids estradiol (E2) and progesterone (P4). The periovulatory phase in women is characterized by high levels of E2 and low levels of progesterone P4, and the luteal phase is marked by a post-ovulatory decline in E2 and a substantial rise in P4 (Stricker et al., 2006). In nonhuman females, E2 treatment suppresses appetite and promotes sexual desire, whereas P4 opposes E2's effects (as reviewed in Schneider, Wise, Benton, Brozek, & Keen-Rhinehart, 2013). The only study to date to address hormonal predictors of food intake and sexual desire across naturally cycling (NC) women's full menstrual cycles suggests that nonhuman animal findings extend to women. That is, Roney and Simmons (2017) showed that salivary E2 negatively predicted women's reported food intake and

positively predicted sexual desire, whereas P4 showed the opposite pattern (i.e., was positively related to food intake and a strong negative predictor of sexual desire).

Unlike NC women, women taking oral contraceptives (OCs) do not experience monthly fluctuations in E2 and P4. Rather, OC women have low endogenous E2 and P4, low and stable serum levels of a synthetic estrogen, and high and stable levels of a synthetic progestin (Speroff & Darney, 2010; Warner Chilcott 2006). As would be expected due to their lack of ovarian steroid fluctuations, OC women do not experience cyclic changes in food intake and sexual desire as do NC women (Eck et al., 1997; Adams, Gold, & Burt, 1978). A not insubstantial subset of OC users do, however, report food- and sex-related side effects of OC use. Indeed, two of most commonly-cited reasons for OC discontinuation are weight gain and decreased sexual desire (Rosenberg & Waugh, 1998; Sanders, Graham, Bass, & Bancroft, 2001). Some speculate that these side effects are the result of OC women's unique hormonal profile of chronically low estrogens and high progestins (Battaglia et al., 2012; Sanders et al., 2001). In partial support of this notion are data that show that OC women's responses to sexual stimuli differ by whether they are actively taking OCs. Specifically, women who are in between OC pill packs (i.e., the time during menstruation when their E2 rises and progestins drop) look longer at and rate more positively sexual stimuli than do OC women who are in the third week of their pill-packs and are thus experiencing low E2 and high levels of progestins (Wallen & Rupp, 2010; Renfro, Rupp & Wallen, 2015).

Together, these data indicate that women's hormonal states modulate the value of food and sexual stimuli – how appealing, captivating, and motivating they are. The mechanisms by which this hormonal modulation of value occurs remain largely unclear. We in particular know little about the neural correlates of hormonal phase shifts in women's evaluations. However,

broader neuroimaging work on reward evaluation and subjective pleasure identifies two neural regions that are prime candidates for potential hormonal effects: the ventral striatum (VS) and the orbitofrontal cortex (OFC) (including the oft-cited and partially overlapping region of the ventromedial prefrontal cortex (vmPFC)) (as reviewed in Peters & Buchel, 2010; as reviewed in Kühn & Gallinat, 2012; Sescousse, Caldu, Segura, & Dreher, 2013; Sescousse, Li, & Dreher, 2014). A large body of work shows that activity in the VS and OFC is related to the subjective and hedonic value of food, sexual stimuli, and a range of other rewards (Kringelbach, O'Doherty, Rolls, & Andrews, 2003; Georgiadis & Kringelbach, 2012; Bartra, McGuire, & Kable, 2013; Montague & Berns, 2002; Blood and Zatorre, 2001).

Research in human and nonhuman animals shows that activity in the VS and OFC track with changes in reward values that result from changes in one's physiological state, such as the devaluation of a food stimulus that occurs with selective satiation to that food item (Gottfried, O'Doherty, & Dolan, 2003; Loriaux, Roitman, & Roitman, 2011; as discussed in Berridge & Kringelbach, 2015). It thus stands to reason that the physiological effects of hormones on the relative value of food and sexual stimuli may also be reflected in VS and/or OFC activity. In support of this possibility is work that shows that activity in both the VS and OFC is sensitive to ovarian hormonal modulation (Scheele, Plota, Stofa-Wagner, Maier, & Hurlemann, 2015; Bazzett & Becker, 1994; Xiao & Becker, 1997; Dreher, et al., 2007; Rupp, et al., 2009). For example, Dreher and colleagues (2007) showed that women's VS and OFC responses to a monetary reward task changed across their menstrual cycles, such that women showed greater activity in these regions in the follicular (i.e., low P4) phase of their cycles than in the luteal (i.e., high P4) phase.

A potential relationship between women's hormonal state and VS and/or OFC activity is further indicated by the few studies to date that have tested the relationship between women's menstrual cycle phase and neural response to food or sexual stimuli; however, results of these studies are quite mixed (Abler et al., 2013; Rupp et al., 2009; Frank et al., 2010; Gizewski, Krause, Karama, Baars, Senf, & Forsting, 2006; Zhu et al., 2010). The lack of coherence among findings is not surprising given the substantial methodological inconsistencies between studies. The hormonal groups compared in the studies vary quite a bit, and surprisingly, in no study were the most potentially meaningful hormonal group effects tested in either NC or OC women. Specifically, periovulatory women have never been compared to luteal women, and OC women on the pill have never been compared to OC women in their pill-free week. Interpretation of the hormonal effects, or lack thereof, on neural response is also difficult because few of the studies (and none of those in which response to food was tested) included measures of subjective response to the stimuli. Without subjective measures, one cannot confirm the effectiveness of the stimuli, test for hormonal effects on behavior, or understand the neural response within the context of the behavior.

Here, we work to address these gaps in the literature and better our understanding of hormonal modulation of the value of food and sexual stimuli. We specifically tested neural and subjective response to food and sexual stimuli in NC women in the periovulatory phase, NC women in the luteal phase, OC women in the pill-free week of their pill-cycles (termed "OC_0" throughout), and OC women in the third week of their pill cycles ("OC_3"). We predicted that NC women in the periovulatory phase of their cycles would rate sexual stimuli more positively than would any other group of women, and that OC women in the pill-free week of their pill cycles would rate sexual stimuli to be more appealing than would women actively taking OCs.

We expected the opposite relationship between hormones and response to food stimuli, such that we anticipated that NC women in the luteal phase would rate the foods to be more appealing than would periovulatory women or OC_0 women, and we predicted that OC_3 women would find food stimuli more appealing than would periovulatory women or OC_0 women. Finally, we anticipated that hormonal effects on subjective response would be similarly reflected in OFC and VS activity (i.e., periovulatory women would show greater neural response in these regions to sexual stimuli than would other groups, whereas luteal women would show greater response in these regions to food stimuli than would periovulatory women, and so on).

Method

Participants

57 women participated in this study (M_{age} = 24.35, SD_{age} = 4.60): 28 naturally cycling (NC) women and 29 women regularly taking an oral contraceptive (OC). Participants were recruited from Emory University and the surrounding Atlanta, GA area via paper and electronic advertisements. Prior to enrollment, participants completed an online screening questionnaire to determine eligibility for study inclusion. Participants were screened for hormonal contraceptive use, menstrual cycle regularity, psychotropic medication use, sexual orientation, dietary restrictions, magnetic resonance imaging (MRI) contraindications, and experience with explicit sexual images. All NC participants reported having regular menstrual cycles and having not taken any hormonal contraceptive for at least three months prior to scheduled participation. All OC participants reported taking a monophasic combination OC for at least three months prior to participation. Because many psychotropic medications affect appetite, sexual desire, or both, women currently taking psychotropic medications were not enrolled in the study (Ahmann et al., 2001; Balon, R., 2006; Masand & Gupta, 2002). Given that the sexual stimuli in the image set

depicted opposite-sex couples engaged in explicit sexual behavior, participants were recruited only if they identified as equally to exclusively opposite-sex attracted (as indicated via a score ≥ 3 [corresponding to equally opposite-sex and same-sex attracted] on the Kinsey scale; Kinsey, Pomeroy, Martin, Gebhard, 1953) and reported prior experience with viewing sexual images. Because previous work shows a relationship between diet and neural response to food images, participants were screened for dietary restrictions, and no participants enrolled indicated adhering to a meat-free, gluten-free, or otherwise substantially-restricted diet (Goldstone et al., 2009; Griffioen-Roose et al., 2014).

Stimuli

Participants saw four categories of images: low-caloric foods ("LC foods"), high-caloric foods ("HC foods"), opposite-sex couples engaged in active but non-emotive tasks (termed here "neutral couples"), and opposite-sex couples engaged in explicit sexual activity ("sexual couples"). Images of LC foods depicted bland starches, vegetables, and legumes, such as plain oatmeal and cucumbers. Images of HC foods depicted palatable sweet and savory foods, such as cakes and cheeseburgers. Representative neutral couple images include images of opposite-sex pairs performing an active task, such as running or walking. wherein they were not touching. Sexual couple images depicted opposite-sex pairs engaged in penile-vaginal intercourse or oral sex. No food images included people and no couple images included food. All images were sized such that the aspect ratio was maintained and the longest image dimension (length in the case of vertically-oriented images and width in the case of horizontally-oriented images) was sized to 700 pixels.

Participants saw a total of 384 images: 256 unique images, and 128 repeats. A subset of the stimuli used were piloted by an independent group of women who did not participate in the

study, and the remaining images were closely content-matched to those that were piloted. Pilot participants rated the images on how appetizing they found them (in the case of the food) and how sexually appealing (in the case of the couples) on a scale from 1 – 9, with 1 indicating the lowest possible rating (corresponding to "extremely unappetizing" or "extremely sexually unappealing"), 5 indicating a "neutral" score, and 9 indicating the highest possible rating (corresponding to "extremely appetizing" or "extremely sexually appealing"). The HC images subsequently selected for the image set were rated as more appetizing than were the selected LC foods (Mean ± SD, HC food = 6.79 ± 0.44, LC food = 4.94 ± 0.60, $p < 0.001$). The sexual couple images selected were rated as more sexually appealing than were the neutral couple images selected for use (Mean ± SD, Sexual couples = 7.09 ± 0.31, Neutral couples = 4.56 ± 0.54, $p < 0.001$)

Study design

Of the NC women, half (n = 13) were assigned to attend the session in the periovulatory phase of their menstrual cycles, and the other half (n = 13) were assigned to attend in the luteal phase of their cycles. To confirm hormonal group assignment, periovulatory participants were asked to take luteinizing hormone (LH) tests for up to seven days around their estimated time of ovulation. Approximate date of ovulation was considered to be 14 days prior to the estimated first day of the participant's next menstrual cycle (cycle start-date estimation was derived from provided start-date of previous cycle and average cycle length). Once a participant received a positive LH test, she emailed a photograph of the result to a secure lab email account. Upon confirmation of the positive result, the participant's test session was scheduled within the following 24 – 36 hours. Luteal women's test sessions were scheduled approximately 4 – 7 days before the estimated first day of their next menstrual cycle. Luteal phase assignment was

subsequently confirmed with participant report that she began her next cycle ≤ 13 days following her test session.

