A Mechanistic Examination of Continuous-Cycle Oral Contraceptive Administration in Binge Eating

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A Mechanistic Examination of Continuous-Cycle Oral Contraceptive Administration in Binge Eating

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Study Product:	**Drospirenone Ethinyl-Estradiol 3/.03mg (oral contraceptive)** **Drospirenone** Active ingredient: synthetic progestin Chemical name: 1,2-dihydrospirorenone **Ethinyl-Estradiol** Active ingredient: Ethinyl Estradiol Chemical name: 17-ethinyl-3, 17-estradiol
IRB Protocol Number:	*19-3149*
IND Number:	*Exempt*

Study Personnel:
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Study Coordinator: Jennifer White

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Late Updated: 1/6/2022

Protocol Updates

1/6/2022: New recruitment and enrollment terminated due to inability to recruit eligible participants [COVID]. Remaining participant(s) will finish out the study and then the full protocol outlined below will be terminated

8/9/2021: IRB approval to hire clinical trial recruitment company

7/14/2021: Update BMI exclusion to >31 with physican approval for BMI 30-31

4/27/2021: Approval to provide participants with mileage reimbursement for travel

9/24/2020: Additional COVID procedures (Appendix B)

7/29/2020: COVID protocols and procedures (Appendix B)

List of Abbreviations

AE	Adverse Event
BAS	Behavioral approach system
BED	Binge Eating Disorder
BIS	Behavioral Inhibition system
BMI	Body Mass Index
BN	Bulimia Nervosa
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
DLPFC	Dorsolateral prefrontal cortext
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DVT	Deep Vein Thrombosis
E2	Estradiol
EDs	Eating Disorders
EC	Ethics Committee
EPT	Combined Estrogen and Progestin Treatment (EPT)

FDA	Food and Drug Administration
HFW	Hormone Free Week
HIPAA	Health Insurance Portability and Accountability Act
IDAS	Inventory of Depression and Anxiety Symptoms
IDS	Investigational Drug Service
IRB	Institutional Review Board
mPFC	Medial Prefrontal Cortext
NIH	National Institutes of Health
OC	Oral Contraceptive
P4	Progesterone
PE	Pulminary Embolism
PHI	Protected Health Information
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
ROI	Region of Interest

SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM-5-TR Axis-I Disorders
UNC-CH	University of North Carolina at Chapel Hill
VTE	Venous Thromboembolism

Study Summary

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<tr><td>Title</td><td>A Mechanistic Examination of Continuous-Cycle Oral Contraceptive Administration in Binge Eating</td></tr>
<tr><td>Short Title</td><td>Birth Control & Binge Eating</td></tr>
<tr><td>Protocol Number</td><td>IRB# 19-3149</td></tr>
<tr><td>Phase</td><td>II</td></tr>
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<tr><td>Objectives</td><td>Pilot study: examine the effect of continuous oral contraceptive use on brain activation in women with binge eating using functional magnetic resonance imagine (fMRI) and behavioral tests.</td></tr>
<tr><td>Number of Subjects</td><td>15</td></tr>
<tr><td>Diagnosis and Main Inclusion Criteria</td><td>A current binge-eating syndrome ED, age 18-34, 18.5 < BMI < 31, and a regular menstrual cycle for at least three months; not pregnant, not lactating and in good medical health, no medications contraindicated for use with study medications (including birth control pills), no history of suicide attempts or bipolar/psychotic disorder, no medical issue contraindicated for use with study medications.</td></tr>
<tr><td>Study Product, Dose, Route, Regimen</td><td>Study Product:
Drospirenone Ethinyl-Estradiol (oral contraceptive)

Drospirenone
Active ingredient: synthetic progestin
Chemical name: 1,2-dihydrospirorenone

Ethinyl-Estradiol
Active ingredient: Ethinyl Estradiol
Chemical name: 17-ethinyl-3, 17-estradiol
Dose:
<table><tr><th>Drug</th><th>Dosage</th><th>Formulation</th></tr></table></td></tr>
</table>

	Drospirenone Ethinyl	3/.03mg	Oral pill

Route:

Drug	Route of Administration
Drospirenone Ethinyl	Oral

Regimen:
After a baseline period, participants will take Drospirenone Ethinyl for 3-months continuously. Prior to medication administration and at the end of treatment, fMRI will be conducted in order to examine changes in activation in dopamine-reward pathways that occur with oral contraceptive administration. Administration of an OC will stop ovulation and stabilize changes in E2 and P4 that occur post-ovulation. This will assess changes in brain activation that occur with the stabilization of ovarian hormones.

Duration of administration	3-months continuously
Reference therapy	Within-group comparisons
Statistical Methodology	Change with study intervention

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. Subjects in this proposal will take oral contracetive birth control of 84 continuous days. This represents an 'off label' use as the pill packs come with 7 days of inactive pills to induce bleeding. However, as described below, this 'off label' practice does not increase participant risk and frequently occurs as part of standard clinical practice.

1.1 Background

EDs are devastating illnesses affecting more than 15 million women in the US,[1] yet the neurobiology remains poorly understood. Binge eating is an important transdiagnostic symptom of the EDs that cuts across all ED diagnosis (i.e., AN binge/purge type, BN, BED). Binge eating in and of itself is also associated with substantial

morbidities. EDs predominantly occurs in women and certain symptoms change in a predictable pattern over the menstrual cycle.[2] Cumulatively, the post-ovulation phases of the menstrual cycle have been identified as risky milieus for ED symptom exacerbation, specifically binge eating.[3] Post-ovulation phases of the menstrual cycle include the mid-luteal (both E2 and P4 are high) and pre-menstrual phases (E2 and P4 are decreasing)—with studies consistently identifying these phases of the cycle as high risk periods for binge eating. In contrast, the follicular and ovulatory phases, which occur pre-ovulation, are protective: across studies binge eating is lowest during these phases.[4-8] During the follicular phase, E2 is rising in preparation for ovulation and reaches peak levels at ovulation whereas P4 is low and relatively stable. Taken together, we have hypothesized women who binge eating are sensitive to fluctuating ovarian hormone levels. These women do not exhibit abnormal hormone levels or fluctuations, rather their behavioral reactions to normal ovarian hormone fluctuations may be dysregulated; therefore, eating behaviors are dysregulated by normal fluctuations in ovarian hormones. Unraveling the neurobiology of binge eating has the potential to open innovative avenues for treatment for EDs.

To date, the effects of ovarian hormones on disordered eating behaviors have been inferred from animal studies[9-11] and from changes in behavior occurring with presumed and measured levels of hormones during the menstrual cycle. Few human experimental designs have been conducted, which are necessary to determine mechanism and causality. One strategy to address the direct impact of fluctuating hormones post-ovulation on binge eating is to stop ovulation. By stopping ovulation from occurring, the hormone changes that occur post-ovulation—when binge eating frequency is highest—would be negated. Intriguingly, OCs, which are commonly prescribed in the population, work by suppressing ovulation, thereby reducing the ovarian hormone changes that occur from pre- to post- ovulation. Thus, OCs are a minimally invasive method to stop the post-ovulatory changes in these hormones that occur after ovulation. We are aware of only one study to date that has addressed the impact of OCs in EDs: in a sample of women with BN. Specifically, after 3-months of treatment with an OC **14% of women no longer met criteria for a BN diagnosis and 29% had a reduction in symptoms from baseline**.[12]

Importantly, these women received OC treatment on a 21-day active pill, 7-day hormone free week (HFW) regimen (21/7), which does not result in consistent ovarian hormone stabilization. The HFW allows follicles to begin to develop, leading to the secretion of endogenous E2. Therefore, not only can symptom exacerbation occur during the HFW due to a lack of ovulation suppression, the resurgence of endogenous E2 can also lead to symptom reoccurrence: once the active pills are restarted, endogenous E2 withdrawal will eventually occur, leading to a reoccurrence of symptoms due to E2 withdrawal. Thus, while the previous study did show improvement in BN symptoms on OC for some women, a 21/7 protocol with a HFW substantially increases the risk for symptom exacerbation and reoccurrence and could play a role in why OC was only beneficial for some women. Thus, we propose continuous-cycle OC use with no HFW. Women will be on active pills throughout their entire treatment protocol (3-months). Continuous-cycle OCs that do not have a HFW minimize cyclic symptoms related to hormone fluctuations, are safe, and are more effective in treating conditions such as the premenstrual exacerbation of depression.