Half of the OC women (n = 13) were assigned to attend their test session in the pill-free week of their pill-packs (termed here "OC_0") and half (n = 14) were assigned to attend in the third week of their pill-packs ("OC_3"). Participant sessions were scheduled in accordance with participants reported start-date of their current pill-pack.

All participants were asked to abstain from eating for 2 hours before the test session. Prior to the scan, participants completed an assessment of their current hunger level (as rated from 0 [not at all hungry] to 100 [extremely hungry]) and mood (as measured from select items on the Positive and Negative Affect Scale [PANAS]; Watson, Clark, & Tellegan, 1988). They also completed a behavioral test of motivation to view images of couples and food (please see Chapter 2 for behavioral data). Although images in the behavioral and neuroimaging tests were similar in content, none of the images seen in the neuroimaging portion of the study were seen in the behavioral session. Participants returned to the behavioral testing room after the scan to rate the images they saw in the scanner, complete another assessment of their hunger level and mood, and to answer questions about their sexual experiences over the course of the previous week (as measured via the Female Sexual Function Index [FSFI]; Rosen, et al., 2000).

Imaging parameters and design

Scanning was performed on a Siemens 3T Trio whole-body scanner in the Facility for Education and Research in Neuroscience at Emory University with a 32-channel head matrix coil. A structural MRI was acquired for each subject with a T1-weighted pulse sequence (TR = 1900 ms, TE = 2.27 ms, flip angle = 9°, 192 sagittal slices, 1 x 1 x 1 mm voxel size) prior to the functional scans. Structural image acquisition lasted 4mins and 26s. To measure blood oxygen

level-dependent (BOLD) response, an echo-planar imaging sequence was used to acquire T2*-weighted images (TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 192 mm × 192 mm, 35 3-mm thick axial slices, and 3 × 3 × 3 mm voxels). Participants underwent a total of 21 minutes of functional scanning: four runs that were each 5mins and 15s in length.

Images were displayed to participants in the scanner using MATLAB 2016b via an angled mirror attached to the head matrix. Participants saw 96 images per run—24 images per image category. Images were presented in a block design, and each block consisted of six images of the same category presented consecutively. Each image was presented for 2 seconds (s) followed by a 0.5s interstimulus interval, yielding a block time of 15s. In addition to the 16 blocks of images per run, there were also five blocks in which participants saw only a white fixation cross on a grey background. Fixation-cross blocks were the same duration as image blocks (15s) (Figure 1).

Each run had a unique block order. For all runs, the first eight image blocks were presented in a pseudorandom order, and the remaining eight were presented in the reverse order of the first. Blocks of HC foods and sexual couples were never shown back-to-back – these image categories were always followed by at least one block of "neutral" images (i.e. the neutral couples or LC foods). To ensure that one stimulus category did not come to predict another, no one image category exclusively preceded any other category (i.e. sexual couple blocks did not always precede neutral couple blocks). All runs began with a fixation block, and a fixation block occurred every four blocks thereafter.

To confirm that participants attended to the images shown in the scanner, all participants were given a button-box to hold during the scan and were instructed to press the button closest to the button-box cord (i.e., the blue button) whenever an image repeated (i.e., when an image was

shown twice in a row; termed a "one-back task"). Of the six images per block, four images were unique and two were repeats. There was no consistent pattern as to which images in the block repeated.

Rating of scanner images

Following the scan, participants returned to the private behavioral testing room and used a desktop computer to rate the 256 images they saw in the scanner on appeal. Images appeared in random order, and participants were able to view each image for an unrestricted amount of time. Participants pressed the spacebar to end image presentation and advance to the rating scale. In the case of the food images, participants were asked to rate the food in the previous image on how appetizing they found it. The rating scale ranged from 1 – 9, with "1" indicating "extremely unappetizing," "5" indicating "neutral," and "9" indicating "extremely appetizing." For couples images, participants were asked to rate how sexually appealing they found the scene in the previous image. The rating scale again ranged from 1 – 9, with "0" indicating "extremely sexually unappealing," "5" indicating "neutral," and "9" indicating "extremely sexually appealing." Participants selected their numerical rating on the desktop keyboard and pressed the spacebar to submit their responses.

Statistical Analyses

All neuroimaging data were preprocessed and analyzed with Analysis of Functional NeuroImaging (AFNI) software. Functional data were slice-time and motion-corrected, aligned to the corresponding anatomical image, normalized onto a common brain-space (Talairach-Tournoux Atlas), and smoothed with an isotropic Gaussian kernel (FWHM = 6mm). Individuals' neural activity for each image category (HC foods, LC foods, sexual couples, and neutral couples) was modeled with a series of 15s boxcar functions that corresponded to the onset of

image category presentation and were convolved with a canonical hemodynamic response function. In addition to image-category regressors, motion parameters were included as factors in the model. Fixation blocks were not explicitly modeled, but rather served as an implicit baseline.

ROIs analyses

To create the VS ROI, we drew two 6mm spheres – one for the left, and one for the right – focused on the location of the nucleus accumbens (NAc) (MNI coordinates for right: [x y z] [9 6 -4] and left: [-9 6 -4]). The VS ROI coordinates were derived from those reported from MRI and stereotactic work on the anatomical location of the NAc, and were used previously to render 6mm spherical VS/NAc ROIs in which activity predicted eating and sexual behavior in a group of 58 women (Neto, Oliveira, Correia, & Ferreira, 2008; Demos, Heatherton, Kelley, 2012). The resulting VS ROI was 72 voxels (Figure 2).

The OFC is a functionally heterogeneous region with considerable cytoarchitectural variability between individuals (Kringelbach, 2005; Chiavaras & Petrides, 2000; Chiavaras & Petrides, 2001). Previous work indicates that although individuals relatively consistently show activation in the OFC in response to food and sexual stimuli, the peak regions of activation are in slightly different locations (Sescousse et al., 2013). To account for individual as well as stimulus-specific variability, we functionally rather than anatomically defined the OFC ROIs. To define the ROI used for the food analysis, we performed a one-way t-test on the linear contrast for HC – LC foods, which yielded a group-level statistical map. We then used this map to identify regions within the OFC that responded more to HC than LC foods and survived a corrected p value of < 0.05 (as determined via a cluster-defining threshold of $p < 0.005$ and a cluster size ≥ 28 voxels). With these criteria, only one region emerged, which was located in the left medial OFC, and this was the region used for subsequent hormonal group analyses (center of

mass located at MNI coordinates [x y z] [-9 51 -5]; 82 voxels). The same approach was taken for definition of the OFC region used for couples analyses, with the exception that the Sexual – Neutral couples contrast was used to produce the statistical map. This analysis similarly yielded only one region in the OFC that responded more to sexual couples than neutral couples and survived a corrected *p* value of < 0.05 (center of mass located at MNI coordinates [x y z] [-6 60 -2]; 34 voxels). The ROI for foods and ROI for couples were located close to each other and partially overlapped, with the food ROI located ventrally and posteriorally to the couples ROI (Figure 3).

For all ROI analyses, we extracted the average beta (ß) value from the ROI for each subject for the condition of interest. The ß values for each image category were used as the dependent variable when testing for image effects in the VS, and change scores (HC foods – NC foods and sexual – neutral couples) were used in tests of hormonal effects. Image category effects were tested with paired t-tests, and hormonal group effects on the VS were tested with a mixed factor analysis of variance (hormonal state [periovulatory vs. luteal vs. OC_0 vs. OC_3]) x 2 (image category [sexual couples - neutral couples vs. HC food - LC food]). One-way ANOVAs were used to test for hormonal effects in the OFC ROIs. In the case of a main effect or interaction, follow-up ANOVAs and/or simple contrasts were performed.

Whole Brain Analysis

Potential hormonal group differences for which we did not have *a priori* hypotheses were tested with two second-level unpaired t-tests (AFNI's 3dttest++): one to test for group differences between NC periovulatory and NC luteal women and one to test for differences between OC_0 and OC_3 women. To correct for multiple comparisons, we used an FWE cluster-based correction threshold calculated with 3dClustsim (Cox, Chen, Glen, Reynolds, & Taylor,

2017). We calculated each subject's spatial autocorrelation function (acf) via 3dfwhmx, averaged these values across subjects to create a group acf (i.e., smoothness estimate), and entered these estimates into 3dClustsim with a specified alpha level of 0.05 and a *p*-value of 0.005. With these parameters, 3dClustsim indicated a corrected *p-value* of < 0.05 with a cluster of 28 voxels.

Behavioral analyses

We tested for hormonal group differences in subjective ratings of images with a 4 (hormonal state [periovulatory vs. luteal vs. OC_0 vs. OC_3]) x 4 (image category [sexual couples vs. neutral couples vs. HC food vs. LC food]) mixed factor ANOVA. Again, in the case of a main effect or interaction, follow-up ANOVAs and/or simple contrasts were performed.

Effect sizes

Effect size estimates were calculated as η_p^2 for ANOVA results, Cohen's *d* for unpaired t-tests, and Cohen's d_z for paired t-tests. Results are expressed as mean ± standard deviation of the mean, unless otherwise noted. A probability value of $p < 0.05$ was considered significant.