Finally, the neurobiological mechanisms underlying *why* the post-ovulation phases of the menstrual cycle are associated with symptom exacerbation remains unknown. One hypothesis for this underlying mechanism is that fluctuating ovarian hormones during the menstrual cycle influence binge eating through effects on reward processes that are altered in women who binge eat. Indeed, women with a binge-eating-type ED tend to be more sensitive to reward,[13-17] display a preference for smaller rewards now vs. larger rewards later (i.e., delay discounting),[18-21] have inhibitory control deficits, and are impulsive.[22-25] Women with a binge eating-type ED may also have decreased dopamine activity[26-28] and reduced brain activation in dopamine-related brain reward pathways.[29] Thus, ovarian hormone neuromodulation of the brain's response to reward may be responsible for the exacerbation of binge eating observed post-ovulation.

The objective of this pilot study is to examine the impact of ovarian hormone stabilization, through the continuous administration of OCs for 3-months, on eating behaviors and reward responsivity (i.e., brain

activation in response to reward) in women who binge eat (*n*=15) using fMRI and questionnaires. Results will provide empirical evidence of our hypotheses and pilot data necessary for larger mechanistic trials. Our primary hypothesis is that continuous OC treatment will have a beneficial/stabilizing effect on outcomes of interest.

Rationale: The direct benefit to participants will be limited and we are not conducting a clinical treatment trial. However, one previous study suggests we may see a beneficial impact of OC on BN symptoms.[12] Women will receive 3-months of OC at no monetary cost. They will also have the option to learn from the PI at the end of the study how their eating behaviors changed in response to the OC, which may be important information for treatment planning. The primary benefit of this study is to aid in understanding the underlying neurobiological mechanisms (i.e., brain activation in response to reward) associated with binge eating. A secondary benefit is to replicate findings that OC result in a decrease or stabilization (symptoms may still be present but do not become exacerbated at post-ovulation as observed during a natural menstrual cycle) of ED symptoms. This line of research could lead to the development of medications that are specifically targeted for women who binge eat or to future clinical trials implementing ovarian hormone stabilization in treatment and treatment maintenance. The ultimate goal of our mechanistic and translational research will be to advance a precision medicine approach to EDs by identifying which type of patient OC treatment is beneficial for and the mechanism through which OC stabilization is beneficial.

1.2 Investigational Agent

Drospirenone/Ethinyl-Estradiol (3mg; 30mcg)

Description

Drospirenone/Ethinyl-Estradiol is a low-dose monophasic contraceptive tablet for oral administration containing 3mg of drospirenone and 30mcg of ethinyl-estradiol. Drospirenone is a synthetic progestin chemically described as 1,2-dihydrospirorenone. Drospirenone is a spironolactone analogue with antimineralcorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, or antiglucocorticoid activity, and exhibits antiandrogenic activity. The two main metabolites of drospirenone found in human plasma were shown to not be pharmacologically active. In *in vitro* studies with human liver microsomes, drospirenone was metabolized only to a minor extent mainly by cytochrome P450 3A4. Ethinyl-estradiol is a syntenic estrogen chemically described as 19-nor-17α-pregna 1,3,5(10)-triene-20-yne-3, 17-diol.

The medication is provided with 21-active pills and 7-inactive (placebo) pills. The inactive pills are taken to induce bleeding (though not technically a menses because ovulation did not occur) and are hormone free. The inactive pills will not be used in this study.

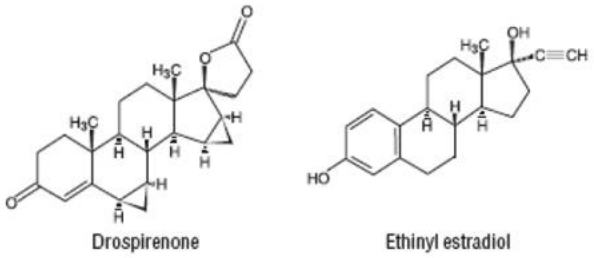


Figure 1. Structural formula for Drospirenone/Ethinyl-Estradiol

Inactive Ingredients: lactose monohydrate NF, corn starch NF, magnesium stearate NF, hypromellose USP, talc USP, titanium dioxide USP, ferric oxide pigment, red NF.

Pharmacology

OCs decrease the risk of becoming pregnant by suppressing ovulation.

Drospirenone is a synthetic progestin that is an analog to spironolactone. Drospirenone differs from other synthetic progestins in that its pharmacological profile in preclinical studies shows it to be closer to endogenous P4. As such it has anti-mineralocorticoid properties and is not androgenic. Preclinical studies show that drospirenone is an antiandrogenic. Ethinyl-estradiol is a semisynthetic alkylated estradiol with a 17-alpha-ethinyl substitution. It has high estrogenic potency when administered orally.

Summary of Previous Human Experience

One study to date has used the proposed OC in a BN population and observed a beneficial effect of use on BN symptoms for some women.[12] No severe adverse events or outcomes were mentioned in the published report.[12]

Drospirenone/Ethinyl-Estradiol is FDA-approved as an oral contraceptive and for the treatment of PMDD. It is effective in reducing the risk for pregnancy and for treating PMDD through its suppression of ovulation. Drospirenone/Ethinyl-Estradiol has been widely researched including in psychiatric populations (i.e., PMDD) and healthy populations, including application in a BN population.[12]

Status of Drug in Other Countries

To our knowledge, the proposed drugs have not been withdrawn in any other country.

1.3 Preclinical Data

Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, or antiglucocorticoid activity, and exhibits antiandrogenic activity.

1.4 Clinical Data to Date

Pharmacological Intervention. One human study used the same OC used in the current report: after 3-months of treatment, 14% of women no longer met criteria for a BN diagnosis and 29% had a reduction in symptoms from baseline.[12] OC can be effective treatments for PMS and PMDD (a more severe form of PMDD).[30, 31]

This is an open label study. After a baseline period, subjects will be administered the OC Drospirenone/Ethinyl-Estradiol continuously for 84 days (~12 weeks). OCs are being used for their intended function: to suppress ovulation. Because ovulation does not occur, the changes in ovarian hormones that occur post-ovulation during a natural menstrual cycle will not occur. Subjects will be instructed to take OCs daily, at approximately the same time each day. Subjects will be instructed to choose the time of day that works best for their schedule (e.g., first waking up in the morning; before bed). However, we will suggest subjects take the pills immediately prior to bed in order to reduce the chance of potential uncomfortable side effects (e.g., nausea). To improve medication compliance, we will recommend subjects download a freely available menstrual cycle monitoring application, if they have a smart phone, which can be programed to send a daily reminder to take the birth control pill. Subjects will only take the active pills—thus, participants will be taking continuous cycle OC. This will ensure hormone stability is consistent whereas placebo pills allow for endogenous hormones to be secreted, followed by E2 withdrawal.

Recruitment and Retention. The investigative team has experience recruiting clinical populations for eating disorders research (i.e., Dr. Baker), for reproductive hormone challenges (i.e., Drs. Schiller and Girdler), and for continuous cycle OC studies specifically (Dr. Girdler). Thus, we will use recruiting methods that have been most successful for us in the past.

Use of OCs and preliminary data. We propose this pilot study in order to obtain pilot data of the effect of continuous cycle OCs on brain activation in response to reward and eating behaviors in women with binge eating. Thus, we do not have specific pilot data for the aims proposed here. However, there is compelling evidence an experimental design is the next logical step in ovarian hormone research in binge eating. Observational studies implicate ovarian hormones in neurobiology such that E2 is inversely and P4 is positively associated with binge eating in women with an ED as well as community samples of women without an ED.[4, 5] Further, studies consistently observe that, compared with the first half of the menstrual cycle, **the second half of the menstrual cycle (i.e., post-ovulation) is associated with binge eating**, both in women with BN and community samples of women.[4, 5] However, observational work is limited: 1) there is no manipulation: thus, causal conclusions cannot be made; 2) mechanisms have been limitedly addressed (and almost exclusively focused on genetic effects). Only with an experimental design can we begin to unravel the independent and mechanistic effects of ovarian hormones on binge eating—providing formative information about the nature of the hormone trigger on binge eating.

Co-I Schiller's early work on the effects of ovarian hormones on binge eating in women with BN provides the foundation for this study.[5] Increased binge eating and inappropriate compensatory behaviors (e.g., self-induced vomiting) were observed during the mid-luteal and premenstrual phases of the menstrual cycle compared with the follicular and ovulatory phase. For binge-eating frequency Z-scores were as follows: ovulatory -.37, follicular -.30, premenstrual -.08, mid-luteal .61. Symptom fluctuation was attributable to changes in E2 and P4: increases in binge eating were associated with decreases in E2 (-.13(0.05), $t(142.89) = -2.82$, $p<.01$) and increases in P4 (.15(0.04), $t(142.55) = 3.49$, $p<.001$), controlling for the effect of the other.