Results

Participants

Of the 57 women tested, 53 are included in the neuroimaging analyses (M_{age} = 24.38, SD_{age} = 4.72). Two NC periovulatory participants were excluded: one woman because we could not confirm the hormonal state she was in at time of test, and one because she was taking medication for treatment of a hormonal condition at time of test. Two OC_0 women were also excluded: one because it was later discovered that she was taking a triphasic rather than monophasic OC, and another because only two runs of data could be acquired due to health and safety concerns. Average BMI across women was within normal range (M = 23.67 ± 4.01), and hormonal groups did not differ in BMI ($F(3,48) = 0.43$, $p = 0.74$) . Hormonal groups also did not

differ on frequency of pornography usage ($F(3,48) = 1.95$, $p = 0.14$), or on measures of positive ($F(3,48) = 0.14$, $p = 0.94$) or negative ($F(3,48) = 1.28$, $p = 0.29$) affect collected at the beginning of the session Two more women were subsequently excluded from the subjective rating analyses: one periovulatory woman because she was an outlier (> 3 SD's from mean), and one luteal woman whose data were rendered unusable because of a software error during data collection. This yielded a dataset of 51 women for subjective rating analyses ($M_{age} = 24.24$, $SD_{age} = 4.55$). With these two women excluded, there remained no group differences in BMI ($p = 0.82$) , pornography usage ($p = 0.09$), or measures of positive ($p = 0.87$) or negative ($p = 0.27$) affect.

fMRI

Attention (one-back performance)

Overall, participants performed the one-back task at over 99% accuracy (Mean correct keypresses = 380.9 SD = 4.39 [of 384 possible correct responses]), and hormonal state groups did not differ in task performance ($F(3,49) = 1.68$, $p = 0.18$, $\eta_p^2 = 0.09$) (Figure 4).

ROI analyses

Ventral Striatum

Prior to testing for potential hormonal effects, we first sought to determine whether indeed the Ventral Striatum (VS) responded more to sexual couples and/or HC foods than to neutral couples and LC foods. Paired t-tests revealed greater VS activity to sexual couples than to neutral couples ($t(52) = 6.92$, $p < 0.001$, $d_z = 0.95$), but no difference in VS activity between HC and LC foods ($t(52) = 0.87$, $p = 0.39$, $d_z = 0.12$) (Figure 5 and 6, respectively).

To test whether women's hormonal state predicted their VS activity to images of food or couples, we ran a four (hormonal state [periovulatory vs. luteal vs. OC_0 vs. OC_3]) x two

(image category [food vs. couples]) mixed factor ANOVA, with the dependent variables entered as the difference in beta values between sexual and neutral images (in the case of couples) and difference in beta values between the HC and LC images (in the case of food). The ANOVA revealed a main effect of image category ($F(1,49) = 17.30$, $p < 0.001$, $\eta_p^2 = 0.26$), indicating that VS response was greater to sexual (– neutral) couples than to HC (– LC) foods, but showed no main effect of hormonal state ($F(3, 49) = 0.79$, $p = 0.50$, $\eta_p^2 = 0.05$), and no interaction between image category and hormonal state ($F(3,49) = 1.21$, $p = 0.32$, $\eta_p^2 = 0.07$).

Orbitofrontal cortex: food

To determine whether women's hormonal state predicted their differential response in the orbitofrontal cortex (OFC) to HC vs LC images, we conducted a one-way ANOVA, which showed that women's hormonal state was not related to their OFC activity to HC (compared with LC) foods ($F(3,49) = 0.90$, $p = 0.45$, $\eta_p^2 = 0.05$) (Figure 7).

Orbitofrontal cortex: couples

We used a one-way ANOVA to test whether women's hormonal state predicted the magnitude of the differential response between sexual and neutral couples in the OFC. As shown in Figure 8, hormonal state was a significant predictor of response to sexual images (vs. neutral) in the OFC ($F(3,49) = 2.96$, $p = 0.041$, $\eta_p^2 = 0.05$), such that OC_0 women showed greater OFC activity to sexual images (vs. neutral) than did OC_3 women ($p = 0.01$, $d = 0.95$) and than did NC women in the luteal phase of their cycles ($p = 0.01$, $d = 0.91$), but not more than did NC periovulatory women ($p = 0.06$, $d = 0.65$).

Whole brain analyses

To determine whether there were hormonal group effects in neural response to images of HC foods (vs. LC foods) or sexual couples (vs. neutral couples) beyond what were tested in the *a*

priori ROIs, we performed a subsequent whole-brain analysis. To test whether NC women differed in activation based on menstrual cycle phase, we performed unpaired t-tests (one for food and one for couples) to compare activation between NC periovulatory women and NC luteal women. We used the same approach to test for differences in neural response between OC_0 and OC_3 women.

There were no regions identified by the whole-brain analysis that were differentially active for NC periovulatory women versus NC luteal women for either HC foods (vs. LC foods) or sexual (vs. neutral) couples. Consistent with our ROI results, whole-brain analysis revealed that OC_0 women showed greater differential activity to sexual vs. neutral couples in the medial OFC / Brodmann's area 10 than did OC_3 women. The analysis additionally revealed OC_0 women to show greater differential activation to sexual couples in a posterior region of the cingulate cortex, and OC_3 women to show greater differential activation in the precuneus (Table 1). Finally, whole-brain analysis of HC – LC foods for OC women revealed that a small region in the medial temporal lobe was more active in OC_0 women compared to OC_3.

Subjective ratings

We used a 4 (hormonal state [periovulatory vs. luteal vs. OC_0 vs. OC_3]) x 4 (image category [sexual couples vs. neutral couples vs. HC food vs. LC food]) mixed factor ANOVA to determine whether women's hormonal state was related to their subjective assessment of the images they saw in the scanner, and if so, whether this effect differed by image category. The mixed-effects ANOVA revealed a main effect of image category ($F(3, 141) = 173.74$, $p < 0.001$, $\eta_p^2 = 0.79$), no main effect of hormonal state ($F(3, 47) = 2.62$, $p = 0.06$, $\eta_p^2 = 0.14$), and a category by hormonal state interaction ($F(9, 141) = 2.00$, $p = 0.04$, $\eta_p^2 = 0.11$) We followed up the main effect of image category with post-hoc tests that revealed that participants rated the HC

food to be more appetizing than the LC foods ($p < 0.001$, $d_z = 2.31$) and the sexual couples images to be more sexually appealing than the neutral couples images ($p < 0.001$, $d_z = 2.02$) (Figure 9 and 10, respectively). To characterize the interaction between category and hormonal state, we performed a multivariate ANOVA, which showed that hormonal state predicted subjective response to images of sexual couples $F(3, 47) = 4.22$, $p = 0.01$, $\eta_p^2 = 0.21$), but did not predict responses to any other image categories (all p's ≥ 0.07). Post-hoc analyses of the main effect of hormonal state on response to images of sexual couples showed that OC_0 women and periovulatory women rated sexual stimuli as more sexually appealing than did NC luteal women ($p = 0.004$ for both contrasts) (Figure 11). OC_0 and periovulatory women did not differ in their ratings ($p = 0.99$), and neither group differed in ratings from OC_3 women ($p = 0.11$ for both contrasts; though with moderate [$d = 0.65$ for periovulatory vs. OC_3] to large [$d = 0.86$ for OC_0 vs. OC_3] effect sizes).

Discussion

We tested here whether women's hormonal state was related to their neural and subjective responses to food or sexual stimuli. Our results lend support to the notion of hormonal modulation of women's hedonic evaluations of sexual stimuli but not of food stimuli. We found that women's hormonal state predicted how sexually appealing they found sexually explicit images and their neural response to those images, as measured via activity in a region in the OFC. In contrast, and unexpectedly, women's hormonal state was not related to how appealing they found images of high-caloric foods or to their neural response to those images.

We focused our investigation of hormonal modulation of neural response on two regions: the VS (as centered on the NAc) and the OFC, both of which are widely considered to be sensitive to the hedonic value of reward stimuli (Peters & Buchel, 2010; Sescousse et al., 2013;

Sescousse & Dreher, 2014; Berridge & Kringelbach, 2015). Across women, we found that VS activity was substantially greater to sexual stimuli than it was to neutral couple stimuli; however, we did not find the magnitude of this differential response (sexual – neutral) to be related to women's hormonal state as we did in the OFC. The hormonal effect in the OFC was such that OC women in the pill-free week of their pill-cycles (OC_0), who were experiencing low levels of progestins, showed greater activation to sexual couples than did OC women in the third week of their pill-cycles (OC_3) or NC luteal women, both of whom were experiencing high levels of progestins. OC_0 women did not significantly differ in their OFC activation to sexual (- neutral) couples from NC periovulatory women. The pattern of hormonal effects identified in OFC activation to sexual stimuli partially aligns with the pattern of hormonal effects on subjective ratings of sexual stimuli. That is, we found that OC_0 women rated the sexual stimuli seen in the MRI to be more sexually appealing than did NC luteal women, but did not differ in their ratings from NC periovulatory women. Although not significantly so, OC_0 women also rated sexual stimuli to be more sexually appealing than did OC_3 women (as indicated via a large effect size [$d = 0.86$]). Together, these data indicate that women's subjective and OFC responses are sensitive to their hormonal state whereas their VS responses are not.

That VS activity did not differ with women's hormonal state as did OFC activity and subjective response is in keeping with meta-analytic findings that the OFC more closely and consistently tracks subjective reward value than does the VS, suggesting different roles for the OFC and VS in hedonic processing (Peters & Buchel, 2010). Although the VS has been shown in a wide range of human and nonhuman animal studies to responsive to a variety of rewards – including both sexual and food rewards – some suggest that VS reward-related activity more accurately reflects aspects of reward processing such as prediction error or the "wanting" of

rewards, rather than of those related to hedonic value (Hare, O'Doherty, Camerer, & Schultz, 2008; Plassman, O'Doherty, & Rangel, 2007; Peters & Buchel, 2010; Berridge & Robinson, 1998). A lack of concordance between VS response to sexual stimuli with reported subjective value of sexual stimuli has been found in recent work by Safron and colleagues (2017). The authors used fMRI to measure VS response to sexually explicit images in women of different sexual orientations and found that heterosexual women's VS responsivity to sexual stimuli did not reflect their stated sexual preference. That is, although heterosexual women showed substantial VS response to the sexual stimuli presented, their VS activity did not differ between nude images of their preferred sex (i.e., men) versus their nonpreferred sex (i.e., women). The authors additionally report that heterosexual women did not differ from bisexual women in their VS response to sexual stimuli (though the women differed in their subjective assessment of the sexual images). Together, Safron and colleagues' findings and our data here suggest that although VS responsivity to sexual stimuli is robust, the magnitude of VS response may not be reflective of the hedonic value of those stimuli. It is possible that VS response to sexual stimuli reflects another aspect of reward processing that is relatively insensitive to physiological, cultural, or experiential modulation. It is also possible that VS response to sexual stimuli represents a more general arousal response. Both of these possibilities, however, require more direct investigation.