1.5 Dose Rationale and Risks/Benefits

Dose Rationale

The dose of OC chosen is an FDA-approved dosage. Further, this specific OC and dose have shown sensitivity to BN symptom change previously.[12] Thus, the drug protocol, route of administration, dosage, dosage regimen, and dosage period, mirrors FDA-approval for this drug and previous research studies using this drug in an ED population. We are not conducting this study to support a new indication, dose, or route of administration for

clinical use. Previous studies have also implemented Drospirenone/Ethinyl-Estradiol continuously and were deemed IND exempt (PI Girdler). Subjects in this proposal will take oral contracetive birth control of 84 continuous days. This represents an 'off label' use as the pill packs come with 7 days of inactive pills to induce bleeding. However, as described below, this 'off label' practice does not increase participant risk and frequently occurs as part of standard clinical practice.

Risks/Benefits

We do not expect serious adverse side effects associated with the pharmacological intervention. Randomized clinical trials have consistently established the safety and efficacy of OCs. OCs are widely prescribed medications in the population. Indeed, the CDC reports: of women using contraception, the OC pill is the second most common method used (with female sterilization being the most common) and approximately 13% of women aged 15-44 are using an oral contraceptive, and that most women use a contraceptive in their lifetime (https://www.cdc.gov/nchs/products/databriefs/db327.htm). Included in these numbers would be women with binge eating as binge eating is not a medical condition that is contraindicated for OC use (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021098s019lbl.pdf). Given the more recent availability of other methods of birth control (e.g., IUD, Depo Shot), the prevalence of OC use has decreased in the past decade. For example, from 2011-2013, 26% of women aged 15-44 were using an oral contraceptive (https://www.cdc.gov/nchs/data/nhsr/nhsr086.pdf). Second, OC are generally associated with limited side effects—so much so that **women in some states, *including North Carolina*, can purchase OCs over the Internet *without a physician's visit or physical exam*.** The medications are prescribed and mailed directly to the individual's home after answering a short online survey regarding medical history (similar to the screening survey our potential subjects will complete).

General side effects associated with combined (synthetic E2 and P4) OCs include: nausea, breast soreness, vaginal discharge, fluid retention, hypertension, and clotting abnormalities that have been associated with the estrogen component. Thromboembolic disorders including thrombophlebitis, pulmonary embolism, and cerebral and coronary thrombosis appear to occur with greater frequency in women taking OC. While the increased incidence of these disorders has been associated with the estrogen component, it is now believed that the progesterone component may contribute to the increased risk. There are relatively few reports associating OC with the development of carcinomas (vaginal, uterine, hepatic, and mammary) despite the vast use of these agents. Some reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies. There is a slight increased risk of heart attack and stroke (1.7 increased odds compared with non-users), yet the absolute risk is low.[32] This risk is primarily in smokers or women with other underlying risk factors such as hypertension, hypercholesterolemia, morbid obesity, and diabetes.

In clinical trials of Drospirenone/Ethinyl-Estradiol, the most frequent adverse reactions were: PMS (13.2%), headache/migraine (10.7%), breast pain/tenderness/discomfort (8.3%), nausea/vomiting (4.5%), abdominal pain/tenderness/discomfort (2.3%), and mood changes (2.3%). Of 2,837 women enrolled in the clinical trials, 6.7% discontinued the study due to an adverse reaction; the most frequent was headache/migraine (1.5%). Serious (but rare) adverse reactions included: depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma. In a clinical trial conducted by collaborator Dr. Girdler (NCT00927095) implementing Drospirenone/Ethinyl-Estradiol in a continuous fashion (as will be done here) in women with PMDD (n = 22) no serious adverse events were reported. The most common non-serious adverse events reported (>50%) were: low mood (77%), breast tenderness (68%), fatigue (63%), irritability (63%) GI symptoms (59%), and spotting (50%). Notably, subjects taking placebo reported similar rates of side effects as those randomized to continuous Drospirenone/Ethinyl-Estradiol, with some side effects being observed *at a higher rate in those women taking placebo* (e.g., 83% of subjects on placebo reported headaches, 75% reported breast tenderness, 62% reported

low mood). Thus, it is very likely some of the reported side effects are due to the participant's expectations regarding publicized OC side effects.

In this proposal, subjects will take the OCs continuously. Drospirenone/Ethinyl-Estradiol 3/.03mg is provided in a 21/7 regimen that includes a hormone free interval of inactive pills. The continuous use of Drospirenone/Ethinyl-Estradiol by Dr. Girdler did not require an IND application to be submitted. Regardless, OCs have been prescribed 'off label' by physicians to be taken in a continuous fashion for decades. In one survey, 70% of providers reported prescribing cyclic OCs in a continuous manner.[33] The advent of OCs marketed for continuous cycle use are not new concepts. Continuous cycle use was first studied in the 1960's and, as stated, cyclic OCs are frequently prescribed to be taken continuously in order to treat menstrual disorders such as menorrhagia, dysmenorrhea, endometriosis, PMS, PMDD, and for convenience. The introduction of continuous cycle OCs allowed for OCs taken continuously to be covered by insurance: the challenge with 'off label' continuous use of OCs is that some insurance companies will not cover the extra pill packs required due to the placebo pills being skipped. Otherwise there is no difference between OCs marketed for continuous use vs. for cyclic use.

Continuous cycle OCs marked for continuous use and traditional cyclic OCs work the same way and each contain an estrogen and progestin component. The metabolic, hormonal, and endometrial effects of continuous cycle and cyclic OCs are also similar. OCs were initially designed to mimic the natural menstrual cycle and to induce a bleed monthly. However, this bleed is not a true menses as ovulation does not occur but is a withdrawal bleed due to endometrial shedding. This shedding does not represent menstruation and there is no health benefit or biological reason for a monthly 'period.' For example, the Faculty of Sexual and Reproductive Health Care in the United Kingdom released updated treatment guidelines stating that it is safe and effective for women to skip the placebo interval and take cyclic OCs in a continuous fashion: because continuous cycle OCs are not currently available in the United Kingdom, the Faculty of Sexual and Reproductive Health Care recommended tailoring cyclic OCs to extended regimens by instructing patients to skip the placebo week (https://www.fsrh.org/standards-and-guidance/documents/combined-hormonal-contraception/).

Additionally, when OCs are taken continuously, there will not be a HFW during which time endogenous E2 can begin to develop and cause E2 withdrawal to occur each month. Continuous cycle OC without a HFW may actually lead to less side effects compared with traditional 21/7 regimens. A Cochrane review[34] indicated that women on continuous OC have less headaches, genital irritation, tiredness, bloating, and menstrual pain. Further, there were no differences observed in contraceptive efficacy, safety profiles, compliance, discontinuation rates, or patient satisfaction between continuous and cyclic users. The most common side effect of continuous cycle OCs is breakthrough vaginal bleeding.

Finally, OCs containing Drospirenone may represent an increased risk of blood clots compared with OCs which contain other synthetic forms of progestin. However, the FDA just approved a Drospirenone-only OC.After an investigation into this increased risk, the FDA required the following on drug labels for OCs containing Drospirenone:

- A 'black box' warning added to the prescribing information that women > 35 who smoke should not take OCs (which is a recommendation across all OCs)
- A revision of drug labels to include that "some, *but not all*, epidemiological studies report up to a 3-fold increased risk in blood clots for OCs containing drospirenone compared with OCs containing other synthetic progestins, whereas other epidemiologic studies found no additional risk of blood clots with drospirenone"

- A summary of the FDA-funded study of blood clot risk on the drug labels (https://www.fda.gov/media/82335/download)

The FDA funded a study to examine increased blood clot risk with Drospirenone. Findings of the FDA-funded study include:

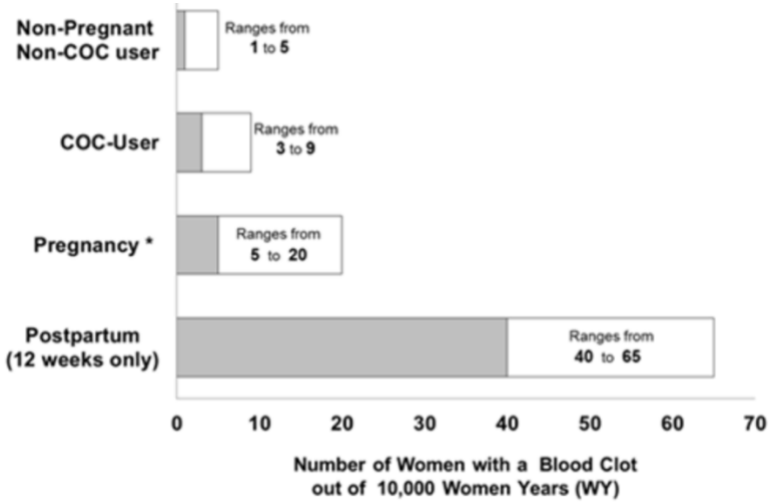
1. 1.74 times increased risk of VTE in women taking drospirenone versus a low-dose estrogen only OC;
2. 2-times increased risk for VTE in the first 3-months of use in women taking drospirenone who were new OC users;
3. Arterial thrombic events were increased in drospirenone but only in women > 35;
4. Drospirenone was not associated with cardiac arrhythmias, acute myocardial infarction, or cardiovascular death.

Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Current Users of Yasmin* Compared to Users of Oral Contraceptives that Contain Other Progestins

Epidemiologic Study (Author, Year of Publication) Population Studied	Comparator Product (all are low-dose COCs; with ≤ 0.04 mg of EE)	Hazard Ratio (HR) (95% CI)
i3 Ingenix (Seeger 2007) Initiators, including new users[a]	All COCs available in the US during the conduct of the study[b]	HR: 0.9 (0.5-1.6)
EURAS (Dinger 2007) Initiators, including new users[a]	All COCs available in Europe during the conduct of the study[c]	HR: 0.9 (0.6-1.4)
	Levonorgestrel/EE	HR: 1.0 (0.6-1.8)
*FDA-funded study" (2011)		
New users[a]	Other COCs available during the course of the study[d]	HR: 1.8 (1.3-2.4)
	Levonorgestrel/0.03 mg EE	HR: 1.6 (1.1-2.2)
All users (i.e., initiation and continuing use of study combination hormonal contraception)	Other COCs available during the course of the study[d]	HR: 1.7 (1.4-2.1)
	Levonorgestrel/0.03 mg EE	HR: 1.5 (1.2-1.8)

When OCs containing drospirenone were compared with OCs containing the same amount of ethinyl estradiol for VTE events, fewer significant differences were observed. Notably, this report also concluded that the transdermal patch and the vaginal ring are associated with increased VTE events compared with other low dose OCs. The FDA report does conclude a higher risk for VTE in OCs containing drospirenone compared with some other OCs, yet because the report was cross sectional in nature definitive conclusions cannot be drawn about the cause of the VTE events. For example, the author's note a significant limitation of the study is the absence of key confounding factors such as BMI, obesity status, smoking, and family history—which play a significant factor in VTE risk. In contrast however, The European Active Surveillance study on Oral Contraceptives,[35] a large prospective cohort study, found no increased risk of VTE or ATE associated with drospirenone compared with other combined contraceptives. Other studies also showed no increased risk for drospirenone compared with other OCs.[36, 37]

Although drospirenone may represent an increased risk of blood clots compared with some other OCs, as stated, *all OCs represent an increased risk* and this increased risk is not unique to drospirenone. Older, 'first/second generation' progestins appear to have a lower risk, whereas the new 'third/fourth generations' (e.g., desogestrel, gestodene, drospirenone) appear to have a higher risk compared with the first generation progestins. For example, across various progestin formulations available, risk for VTE were as follows:[38] desogestrel (4.28), gestodene (4.27), drospirenone (4.12) and cyproterone (4.27) compared with levonorgestrel (2.38), norethisterone (2.56), and norgestimate (2.53) whereas the increased risk for VTE with any



OC exposure is approximately 3, compared with no OC exposure.[32, 38] The benefit of the later generation progestins is the decrease in androgen effects, which are primarily responsible for the negative side effects associated with OC (e.g., acne, weight gain). Newer progestins tend to have a lower androgen effect or even an anti-androgenic effect (i.e., drospirenone). Drospirenone is the only anti-androgen OC available. It is also important to note that, despite the increased risk, the absolute risk of VTE while taking OCs is still minimal and a rare occurrence. For example, the risk of a blood clot during pregnancy or post-partum is significantly greater (**Figure**).

Women who binge eat are not at increased risk for side-effects or decreased acceptability to take OC. Indeed, a previous study suggests the specific OC used here may be beneficial for BN symptoms and did not report the occurrence of any serious adverse events. Further: given the prevalence of binge eating is up to 15% in the population, a substantial portion of the general population prescribed OCs include women with an eating disorder or who binge eat.

After discontinuing OCs, menses generally resumes within 60 days for 95% of women. OCs have no long-term effects on fertility or reproduction.

2 Study Objectives

The objective of this study is to examine the impact of stopping ovulation/ovarian hormone stabilization, through the continuous administration of OCs for 3-months, on brain activation in response to reward and eating behaviors in women who binge eat (n=15) using functional magnetic resonance imaging (fMRI). Participants will complete fMRI imaging and self-report questionnaires prior to OC administration and at the end of OC administration. We will examine within-subject changes that occur in these measures with OC administration.

Results will ultimately provide the pilot data necessary for larger mechanistic trials. We plan to accomplish the objective of this application by pursuing the following specific aims:

Aim 1: Quantify the effect of ovarian hormone stabilization on eating behaviors in women with binge eating.

Aim 2: Examine the effect of ovarian hormone stabilization on response to reward using fMRI and self-report questionnaires in women with binge eating.

3.1 General Design

This 16-week single-site study includes 4 primary visits, the hormone manipulation, and two check-in visits. The experimental protocol will last 3-months with a single follow-up assessment. Participants will undergo screening and consent (T0), a baseline assessment (T1), testing at the end of the experimental phase (T2), and a follow-up assessment one month post-intervention (T3). There will also be two check-in visits, approximately every 4-weeks during OC administration, to assess side effects and compliance. FMRI sessions will occur at T1 and T2. The study timeline is depicted in **Figure 2**, and the specific procedures that will take place are outlined in **Table 2** and detailed below in Section 6.

3.2 Outcome Variables

The primary endpoints for the Specific Aims are: 1) self-reported binge eating; 2) brain activation in dopamine-reward pathways, ROI include: nucleus accumbens, dorsal striatium, and DLPFC. Secondary end points include self-report measures of reward.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Participants will be women aged 18-34, normal weight, and engage in binge eating behaviors. Underweight individuals (BMI < 18.5) and overweight individuals (BMI > 31) will be excluded due to empirical reasons (i.e., the hypothesized mechanism may act differently in underweight EDs) and subject safety (e.g., increased risk of blood clots), respectively. Only participants capable of giving informed consent and understanding the risks associated with the study will be enrolled. Participants will be compensated upon completion of the study.

Inclusion Criteria.
1) Current binge eating;
2) Age 18-34;
3) Regular menstrual cycle for at least 3-months;
5) Free of medication or medical illness that is contraindicated for use with the study medication;

4.2 Exclusion Criteria

Patients will not be permitted to enter this protocol if they meet any of the following. Notably, the individual factors that are associated with heightened risk for serious side effects from OCs are part of the exclusion criteria (i.e., smoker, 35+ years of age, hypertension, obesity, blood clotting disorder, liver/kidney/adrenal disease). The exclusion criteria used here are *much more conservative than used in the general practice of prescribing OCs.*

- any foreign metal objects or implants in your body as determined by the safety questionnaires (due to fMRI)
- use of birth control or hormones in the past 3-months
- hormonal contraceptives that are implanted (i.e. progestin IUD or implant)
- current pregnancy, lactation, or < 12-weeks postpartum
- previous serious, negative reaction to birth control
- current cigarette smoker
- < 18.5 BMI > 31
- history of bipolar disorder or psychotic episodes
- previous suicide attempt
- abnormal/undiagnosed vaginal bleeding; endometriosis
- recurrent migraine headaches or headaches with focal neurological symptoms
- hypertension or vascular disease (i.e., coronary artery disease, congestive heart failture, cerebrovascular disease)
- diabetes or other circulation problems
- blood clotting disorder

- porphyria
- breast, uterus/cervix, or vaginal cancer
- medical condition or medication use that increases serum potassium levels (including frequent laxative or diuretic use)
- high cholesterol
- history of VTE, DVT, PE, phlebonthrombosis, coronary thrombosis, thromboembolism, thrombophlebitis, or any type of blood clot or blood clot disorder (e.g., thromboembolic disease, Factor V Leiden), protein C or S deficiency, heart attack or stroke, atrial fibrillation, heart, liver, kidney, or adrenal disease, endocarditis, liver cancer, malignant melanoma, cholecystitis or pancreatitis, VTE or jaundice caused by pregnancy or birth control pills, recent significant period of immobility (e.g., pregnancy bed rest)
- Women determined to have any other symptoms, or any other potential contraindicated condition, that may impact their safety during the protocol will also be excluded from participation.