The hormonal effects identified in OFC responsivity to sexual stimuli align only partially with our hypotheses. We predicted that OC women who were in the pill-free week of their cycles and were thus in a low progestogenic state would react more favorably to sexual stimuli than would OC women who were actively taking the pill and in a high progestogenic state, and this prediction was borne out by the data. However, we additionally predicted that periovulatory

women would show the most OFC activity to sexual stimuli than would all other women, and this prediction was not supported by the data. That is, we did not find that periovulatory women showed greater OFC activation to sexual couples than did luteal or OC_3 women. Although periovulatory women's activity in the OFC for sexual (- neutral) couples was numerically almost double that of luteal and OC_3 women's (as measured via ß values), there was a great degree of variance in all three groups, and the group differences were not statistically indicated to be reliable.

Luteal and OC_3 women were strikingly similar in their OFC response to sexual stimuli (see Figure 8), and they were also hormonally similar in that both groups were experiencing high levels of progestins at time of test (Stricker et al., 2006; Warner Chilcott, 2006). That luteal and OC_3 women showed the least OFC activation to sexual stimuli of the four groups of women sheds light on potential neural mechanisms driving previous findings that high progestogenic state are negatively related to cognitive and subjective responses to sexual stimuli and to sexual motivation more generally (Renfro, Rupp, & Wallen, 2015; Roney & Simmons, 2013; Wallen & Rupp, 2010). The neuroimaging data are complemented by the subjective response data, which show that luteal women also rated the sexual stimuli to be less appealing than did the periovulatory women or OC_0 women, and although not statistically significant, there were moderate-large effects indicating that OC_3 women rated the sexual stimuli to be less sexually appealing than did periovulatory (d = 0.65) or OC_0 women (d = 0.86). That relatively weaker OFC response to and less favorable evaluations of sexual stimuli reflects progestin inhibition rather than lack of estrogenic promotion is suggested by comparison between the periovulatory and OC_0 groups.

Periovulatory and OC_0 women did not differ in their subjective ratings or OFC responsivity to sexual stimuli. The periovulatory and OC_0 hormonal states are similar in that they are both characterized by low levels of P4 (and no synthetic progestins), but they are dissimilar in that the periovulatory phase is characterized by a notable peak in E2 that is likely much greater than E2 experienced in the OC_0 phase. The OC_0 phase is considered to approximate NC women's early follicular phase (van Heusden & Fauser, 2002), during which E2 levels are 15 – 20% that of women in the periovulatory phase (Stricker et al, 2006). If E2 were substantially modulating women's neural or subjective responses, one would expect responses to differ between periovulatory and OC_0 women, which is not what we found here. Indeed, it is of note that although OC_0 and periovulatory women did not significantly differ in their OFC response to sexual stimuli, there was a moderate effect such that OC_0 women showed greater OFC activation to sexual stimuli than did periovulatory women. Although these data fit with previous work from our lab showing that OC_0 women showed more cognitive interest (as measured via looking time) in sexual images than did periovulatory women (and substantially more than did OC_3 women) (Wallen & Rupp, 2010), it is not clear what – if any – hormonal mechanism might account for this difference. Given that periovulatory and OC_0 women also hormonally differ in that OC_0 women are otherwise in a constantly high progestogenic state whereas NC women are not, it is possible that relatively greater response from OC_0 women reflects a compensatory increase in motivation for sexual stimuli that results from release from progestin inhibition. It is, of course, also possible that the difference is reflective of a sociocultural, attitudinal, or relational variable that differs between NC and OC women, or (perhaps most likely) an interaction between these factors and women's hormonal state.

Measurement of circulating levels of steroids and test of their relationship to women's OFC response to sexual stimuli would be helpful in teasing apart these potential factors.

The lack of a hormonal effect on subjective and OFC response to high-caloric foods, as well as the overall lack of distinction in VS activity between HC and LC foods warrants discussion. Although women collectively rated HC foods to be much more appetizing than they rated LC foods to be, this subjective differential was not reflected in differential VS activity. Both these data and our data regarding VS response to sexual stimuli suggest that VS activity is not reflective of the hedonic value of natural reward stimuli. These data are contrary to our predictions, but, again, support previous work that did not find alignment between hedonic value and VS activity, and suggest that VS activity may more specifically indicate other aspects of reward processing, such as prediction error (as reviewed in Peters & Buchel, 2010).

Alternatively, it is possible that the lack of distinction in VS activity between HC and LC foods is due to a methodological aspect of the study. For example, given the relatively low VS activation to HC foods as compared to baseline or to sexual couples, it is possible that our ROI was in the wrong location to test for hedonic effects on VS response to food. That is, there may be a distinct VS subregion outside of the scope of our ROI wherein the overall appeal of food would be reflected in activation patterns. Although we in part chose this ROI because activity in it in response to images of food and sex had been shown to be predictive of women's later eating and sexual behavior (Demos, Heatherton, & Kelley, 2012), a meta-analysis by Sescousse and colleagues (2013) indicated that the locations of peak VS activity in response to food and sexual stimuli differ. The significance of the difference in these two locations is, however, difficult to directly interpret given that the food studies from which the peak voxel was derived were largely those in which food or food odors were administered in the MRI – not images of foods. Future

work using functional rather than anatomical VS ROIs could help illuminate if drawing distinct sex and food ROIs is necessary in future work.

Unlike the VS, the OFC ROI was defined to specifically reflect an area that responded more to HC than to LC foods. Within this region, however, we did not detect hormonal effects. The lack of hormonal effects on OFC activation are perhaps not surprising given that we did not find hormonal effects on subjective response (thus indicating that the value of HC foods was not related to women's hormonal state). Our subjective ratings findings are in contrast to work by Frank and colleagues (2010), who identified a mid-cycle decline in how appealing women rated HC foods (with no change in ratings of LC foods). Frank and colleagues (2010) detected this effect in a sample of 182 women, whom they followed across an entire menstrual cycle. It is possible that the effect of women's hormonal state on subjective evaluations of food is relatively modest, requiring large sample sizes and within-subjects designs to be detected. Given that most work on hormonal modulation of women's responses to food has been on modulation of food intake, much remains to be learned about possible hormonal effects nonconsummatory endpoints such as subjective evaluation.

Limitations

In interpretation of the finding presented here, we must also keep in mind a number of study limitations. Although similar—and in some cases smaller—group sizes have been used in between-subjects investigations of hormonal effects on neural response, our group sizes remain relatively small for detection of hormonal effects, which are often moderate in size (Abler et al., 2013; Rupp et al., 2009; Frank et al., 2010; Gizewski et al., 2006). Indeed, despite our efforts to reduce sources of potential error via implementing relatively restrictive enrollment criteria (e.g., participants were screened for diet, psychotropic medication use, etc.), we found substantial

variance in neural response within groups. Beyond recruitment of additional subjects, the issue of group sample size could be addressed by collapsing across all hormonal groups and testing for continuous relationships between women's hormones and behavioral/neural endpoints.

Another means of reducing error in our groups would have been to collect more data from each individual. Although we used a block design to increase power and were sufficiently powered to detect robust effects such as differential VS activity between sexual and neutral couples, more data from each person would have allowed us to functionally define OFC regions in each participant using half of their data, and extract values from the individual's specific ROI from the other half of their data, rather than extracting values from an ROI defined at the group level. Drawing individual ROIs as opposed to group ROIs allows for greater specificity and would help ensure that we indeed capture each individual's ROI.

Finally, we must keep in mind that these data are by nature correlational. It is thus of course possible that there is some nonhormonal factor that varies between the groups and underlies the group differences identified here. Future research in which women are tested prior to and following a hormonal manipulation, such as initiation of use of OCs, injectable contraceptives, or hormone replacement therapy, hold potential for shedding light on the potential causal role of steroids in affecting women's hedonic responses to sexual stimuli.

Conclusions

We provide here converging behavioral and neural evidence that women's hedonic evaluations of sexual stimuli are related to their hormonal state. A great deal of data show that women's sexual behavior changes with their hormonal state (as reviewed in Cappelletti & Wallen, 2016). The data presented here raise the possibility that changes in the hedonic value of sexual stimuli contribute to women's likelihood of engaging in sexual behavior. In contrast to

our findings with sexual stimuli, we found neither behavioral nor neural evidence for a relationship between women's hormonal state and their hedonic responses to food stimuli. It is thus possible that previously identified changes in food intake across women's ovarian cycles (as reviewed in Buffenstein et al., 1995) do not reflect changes in how much women like or value food, but rather reflect hormonal modulation of consummatory-specific aspects of eating, such as satiety. Together, these data demonstrate that understanding the role of women's hormonal state in modulating their reward-based behaviors is complex with much work remaining to be done.

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Table 1.

Sexual - Neutral	Region	L/R	x	y	z	t	k
OC_0 > OC_3	Medial frontal gyrus / BA 10	L	-14	48	5	4.32	50
	Cingulate gyrus	L	-1	-17	44	4.33	38
OC_3 > OC_0	Precuneus	R	15	-67	57	5.29	34
Periovulatory > Luteal	*No sig. activation clusters*						
HC - LC							
OC_0 > OC_3	Uncus	R	31	-4	-29	4.07	29
Periovulatory > Luteal	*No sig. activation clusters*						

Table 1. Table reflects the MNI coordinates of peak activation (x, y, z) , t-statistic of peak activation (t), and cluster size (k number of voxels) for all significant clusters ($p < 0.05$, cluster-corrected for multiple comparisons).

Figure 1.

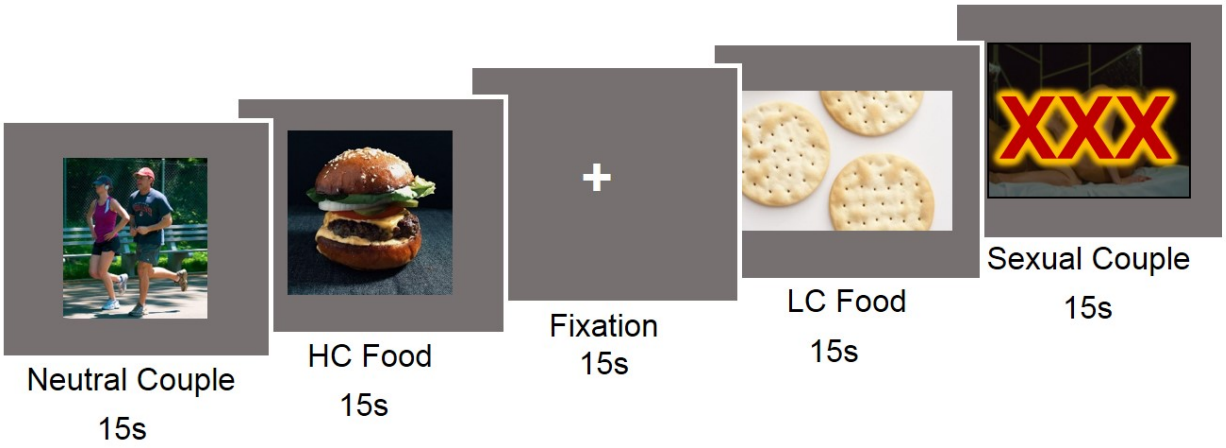

Figure 1. Imaging paradigm. Participants saw blocks that were 15s in length and consisted of six images presented for 2s followed by a 0.5 interstimulus interval.

Figure 2.

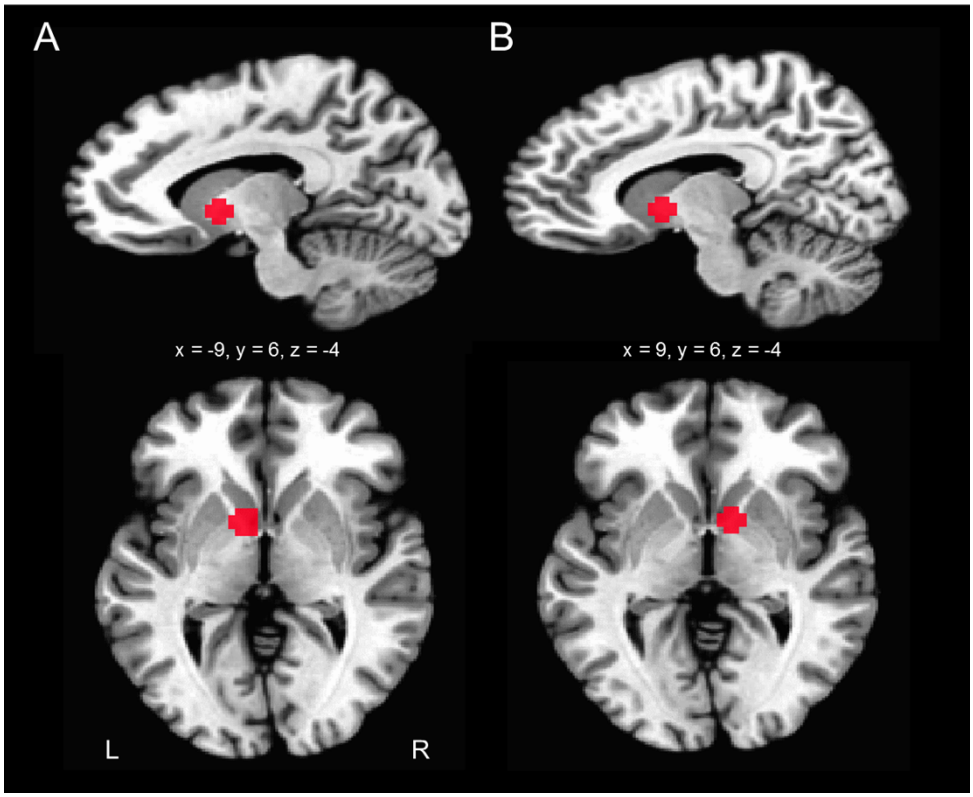

Figure 2. A) Left anatomical VS (centered on NAc). ROI reflects a 6mm centered on the provided MNI coordinates. B) Right anatomical VS (centered on NAc) ROI reflects a 6mm centered on the provided MNI coordinates.

Figure 3.

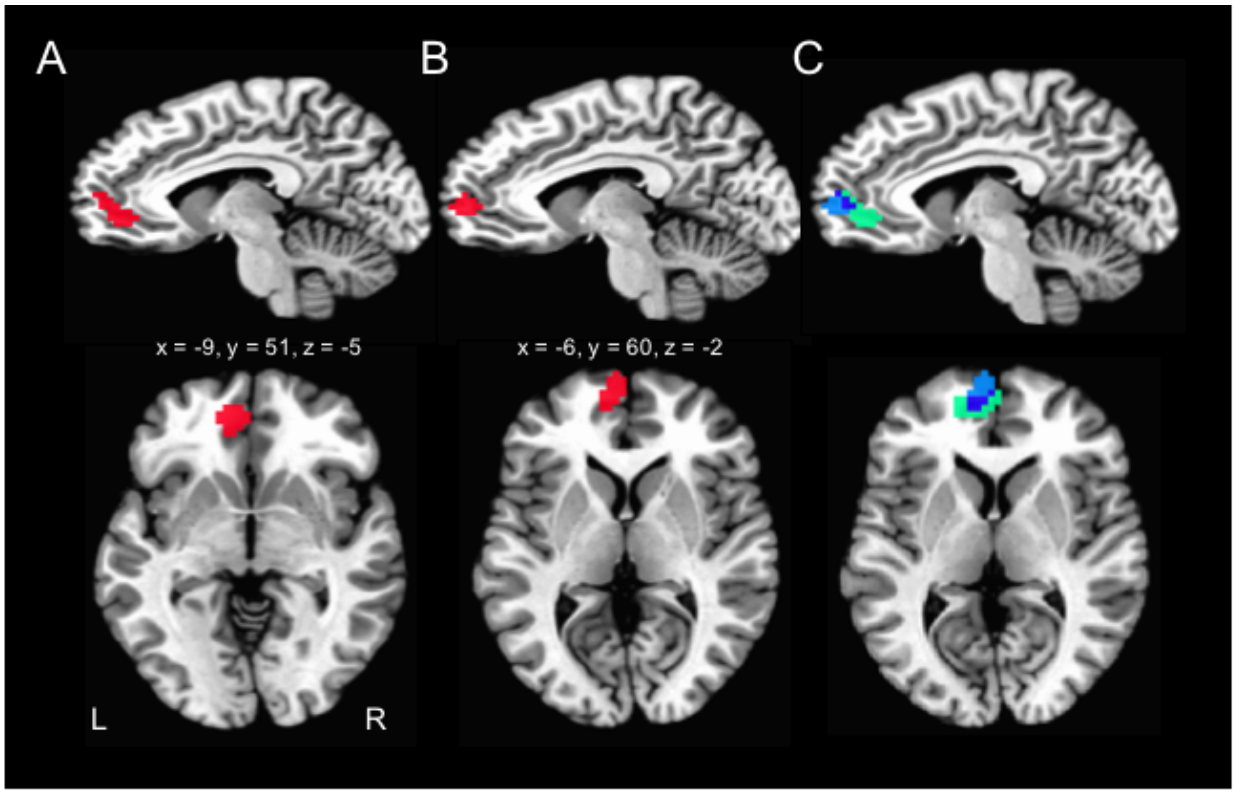

Figure 3. A) OFC ROI defined from HC – LC contrast. B) OFC ROI defined from Sexual – Neutral contrast. C) Overlap (dark blue) between food (green) and couples (light blue) OFC ROIs. Coordinates reflect the MNI coordinates for the center of mass of the ROI.

Figure 4.

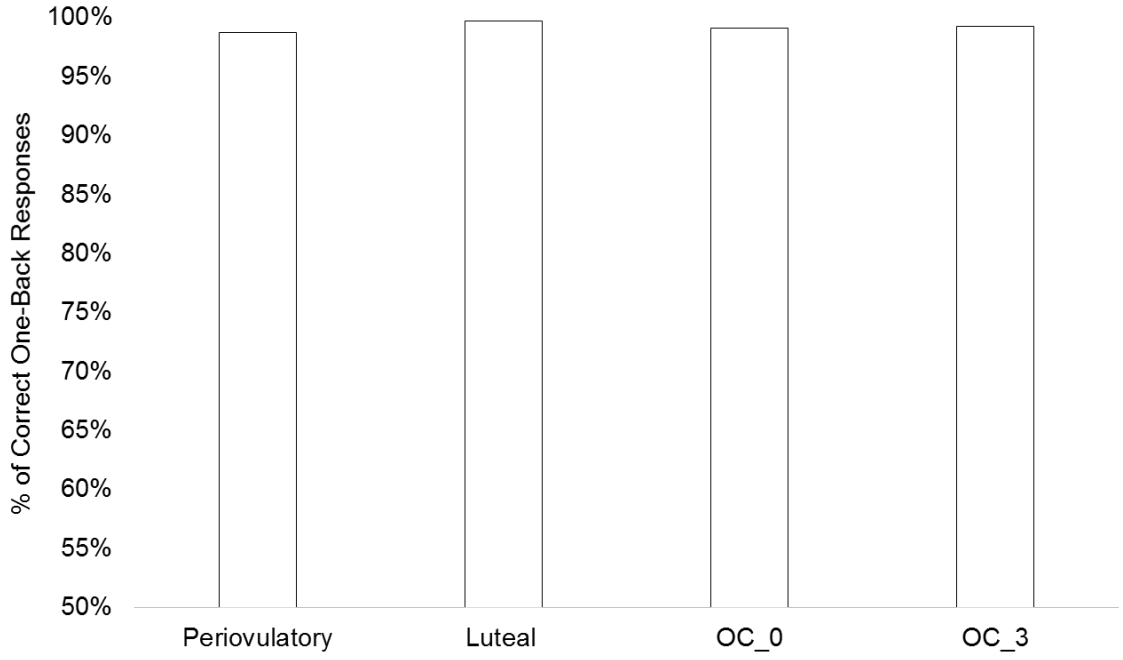

Figure 4. Performance on the one-back task by hormonal group. Hormonal groups did not differ in one-back task performance.

Figure 5.