Pregnant women will be excluded from participation and women who become pregnant (although unlikely) will be withdrawn. Prior to enrollment, a pregnancy test will be completed. Heterosexual participants will be asked to use non-hormonal forms of birth control (e.g., barrier methods) to avoid pregnancy during this study. If a woman becomes pregnant during the study, participation will be discontinued.

4.3 Subject Recruitment and Screening

Methods of recruiting for this study include:

We will utilize recruitment methods that have been highly successful in the past including:

1) **Recruiting directly from the UNC Center of Excellence for Eating Disorders (CEED) outpatient treatment and research program**: CEED evaluates between 200-220 new patients per year and has an excellent track record of successful recruitment of women with EDs for research studies.[39] Specifically, we will recruit women from the CEED via flyers, brochures, and direct recruitment by speaking with women who expressed interest in research on their referral form. In a recent clinical treatment trial for BN,[39] 214 women contacted study staff and completed the phone screen and 80% were randomized.

2) **Established research registries at CEED and within the Department of Psychiatry at UNC:** CEED houses a research registry, which any member of the community (including current CEED patients) can join and consent to be contacted about future studies. There are currently 535 individuals signed up for the registry. CEED also has a registry of previous research study participants who consented to be re-contacted for future studies. Additionally, Dr. Schiller has an established registry of individuals (3,000+) who previously completed online screening questionnaires for her hormone manipulation studies who agreed to be contacted for future studies.

3) **Targeted social media and website advertisements** (e.g., Facebook; ResearchMatch.org; Craigslist): In past studies, we have found social media to be an extremely effective strategy for recruitment at CEED.[40, 41]

4) **Flyers, brochures, and mass emails**: these will be disbursed in UNC Hospitals, across the university, across the larger community, and with established community partners who allow us to advertise and recruit for active studies (e.g., local medical offices). Mass emails will be sent monthly.

5) **Large-scale research registries:** UNC houses two large-scale research registries available to researchers: The Carolina Data Warehouse (CDW), a central data repository containing clinical, research, and administrative data sourced from the UNC Health Care System, and the website Join the Conquest. Within CDW currently, 557 female patients aged 18-35 have a diagnosis of BN within the medical record, with 151 of these diagnoses being made since 2017.

6) **NC TraCS Research Recruitment Service**: We will capitalize on the TraCS Research Recruitment Service's expertise in enrolling members of communities historically under-represented in research.

Eligibility screening will include:

- An initial phone or online screening that includes questions about past medical and mental health history to assess potential participants eligibility based on the criteria listed in sections 4.1 and 4.2.
- Participants will undergo a Clinical Screening Process to determine whether they are eligible to participate in this study.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Participants with significant clinical abnormalities will not be enrolled in the study or discontinued from the study.

Participant safety will be managed in several ways. First, risk is managed through study eligibility criteria. **The eligibility criteria used here are much more stringent than is used in general practice when prescribing OCs.** Once medication administration begins, subjects will complete weekly surveys that assesses the presence and intensity of symptomatology and side effects. This will include items related to mood, eating disorder symptoms, and OC side effects. The questionnaire will be completed online by subjects, and ratings will be transmitted to the study team in real-time. Members of the study team will receive immediate notification if a subject endorses active risk or severe adverse effects on the study form. Subjects will be contacted directly by Dr. Baker and an assessment will be conducted. If a subject does not complete the weekly form, a member of the study staff will contact them and conduct a safety assessment over the phone. Third, participants will complete a monthly visit to assess side effects and compliance. During monthly visits, mood symptoms will be monitored by administering the IDAS and eating disorder symptoms will be monitored with the EDEQ.

If a subject is deemed at elevated suicide risk at the enrollment appointment, they will not be enrolled in the study. If a subject is deemed at elevated suicide risk after study enrollment, they will be discontinued from the study protocol. Although we will not provide treatment or pay for treatment costs for subjects who are discontinued from the study, we will ensure subjects have appropriate treatment contacts and the risk is managed before terminating contact with the subject. For example, subjects deemed at emanate risk will be escorted to UNC Hospitals Emergency Department.

Any patient experiencing clinically significant and untolerable physical side effects will be discontinued. Any patient who is non-compliant with the medication will also be discontinued. This study will not provide treatment or pay for medical or psychological treatment costs for subjects. Patient's needing medical care will be referred to their primary care physician or provided appropriate referrals.

Should an AE occur, we will comply with reporting requirements for adverse events. As Principal Investigator, Dr. Baker will be responsible for the documentation, investigation, and follow-up of all study-related AE. All AE will be reported according to IRB guidelines. All moderate or severe AE will be reported to the UNC IRB within 7 days.

Because this is an open label study with no blinding and Dr. Baker has direct access to all data collected, PI Dr. Baker will primarily oversee subject safety, in collaboration with study co-investigators, and make the determination of when to withdraw subjects.

5 Study Drug

5.1 Description

Drug	Dosage	Formulation
Drospirenone Ethinyl-Estradiol 3/.03mg (oral contraceptive) **Drospirenone** Active ingredient: synthetic progestin Chemical name: 1,2-dihydrospirorenone **Ethinyl-Estradiol** Active ingredient: Ethinyl Estradiol Chemical name: 17-ethinyl-3, 17-estradiol	3/0.03 mg daily	Oral tablet

5.2 Treatment Regimen

Participants complete a 84-day regimen of Drospirenone .30mg Ethinyl-Estradiol .03mcg. Subjects will begin OC administration on the first day of their period after the T1 visit. OCs will be taken continuously for 84 days.

5.3 Method for Assigning Subjects to Treatment Groups

All subjects will receive the same drug protocol in an open label fashion—there will be no blinding or placebo.

5.4 Preparation and Administration of Study Drug

All study drugs will be stored, prepared and dispensed from the UNC Investigational Drug Service (IDS).

Contact:
Investigational Drug Service
Department of Pharmacy
UNC Hospitals
CB 7600, Room 3001
101 Manning Drive
Chapel Hill, NC 27514
Office: 919-966-1766
Fax: 919-966-6359

5.5 Subject Compliance Monitoring

We will monitor participants' compliance through self-report and by counting the remaining pills at person visits.

5.6 Prior and Concomitant Therapy

Women are required to be free of any medications that influence ovarian hormones or are contraindicated for use with the study medications; however, prior medication usage will not preclude participation in the study.

5.7 Packaging

The UNC Investigational Drug Service will receive the active drug from their Pharmacy storeroom.

5.8 Blinding of Study Drug (if applicable)

N/A

5.9 Receiving, Storage, Dispensing and Return

The UNC Investigational Drug Service will receive the study drugs from the UNC Pharmacy Storeroom and will dispense the drug to the research coordinator to deliver to participants. Any unused drug will be returned to the UNC Investigational Drug Service.

5.9.1 Receipt of Drug Supplies

The research coordinator will be primarily responsible for picking up the prescription from IDS. Upon receipt, the coordinator will check the pill bottle to ensure the prescription is for the correct participant.

5.9.2 Storage

Medication will be stored at 20° to 25° C in a temperature-controlled facility.

5.9.3 Dispensing of Study Drug

Drugs will be dispensed in tight, light-resistant containers and defined in the USP, with a child-resistant closure.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

Overview. This single-site study will include 4 primary study visits and the OC administration (**Figure 2**). The experimental protocol will last 12-weeks and the entire study will last approximately 4-months with a single follow-up assessment. Participants will undergo screening and consent (T0), a baseline assessment (T1), testing at the end of OC administration (T2), brief testing monthly to examine side effects and protocol adherence, and a follow-up assessment one month post-intervention (T3). Participants will complete fMRI imaging and self-report questionnaires prior to OC administration and at the end of OC administration: T1 and T2. At the completion of the study and after T3, subjects will be given the option to meet with the study PI and discuss whether their ED symptoms changed during OC administration.

The study timeline is depicted in **Figure 2** in Section 3, and the primary procedures that will take place are outlined in **Table 2** and detailed below.