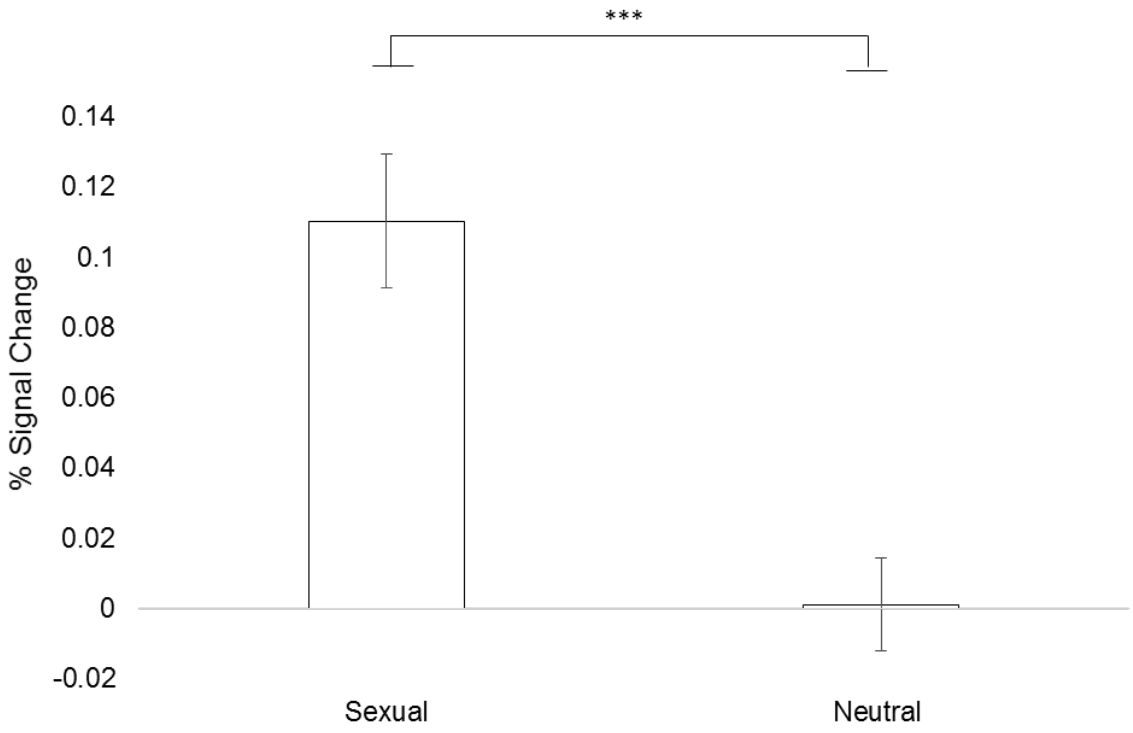

Figure 5. Ventral Striatum (VS) response across all women to images of sexual couples and neutral couples . Women showed greater VS response to sexual couples images than neutral couples (***$p < 0.001$).

Figure 6.

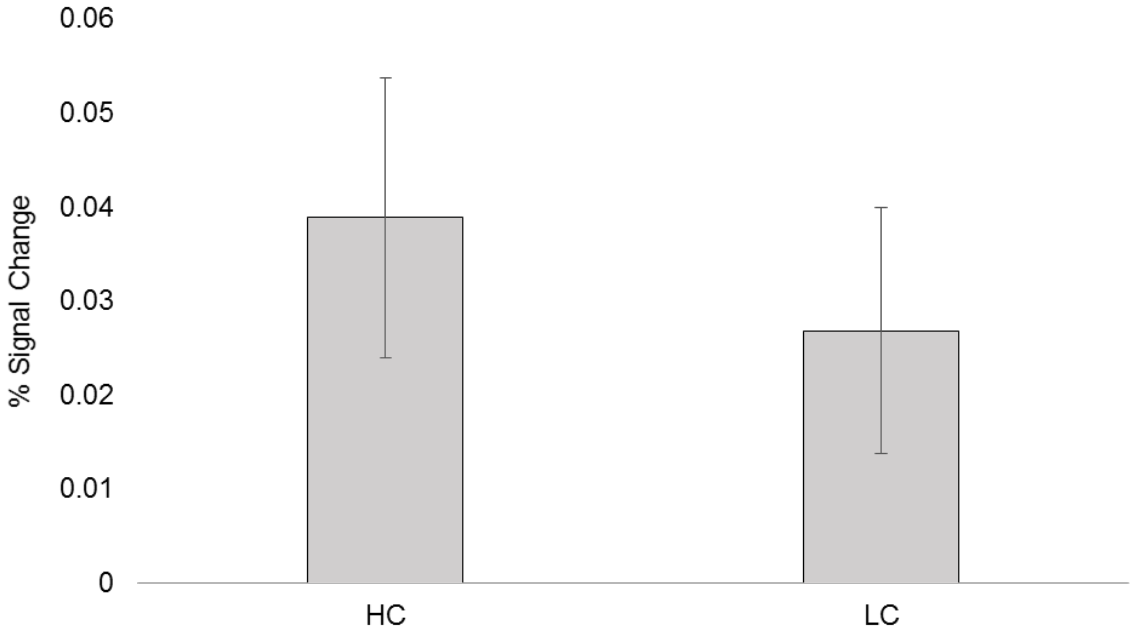

Figure 6. Ventral striatum (VS) response across all women to images of high-caloric and low-caloric foods. Women did not show differential VS activity to HC vs. LC foods.

Figure 7.

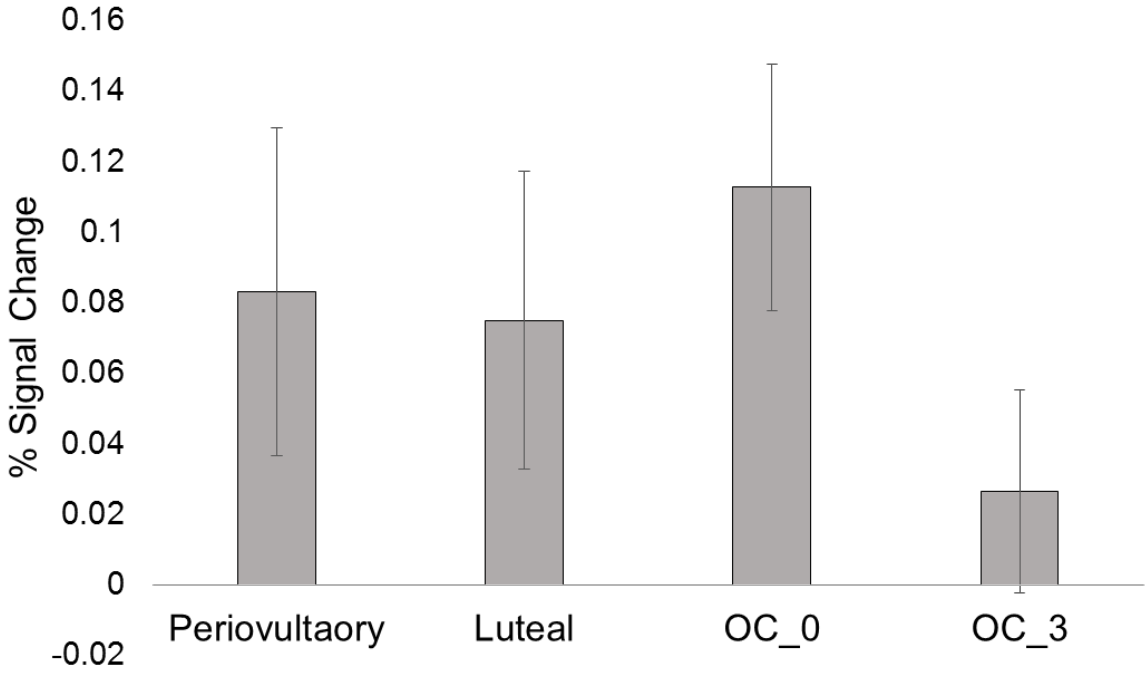

Figure 7. Women's orbitofrontal cortext (OFC) response to high-caloric – low-caloric foods by hormonal state at time of test. Hormonal groups did not differ in their OFC response to HC – LC foods.

Figure 8.

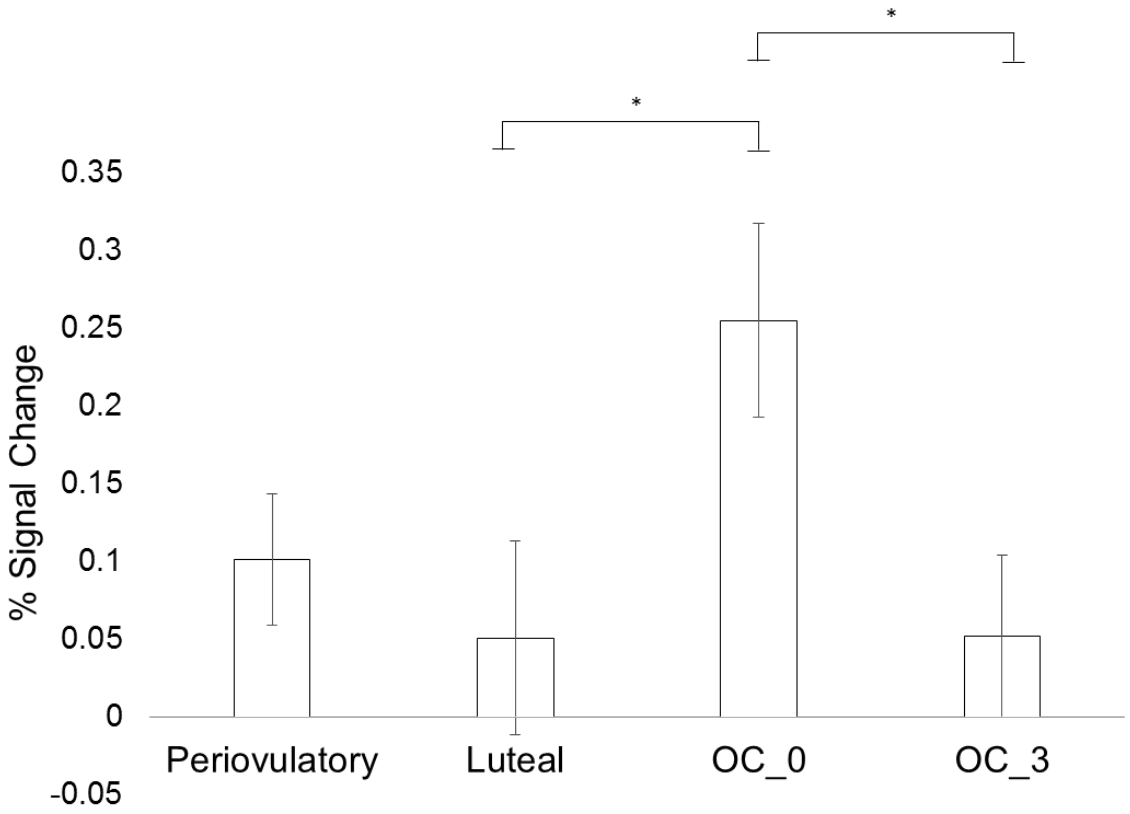

Figure 8. Women's orbitofrontal cortext (OFC) response to sexual – neutral couples by hormonal state at time of test. There was a main effect of hormonal state, and post-hoc analyses showed that OC women in the pill-free week of their cycles showed greater differential activity than did naturally cycling women in the luteal phase of their cycles and than did OC women in the third week of their pill-packs (*$p < 0.05$).

Figure 9.

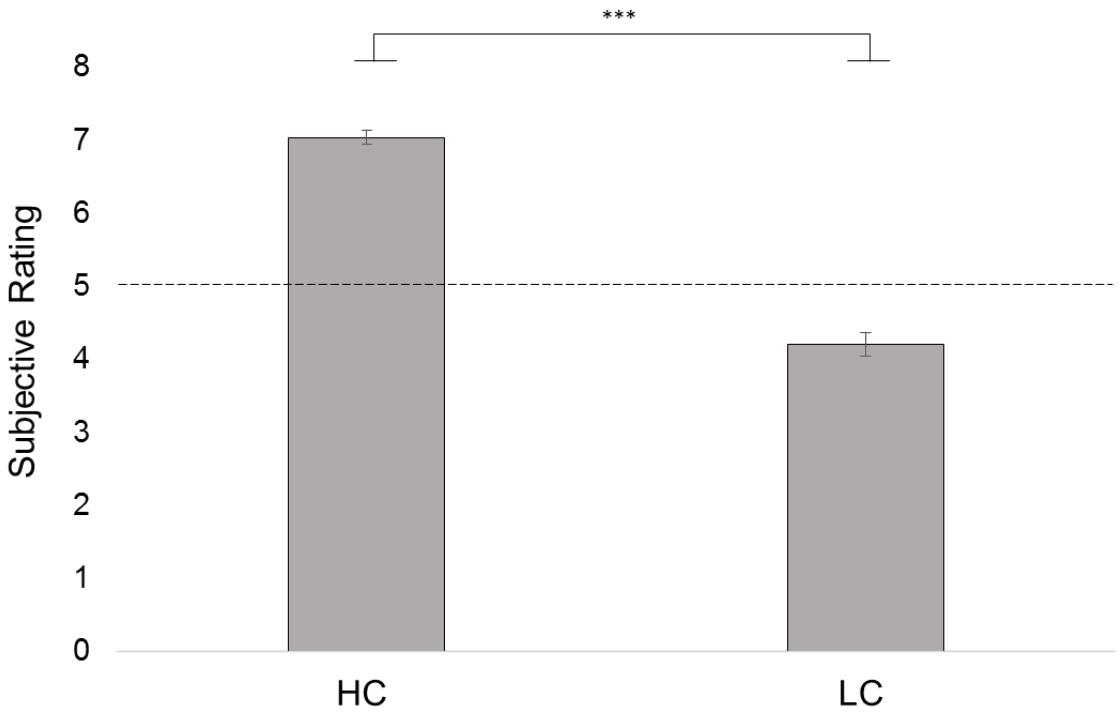

Figure 9. Women's overall ratings for how appetizing they found high-caloric (HC) and low-caloric (LC) foods. Ratings ranged from 1 – 9, from most negative assesment to most positive, with "5" reflecting "neutral." Overall, women rated the HC foods to be more appetizing than the LC foods (***$p < 0.001$).

Figure 10.

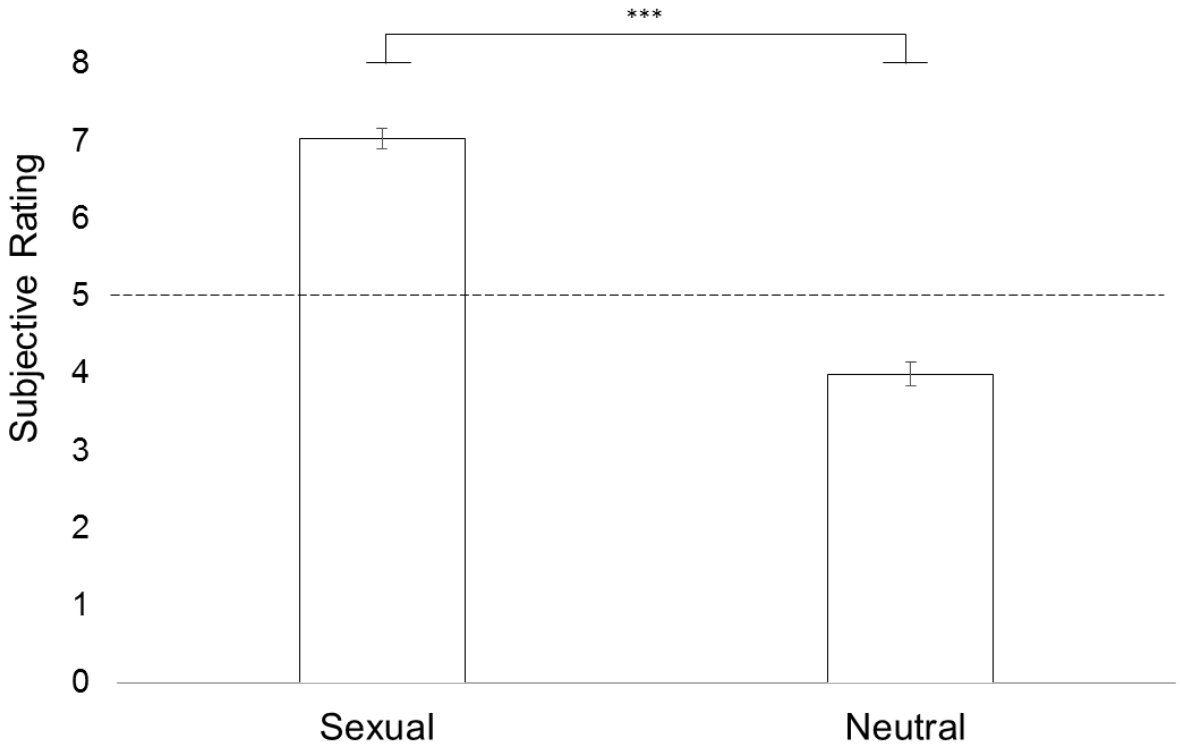

Figure 10. Women's overall ratings for how sexually appealing they found sexual couples images and neutral couples images. Ratings ranged from 1 – 9, from most negative assesment to most positive, with "5" reflecting "neutral." Overall, women rated the sexual couples to be more sexual appealing than the neutral couples (***$p < 0.001$).

Figure 11.

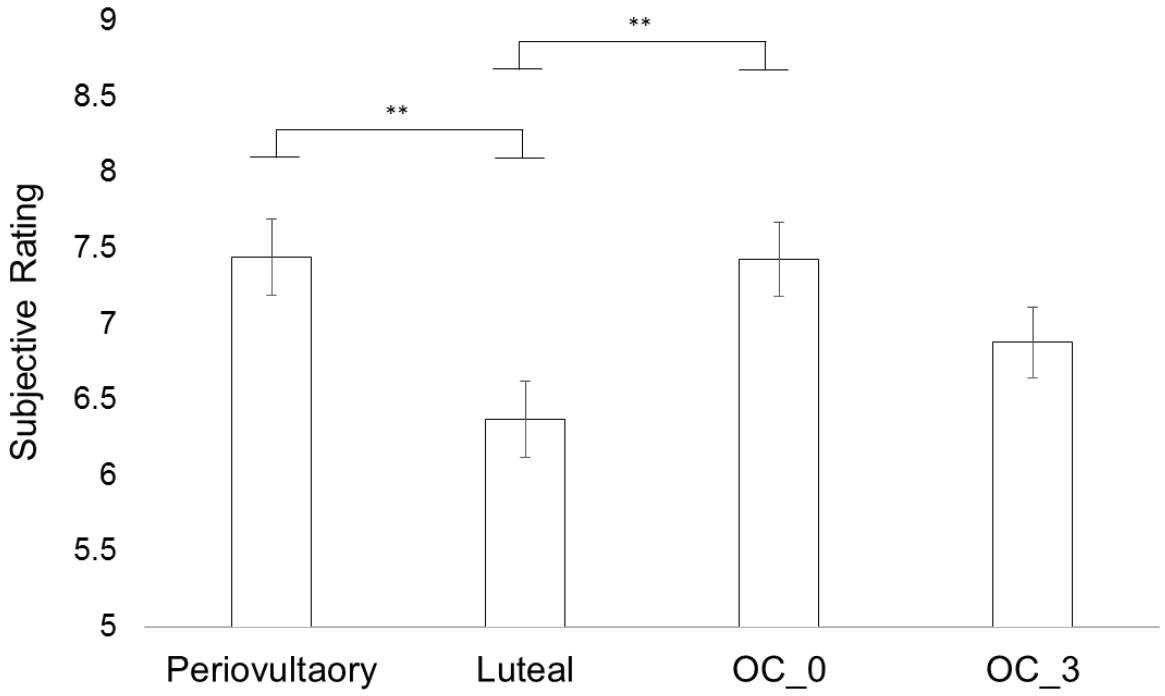

Figure 11. Women's ratings for how sexually appealing they found sexual couples images divided by hormonal state. There was a main effect of hormonal state, and post-hoc analyses showed that OC women in the pill-free week of their cycles ("OC_0") and naturally cycling (NC) women in the periovulatory phase of their cycles rated sexual couples images to be more sexually appealing than did NC women in the luteal phase of their cycles (**$p < 0.01$).