Table 2: Study Visit Procedures

Primary Study Procedures					
Procedure	**T0**	**T1**	**T2**	**T3**	**Monthly Visit**
Informed Consent	x				
Clinical Health Interview	x				
Venipuncture	x				x
Side Effects and Adherence			x		x
Self-report Questionnaires					
Demographics	x				
EPSI	x	x	x	x	x
BIS/BAS		x	x	x	
SPSRQ		x	x	x	
Kirby Delay Discounting Questionnaire		x	x	x	
fMRI Tasks					
MIDT		x	x		

Participants. Women between the ages of 18-34 with a normal weight binge-eating syndrome. All participants will undergo the same drug protocol in an open label manner.

OC Administration. Participants will begin taking OC for 84 days (i.e., 12-weeks) continuously on the first day of their period after T1. During the final two weeks of OC administration, T1 assessments will be repeated (T2).

Clinical Assessments. Specific study procedures, measures used to obtain primary and secondary outcomes, and the assessment schedule for the protocol are shown in **Table 2**. All study measures are empirically valid and reliable. The focus of this pilot study is on the primary outcomes of binge eating and brain activation in response to reward examined via fMRI.

Clinical Interviews

SCID-5: Structured Clinical Interview for DSM-5[42] will be administered by trained study staff at T0, and supervised by Dr. Baker, to confirm eligibility and assess lifetime comorbid psychiatric diagnoses. The ED module of the SCID-5 will be repeated at T2.

Self-report Questionnaires

Self-report questionnaires will be completed through secure, encrypted, online survey (i.e., Qualtrics), and scored by standard conventions. Primary and secondary outcome measures are bolded. Some measures are included to overlap an anticipated protocol for a larger study based off of these pilot data and due to previous studies showing they may be related to ovarian hormone sensitivity (i.e., they may predict who is sensitive to changing hormones); however, these measures will not be examined as outcomes in the current study. A long term goal of this line of work is to develop models to predict sensitivity to ovarian hormone fluctuations.

a) Demographics: at baseline, subjects will be asked to self-report relevant demographic information in order to address eligibility and to characterize the sample: age, race, ethnicity, marital status, and education level.
b) Life Events Checklist: will be completed at baseline only to obtain information on the number of adverse life events experienced by the participant. Previous studies have suggested that ovarian hormone sensitivity is greater in women with a history of adverse life events.[43] It will be included in the larger mechanistic trial.
c) UPPS-P Impulsive Behavior Scale: The UPPS-P Impulsive Behavior Scale[44] is a 59-item self-report questionnaire that assesses distinct dimensions of impulsivity. Here we include the negative urgency, lack of premeditation, and sensation seeking subscales. It will be completed at baseline only and be included in the larger mechanistic trial.
d) Inventory of Depression and Anxiety Symptoms (IDAS):[45] is a 64-item questionnaire that comprehensively assesses anxiety and depression symptoms, including ill temper, dysphoria, panic, social anxiety, appetite change, lassitude, well-being, suicidality, traumatic intrusions, and insomnia. The full IDAS will be given at T0. The dysphoria, suicidality, appetite, and well-being subscales will be given at the monthly visits to monitor subject safety.
e) Eating Disorder Examination Questionnaire (EDEQ): The EDEQ[46] is a self-report measure of ED symptoms. The EDEQ will be used as a distinct assessment measure to monitor subject safety at the monthly visits.
f) **Eating Pathology Inventory (EPSI):** The EPSI is a 45-item self-report questionnaire assessing various aspects of eating disorder symptomatology and will be included in order to obtain a more detailed examination of symptoms compared with frequency counts only. The EPSI includes eight subscales; however, we only include the following subscales in the current project: binge eating, body dissatisfaction, cognitive restraint, purging, excessive exercise, and restricting. A majority of the previous studies to date examining symptom change over the menstrual cycle have focused on symptom-scores, including pilot data from our own group using the EPSI.[41]
g) Three-Factor Eating Questionnaire-Hunger (TFEQ-Hunger) Subscale: The TFEQ-Hunger subscale[47] will be used to assess self-reported hunger. It will be included in the larger mechanistic trial.
h) EEI: The Eating Expectancies Inventory (EEI) will be given at T1. The EEI measures learned expectations about eating and contains five subscales. We include the eating helps manage negative affect, eating is useful as a reward, and eating leads to feeling out of control subscales. It will be included in the larger mechanistic trial.
i) Perceived Stress Scale (PSS): The PSS is a 10-item measure of general stress. It measures the degree to which situations in one's life are percieved as stressful. It measures perceived stress over the past month. It will be completed at T1 and addressed as a potential predictor of hormone sensitivity in the larger mechanistic trial.
j) **Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS):** The BIS/BAS Scales [48] is a 24-item measure designed to measure behavioral inhibition and behavioral activation. It is comprised of four subscales: BIS, Reward Responsiveness, Drive, and Fun Seeking, and 20 items total that assess behavioral inhibition and behavioral activation. Primary outcome of interest is the behavioral inhibition subscale. The BIS/BAS scales are associated with neural markers of psychopathology.
k) **Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ):** The SPSRQ[49] is a 48-item self-report questionnaire used to assess sensitivity to reward and sensitivity to punishment. Primary outcome of interest is the sensitivity to reward subscale.
l) **Kirby Delay Discounting Questionnaire:** is a measure of temporal discounting. Participants complete a series of 27 questions that each require choosing between a smaller, immediate monetary reward today versus a larger reward later. An individual's rate of delay discounting is quantified using a hyperbolic discounting function:

$$V = A/(1 + kD),$$

where *V* is the present value of the delayed reward *A* at delay *D*, and *k* is a free parameter that determines the discount rate. The higher one's discount rate (*k*) is, the more they discount larger future rewards. An example of applying this formula: ("$31 today" or "$85 in 7 days"), where *V* = $31, *A* = $85, and *D* = 7. Solving for *k* generates the listed *k* value of .25. Syntax has been created to calculate the k parameter from questionnaire responses.[50]

Scoring for Primary and Secondary Outcomes Self-report Questionnaires			
Scale	**Likert Scale**	**Minimum Score**	**Maximum Score**
EPSI	5 point		
Binge eating		0	32
BIS/BAS	4 point		
Behavioral inhibition		7	28
SPSRQ	2 point(T/F)		
Sensitivity to reward		0	24

Functional MRI

The following task, along with a resting scan, will be included in each of the two, one hour-long fMRI sessions:

a) **Monetary Incentive Delay Task (MIDT)[51]:** Two event-related MID runs consist of 6-second trials during which women will be presented with a cue shape, a fixation crosshair (for variable duration), the target, and performance (win/loss/neutral) feedback. Cues indicate whether it is an incentive (gain, loss) or non-incentive trial. In incentive trials, women can gain or lose money by pressing a button during target presentation; difficulty is based on individual reaction times. MIDT defines reward response as the average speed of responses to reward vs. non-reward trials during a reward task. The MIDT will be completed in the fMRI scanner. A resting state FMRI will also be completed.

b) Positive Affect Negative Affect Schedule: The PANAS[52] is a 10-item questionnaire that measures current positive and negative affect. The measure will be given to subjects prior to the fMRI task.

c) Food Intake: We will ask women to self-report their food intake prior to fMRI. Detailed information will be obtained so that estimated caloric intakes can be determined based on the provided information as well as the number of meals and snacks eaten.

FMRI Data Acquisition and Image Processing:
Scanning is performed using a Siemens Prisma scanner at the UNC BRIC. High-resolution, T1-weighted anatomical images will be acquired using an MPRAGE sequence. Whole-brain functional images will be acquired using a single-shot, gradient recalled echoplanar pulse sequence sensitive to blood-oxygen-level-dependent (BOLD) contrast. Each of 2 runs will consist of the acquisition of 195 successive brain volumes. fMRI image preprocessing, processing, and analysis will be conducted using FSL and custom MATLAB scripts. FMRI analyses will include an event-related BOLD response analysis within a priori ROI. Contrats of interest will include win vs. non-win outcomes. Mr. Bizzel will be responsible for FMRI data acquisition and initial imaging processing and provide the data to Dr. Schiller for analysis.

Daily and Weekly Symptom Assessment

a) **Daily/Weekly Rating Form:** We created a survey for daily and weekly assessment of symptoms based off of the 20-item DSRP[36] and the 6-item Short Evaluation of Eating Disorders (SEED). The DSRP was designed to assess the presence and intensity of physical and mood symptoms that

accompany ovarian hormone changes whereas the SEED was developed to monitor ED symptom change. Generally, these measures were combined in order to address ED symptoms and physical/mood symptoms. Prior to OC administration, subjects will complete this monitoring form daily in order to capture symptoms during a natural menstrual cycle. During OC administration, participants will complete this form weekly. **During medication administration, ratings will be transmitted to the study team in real-time to monitor safety.**

Assessment Schedule.