General Discussion

Together, the results of this dissertation inform our understanding of the behavioral and biological factors that modulate women's interest in, motivation for, and responses to food and sex. The first manuscript reviews the nonhuman and human literature on ovarian steroid modulation of motivation for food and sex in females. The review clarifies that there is a cyclic pattern of food intake and sexual behavior that is remarkably consistent across species: food intake reaches a nadir at ovulation and increases post-ovulation, and sexual behavior and desire follow the opposite pattern, peaking at ovulation and declining in the post-ovulatory phase (Buffenstein et al., 1995; Asarian & Geary, 2006; Schneider et al., 2013; Roney & Simmons, 2013; Roney & Simmons, 2017). After establishing in the review that this cyclic pattern of food intake and sexual behavior extends to women – but perhaps with more nuance than in females of other species – the dissertation follows with two empirical papers to better our understanding of how women's hormonal state is related to their responses to food and sex. The two papers focus specifically on determining whether women's hormonal state modulates: a) how much they desire food and sexual stimuli (i.e., how motivating they find them), b) how much they like them, and c) how they neurally respond to them. Manuscript two addresses issue a, and issues b and c are addressed in manuscript three. The two papers describe a relatively consistent pattern of hormonal effects on wanting, liking of, and neural response to sexual stimuli, but report a weak or nonexistent relationship between women's hormonal state and any measured response to food stimuli. Below, the hormonal and lack-of-hormonal findings and their potential implications are discussed.

Hormonal state and response to sexual stimuli

Across the two papers, a pattern emerged such that women in the luteal phase of their menstrual cycles and women taking oral contraceptives (OCs) who were in the third week of their pill-cycles ("OC_3") showed less interest in sexual stimuli than did women in the periovulatory phase or OC women in the pill-free week of their pill-cycles ("OC_0"). In paper two, OC_3 and luteal women's lack of interest manifested as less motivation to view sexual stimuli. In paper three, OC_3 and luteal women were shown to rate sexual stimuli as less appealing, and we provided data that the relatively more negative subjective responses were accompanied by less orbitofrontal cortex (OFC) activity in response to sexual stimuli. We argue in the discussion sections of paper two and three that luteal and OC_3 women's relatively less favorable behavioral responses to and blunted OFC response to sexual stimuli may reflect their high progestogenic state, given that both endogenous progesterone (P4) and synthetic progestins have been shown to be negatively related to sexual desire and behavior in nonhuman primates and women (Kendrick & Dixson, 1985; Pazol, Wilson, & Wallen, 2004; Roney & Simmons, 2013). We speculate that luteal and OC_3 women's responses reflect progestin inhibition of sexual interest and motivation rather than lack of estrogenic promotion for two reasons. The first is that luteal women have higher levels of estradiol (E2) than do OC_0 women (van Heusden & Fauser, 2002; Stricker et al., 2006), and OC_0 women showed much greater interest in the sexual stimuli (as indicated via every metric used in paper two and three) than did luteal women. The second reason is that we found in both studies that periovulatory and OC_0 women did not significantly differ in their responses, and data indicate that periovulatory and OC_0 women are similar in their levels of P4 but dissimilar in their levels of E2. That is, the periovulatory phase is characterized by much higher E2 levels than is the OC_0 phase (Fauser & van Heusden, 2002; Stricker et al., 2006).

Data indicate that P4 accounts for more variance than do E2 or testosterone (T) in women's reported sexual desire (Roney & Simmons, 2013). Despite this finding, of the three steroids, perhaps the least is known about the impact of P4 on sexual behavior. It is possible that the lack of data on P4 and sexual behavior reflects that researchers and/or funding agencies are more invested in studying excitation of sexual desire than its inhibition – perhaps because increasing sexual desire holds greater potential for identifying clinical therapies for low sexual desire. It is also possible that we know relatively little about P4 and women's sexual desire because P4 works differently in rats, which are by far the most commonly-used animal model of human behavior. Rats differ progestogenically from primates in at least two ways: 1) in rats, P4 is necessary for sexual receptivity and thus a promoter of sexual behavior (Boling & Blandau, 1939; Whalen, 1974), and 2) rats do not experience periods of prolonged exposure to P4 because they do not have a post-ovulatory luteal phase. The second point – that primates experience prolonged P4 exposure – is of particular note. Indeed, when one considers that P4 during the luteal phase is secreted in at least eight-fold greater amounts than is peak E2 (Stricker et al., 2006), it is all-the-more surprising that we know so little about the resulting behavioral effects of P4 fluctuations as compared to E2 fluctuations. What the consequences of these dramatic fluctuations in and levels of P4 are for sexual interest and behavior warrant further investigation.

Hormonal state and response to food stimuli

We found no consistent relationship between women's hormonal state and their responses to food stimuli in either study. That is, women's hormonal state was not related to their motivation for, liking of, or neural response to food stimuli. There are potentially are methodological reasons for our findings – perhaps the food stimuli differed in their intrinsic motivational properties from the sexual stimuli or perhaps hormonal effects on response to food

stimuli are relatively more modest than are effects on sexual stimuli and thus require larger samples to be detected. A distinct possibility, however, is that women's hormonal state does not modulate the motivational or hedonic value of food stimuli, and that cyclic changes in food intake more closely reflect ovarian steroid modulation of satiety. This possibility is supported by work in nonhuman animals that shows that reduced calorie consumption in the periovulatory phase is due to meal size rather than meal frequency (Eckel, 2011; Butera, 2010), suggesting that it is not the seeking out of food that varies across the cycle, but rather the consumption of it at mealtime.

Methodological point on the study of hormonal modulation of natural rewards

Roney and Simmons (2017) argued that ovarian steroids function as motivational switches, dynamically modulating the respective value of food and sex thus promoting prioritization of sex and the deprioritization of food when conception is possible (i.e., near ovulation). The authors sought to highlight this point in previous work via calculating change scores between standardized values (z-scores) of daily food intake and sexual desire across women's cycles. The change scores were negative (indicating a preference for food) in the periovulatory phase and positive in the luteal phase (when food intake was greater than sexual desire), which the authors argue supports the notion of cyclic tradeoffs in motivational priorities. Of note is that the cyclic pattern in our data would look quite similar to that of Roney and Simmon's if we were to calculate difference scores between responses to food and sexual stimuli. For example, as shown in Figure 1, the relative preference for sexual stimuli over food stimuli as measured via key pressing is seen in the periovulatory group, whereas this preference is reversed in the luteal group. We have shown here that this group difference in preference (between luteal and periovulatory women) is due only to a difference in motivation to view

sexual stimuli, and not to a difference between the two groups in motivation to view food stimuli. However, if change scores were presented in isolation, these data could also fit with the notion that periovulatory increased motivation for sexual stimuli is accompanied by corresponding decreased motivation for food stimuli, and the luteal decreased motivation for sexual stimuli accompanied by increased motivation for food stimuli. This point is raised primarily to emphasize the importance of reporting complete data so as to promote precision in reporting of effects and allow for alternative interpretations.

Implications

These data collectively offer us insight into the hormonal, cognitive, and behavioral underpinnings of long-reported changes in food intake and sexual behavior across women's menstrual cycles. We add to our understanding of the relationship between women's hormonal state and responses to food or sexual stimuli by testing women in hormonal states who have largely been excluded from previous research in this area (i.e., women in the hormonally-confirmed periovulatory phase of their cycles and women who regularly take OCs but are in the pill-free week of their pill-packs). We also extend the literature by moving beyond measures such as overall food intake or incidence of sexual behavior to ask which specific behavioral, cognitive, and neural responses to food and sex are modulated by women's hormonal state.

More broadly, our data speak to oft-reported side effects of suppression of menstrual cycles via OC use, such as decreased sexual desire (Sanders et al., 2001). Given that hormonal regulation of reproduction is now the norm rather than the exception (Mosher & Jones, 2010), it is increasingly important to understand not only how endogenous steroids modulate behavior, but also what happens to behavior when endogenous steroids are suppressed with synthetic ones. Our findings suggest that OC use is related to lower motivation for and liking of sexual stimuli.

These data shed light on adverse sexual side effects of OC use, which are noted to be one of the best predictors of OC discontinuation (Sanders et al., 2001). Additional work on the biological and behavioral mechanisms by which OCs suppress sexual desire is clearly warranted – both to inform understanding of OC use and adherence, as well as to afford women the opportunity to make informed decisions regarding their reproductive health.

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Figure 1.

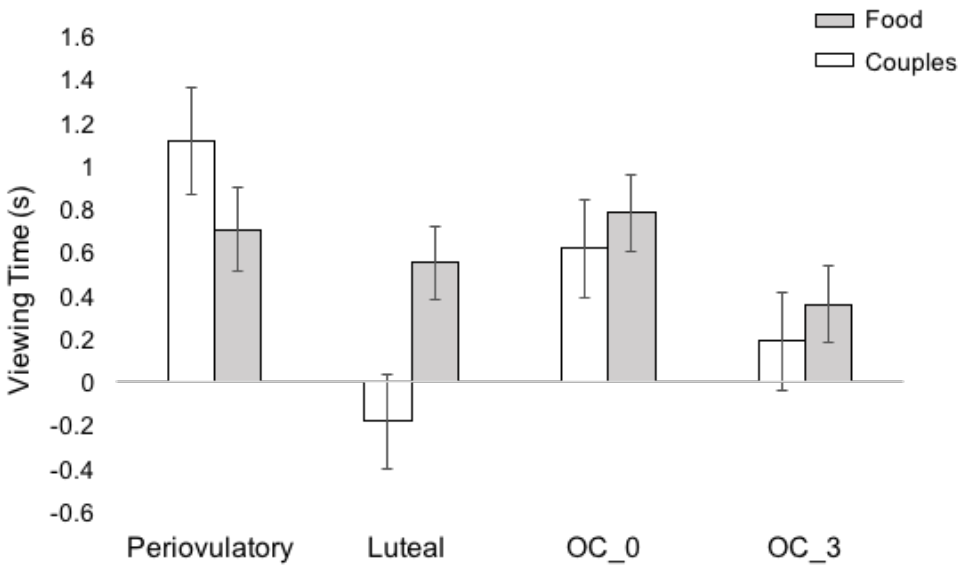

Figure 1. Mean viewing time for couples images (sexual – neutral) and food (HC – LC) images by hormonal state during session 1.