Eligibility. Interested participants will initially complete an online screening survey to assess potential eligibility. No more information than required to determine an accurate representation of eligibility will be collected. This can also be completed by telephone interview if needed. Women who screen eligible on the survey and are interested in participating in the study will be contacted by a member of the study staff to schedule a screening assessment to confirm eligibility and review consent. This is done in order to decrease participant burden (having clearly ineligible individuals complete an in-person screening).

Screening (T0). At this initial screening visit (T0), consent forms will be reviewed, eligibility confirmed, and clinical interview completed. A Clinical Health Screening will be completed to examine inclusion/exclusion criteria. For those participants who appear eligible, blood will also be drawn and a pregnancy test completed prior to enrollment. Similar to our previous studies, this will include a laboratory panel (CMP) and cholesterol. Prior to final enrollment, the investigative team will review the findings of the Clinical Screening to determine appropriateness and eligibility for the study.

After enrollment, participants will complete the Daily Symptom Assessment for one menstrual cycle. This form will be completed each morning and ask questions about the previous day. We expect the completion of the Daily Symptom Assessment to take no longer than 5 minutes. During the screening period, participants will also be given ovulation test kits to use in home. This will pinpoint when during the subject's menstrual cycle ovulation occurs, so that the mid-luteal phase can be determined (see below for more details).

Baseline (T1). Prior to beginning OC administration, participants will complete a baseline assessment including self-report questionnaires. The baseline fMRI will also occur at this visit. This visit will be scheduled during the mid-luteal phase of the subject's menstrual cycle as this is when symptoms are expected to be at their "worst." The mid-luteal phase will be determine via the ovulation test kits provided to each subject. Beginning with OC administration, subjects will begin the Weekly Symptom Assessment (similar to the Daily Assessment but completed Weekly). Based on anticipated risk-benefit ratio and participant burden, we have subjects complete this form only weekly during medication administration. Given side effects for OCs are expected to be relatlively minimal (if present at all), having subjects complete this form daily for 12-weeks would represent significant and unnecessary participant burden.

End-of-OC administration (T2). During the last two weeks of OC administration, participants will repeat the study procedures from T1, including fMRI.

Side Effects. Two check-ins with study staff will occur during the 84 day OC administration period—approximately 4-weeks after OC administration begins and approximately 8-weeks after OC administration begins (i.e., monthly). During these check-ins, side effects and protocol adherence will be monitored. During the first check-in visit (4-weeks post-OC administration), a basic metablic panel will be redrawn.

Follow-up (T3). One month after study completion, a brief online follow-up assessment will be completed by participants to assess symptoms after discontinuation of study medications. At the completion of the study and after T3, subjects will be given the option to meet with the study PI and discuss whether their ED symptoms changed during OC administration.

7 Statistical Plan

The project coordinator and Dr. Baker will be the primary database managers. Dr. Schiller will oversee the processing of the neuroimaging data. Dr. Baker will oversee the completion of Aims 1-2 and Dr. Schiller will oversee Specific Aim 3.

7.1 Sample Size Rationale

This is a pilot study to obtain pilot data for larger studies. One goal of any pilot study is to obtain variance estimates so sample sizes for a larger study can be determined. Because this is a pilot study, we do not focus on significance (p<.05). Nonetheless, our own research supports a large effect of ovarian hormones on binge eating[5] (our primary Aim): in linear models, E2 and P4 accounted for R^2=24% of the variance in binge eating and within-subject correlations[5] between E2 and binge eating indicate a maximum Cohen's d=1.4 and between P4 and binge eating a maximum Cohen's d=1.7. Calculating power based on the effect of P4 on binge eating[5] (d=1.7; given that the effect of OC administration on binge eating is hypothesized to occur via the abensce of P4), n=15, and alpha=.05, we have >95% to detect an effect.

Further, a general power calculation (estimating the required effect size to determine a significant effect with a projected sample size), with a projected sample of n = 15, an effect size of .77 is required to detect a treatment difference at a two-sided .05 significance level at 80% power (calculated in G*Power based off of projected sample size and desired power).

Finally, we take steps to reduce missing data by having the study coordinator review all in-person assessment measures for completeness and skipped items.

7.2 Statistical Methods

Statistical analyses are completed using the most recent version of SAS.[53] Primary outcome measures are self-reported binge eating and brain activation in response to reward examined via fMRI (see below). All assessment measures are empirically valid. Measures will be scored according to standard conventions and scoring procedures and are primarily continuous. Descriptive statistics and graphics will be used to screen for errors, outliers, and potential influential observations and to check distributional assumptions.

PRIMARY OUTCOMES

Binge eating will be defined as: 1) the EPSI subscale binge eating score (T1, T2), which represents a continuous score of symptoms over the previous month (higher scores indicate more symptoms); 2) weekly binge eating frequency based on the weekly assessment (higher scores indicate greater frequency). **Reward response** will primarily be defined by brain activation (BOLD signal) in response to the MIDT as measured by fMRI. Specifically, brain activation in dopamine-reward pathways, ROI include: nucleus accumbens, dorsal striatium, and DLPFC.

SECONDARY OUTCOMES

Self-report questionnaires of reward responsivity. The **BIS/BAS**, **SPSRQ**, and **Kirby Delay Discounting** will be included as self-report measures of reward response. Specifically, we will include the behavioral inhibition subscale of the BIS/BAS as self-report correlate of the reward response. The SPSRQ will be used to assess sensitivity to reward sensitivity. Kirby Delay Discounting will be defined by the individual's rate of delay discounting (k).

Hypotheses. Our overarching hypothesis for the following aims is that post-ovulation changes in ovarian hormones are responsible for the changes in binge eating observed across the menstrual cycle and that the mechanism underlying this change in change in brain activation in response to reward. Thus, we hypothesize

that OC will be beneficial for the primary outcomes of interest. We hypothesize "benefical" may manifest in one of two ways: *hypothesis 1a:* symptomatology *decreases* from OC use or *hypothesis 1b:* variability of symptoms that occurs during a natural menstrual cycle does not occur with OC use.

As such, our null hypothesis is that there is no effect of OC on behaviors of interest.

Aim 1: Investigate the effect of ovarian hormone stabilization on eating behaviors in women with binge eating.

Null hypothesis: There is no effect of birth control on binge eating.
Alternative hypothesis: Birth control administration directly changes binge eating behaviors.

Dependent variable: binge eating (EPSI subscale, weekly binge eating frequency)
Independent variable: treatment condition (T1 vs T2)

Analysis
A paired sample t-test will compare within-person change between pre- and post-intervention outcomes (EPSI subscale score; weekly frequency). Binge eating variability/fluctuation pre- and post- intervention is tertiarily explored by plotting weekly variance estimates in reported binge eating frequency.

Aim 2: Examine the effect of ovarian hormone stabilization on brain activation in reward pathways in women with binge eating.

Null hypothesis: Birth control has no effect in reward pathways in women with binge eating as measured by fMRI.
Alternative hypothesis: Birth control administration has a measurable difference on brain activation in reward pathways in women with binge eating as measured by fMRI.

Dependent variable: ROI: nucleus accumbens, dorsal striatium, and DLPFC.
Independent variable: treatment condition (T1 vs T2).

> Dependent variable (percent signal changed in ROI): Nucleus accumbens, dorsal striatium, and DLPFC connectivity will be assessed during the MIDT fMRI task at study visits T1 and T2. Functional connectivity expresses the statistical dependency among activations in different brain regions and results in undirected (symmetrical) connectivity matrices and will be calculated according to standard procedures (Walsh et al., 2017). We will use a generalized psychophysiological interaction (gPPI) approach for detecting context-dependent functional connectivity (Cisler, Bush, & Steele, 2014; McLaren, Ries, Xu, & Johnson, 2012). Replicating the methods of Walsh et al. (2017), we will use an ROI approach to target the nucleus accumbens, dorsal striatium, and DLPFC, which will be defined using the Harvard-Oxford subcortical atlas. Voxel-wise models will be used to evaluate connectivity. For each participant, mean fMRI time courses will be extracted using the "fslmeants" program in FSL, then multiplied by each psychological regressor of interest (i.e., task condition) to form the PPI interaction terms. The gPPI model will include physiological and psychological regressors, as well as their interaction terms to describe the unique effect of these interactions above and beyond the main effects of seed time courses and task conditions. Our primary contrast of interest will evaluate the difference between connectivity during presentation of reward versus non-rewarding stimuli. Contrasts of interest will include win vs. non-win outcomes.This allows for the characterization of connectivity patterns specific to reward response.

Analysis: Treatment phase differences will be evaluated with respect to seed-based connectivity specific to reward processing using a paired t test.

Secondary outcomes will be analyzed as described in Aim 1: paired t test will compare within-person change between pre- and post-intervention. Reward responsitivity (BIS/BAS, SPSRQ, Kirby Delay Discounting) will be the dependent variable and treatment condition the independent variable.

We will also tertiarily explore Pearson correlations between activation signals and change in brain activation and change in binge eating between T1 and T2. Binge eating will be defined by the EPSI subscale score. Reward response will include brain activation in ROI.

Missingness. We will use multiple imputation to correct for data determined to be missing at random, given that it is a reliable method for obtaining valid inferences in both behavioral and fMRI research (Rubin, 1987; Vaden, Gebregziabher, Kuchinsky, & Eckert, 2012). Data for any dropouts will be compared with data for those who complete the study to determine the extent to which excluding their data will introduce selection bias, and selection bias will be identified as a weakness in any resulting publications or presentations. Finally, as described above, we take steps to reduce missing data by having the study coordinator review all in-person assessment measures for completeness and skipped items. If missing data is considertable, which we consider unlikely for the data collected in person at study visits, longitudinal analysis via linear mixed-effects models will be implemented.

Sensitivity Analysis. In addition to the statistical tests described above, we will tertiarily use sensitivity analyses to evaluate the robustness of the main results of the study to reasonable perturbations of the statistical methods and assumptions used and to help ensure reproducibility of the main results. Sensitivity analysis will address the inclusion/exclusion of questionable data values (i.e., outliers), the use of alternative methods of coping with missing values and dropouts, and modeling assumptions. We will additionally examine whether associations differ based on specific ED diagnosis or frequency of binge eating behaviors at baseline.

7.3 Subject Population(s) for Analysis

Studies consistently observe post-ovuation exacerbations of binge eating in both women with and without a clinical ED. Thus, our sample population of women with a binge-eating syndrome is empirically supported.

8 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

9 Study Finances

9.1 Funding Source

This study is financed through a private foundation grant through the Foundation of Hope, Raleigh, NC.

9.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) will have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All UNC investigators will follow the University conflict of interest policy.

9.3 Subject Stipends or Payments

Participants will be compensated up to $200 upon completion of the study. Payment is processed through the UNC Department of Psychiatry. Only participants who complete all study activities as outlined below will receive the full $200. This will be clearly outlined and stated in the informed consent. If a participant is withdrawn due to an adverse event, they will be provided prorated comepensation.

Payment will be made in the below increments, with a majorty occurring at T2. All potential participants will receive $10 for completing the enrollment visit (T0), regardless of their final eligibility for the study.

	Total Amount	**When Recieved**
Enrollment Visit (T0)	$10	Completion of T0
Screening Period and Ovulation Testing	$10	Completion of T2
First fMRI Visit (T1)	$70	Completion of T2*
Check-in Visits (x2): $5.00 each	$10	Completion of T2
Second fMRI Visit (T2)	$70	Completion of T2*
Medication Adherence and Weekly Survey Completion $0.90 per weekly survey (12 surveys); $0.10 per day for medication compliance (84 days). Total: $19.80, rounded to $20 for 100% compliance	$20	Completion of T2
Follow-up (T3)	$10	Completion of T3
*participants will receive a porition of T1/T2 incentive immediately at the T1/T2 visit as part of their participation in the MIDT. During the MIDT, participants can "win" money. Money won during the task is given to particpants immediately, at the end of the study visit (this is what makes the task "rewarding"). This will be subtracted from their total incentive for participation, so that the total amount of money that can be received is $200 for everyone.		

10 Publication Plan

The results of this proposal will be published in the scientific literature and presented at relevant conferences. The trial will be registered with clinicaltrials.gov.

11 References

1. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition*2013, Washington, DC: American Psychiatric Press.
2. Baker, JH, Girdler, SS, and Bulik, CM. The role of reproductive hormones in the development and maintenance of eating disorders. Expert Rev Obstet Gynecol. 2012;7(6):573-583.
3. Klump, KL, Culbert, KM, and Sisk, CL. Sex Differences in Binge Eating: Gonadal Hormone Effects Across Development. Annual review of clinical psychology. 2017;13:183-207.
4. Klump, KL, Keel, PK, Culbert, KM, and Edler, C. Ovarian hormones and binge eating: exploring associations in community samples. Psychol Med. 2008;38(12):1749-1757.
5. Edler, C, Lipson, SF, and Keel, PK. Ovarian hormones and binge eating in bulimia nervosa. Psychol Med. 2007;37(1):131-141.
6. Lester, NA, Keel, PK, and Lipson, SF. Symptom fluctuation in bulimia nervosa: relation to menstrual-cycle phase and cortisol levels. Psychol Med. 2003;33(1):51-60.
7. Price, WA, Torem, MS, and DiMarzio, LR. Premenstrual exacerbation of bulimia. Psychosomatics. 1987;28(7):378-379.
8. Gladis, MM and Walsh, BT. Premenstrual exacerbation of binge eating in bulimia. Am J Psychiatry. 1987;144(12):1592-1595.
9. Asarian, L and Geary, N. Modulation of appetite by gonadal steroid hormones. Philos Trans R Soc Lond B Biol Sci. 2006;361(1471):1251-1263.
10. Eckel, LA. The ovarian hormone estradiol plays a crucial role in the control of food intake in females. Physiol Behav. 2011;104(4):517-524.
11. Yu, Z, Geary, N, and Corwin, RL. Ovarian hormones inhibit fat intake under binge-type conditions in ovariectomized rats. Physiol Behav. 2008;95(3):501-507.
12. Naessén, S, Carlstrom, K, Bystrom, B, Pierre, Y, and Hirschberg, AL. Effects of an antiandrogenic oral contraceptive on appetite and eating behavior in bulimic women. Psychoneuroendocrinology. 2007;32(5):548-554.
13. Wierenga, CE, Ely, A, Bischoff-Grethe, A, Bailer, UF, Simmons, AN, and Kaye, WH. Are Extremes of Consumption in Eating Disorders Related to an Altered Balance between Reward and Inhibition? Front Behav Neurosci. 2014;8:410.
14. Wu, M, Brockmeyer, T, Hartmann, M, Skunde, M, Herzog, W, and Friederich, HC. Reward-related decision making in eating and weight disorders: A systematic review and meta-analysis of the evidence from neuropsychological studies. Neurosci Biobehav Rev. 2016;61:177-196.
15. Monteleone, AM, Monteleone, P, Esposito, F, Prinster, A, Volpe, U, Cantone, E, Pellegrino, F, Canna, A, Milano, W, Aiello, M, Di Salle, F, and Maj, M. Altered processing of rewarding and aversive basic taste stimuli in symptomatic women with anorexia nervosa and bulimia nervosa: An fMRI study. Journal of psychiatric research. 2017;90:94-101.
16. Harrison, A, O'Brien, N, Lopez, C, and Treasure, J. Sensitivity to reward and punishment in eating disorders. Psychiatry research. 2010;177(1-2):1-11.
17. Eneva, KT, Murray, S, O'Garro-Moore, J, Yiu, A, Alloy, LB, Avena, NM, and Chen, EY. Reward and punishment sensitivity and disordered eating behaviors in men and women. J Eat Disord. 2017;5:6.
18. Kekic, M, Bartholdy, S, Cheng, J, McClelland, J, Boysen, E, Musiat, P, O'Daly, OG, Campbell, IC, and Schmidt, U. Increased temporal discounting in bulimia nervosa. Int J Eat Disord. 2016;49(12):1077-1081.

19. Bartholdy, S, Rennalls, S, Danby, H, Jacques, C, Campbell, IC, Schmidt, U, and O'Daly, OG. Temporal Discounting and the Tendency to Delay Gratification across the Eating Disorder Spectrum. Eur Eat Disord Rev. 2017;25(5):344-350.
20. McClelland, J, Dalton, B, Kekic, M, Bartholdy, S, Campbell, IC, and Schmidt, U. A systematic review of temporal discounting in eating disorders and obesity: Behavioural and neuroimaging findings. Neurosci Biobehav Rev. 2016;71:506-528.
21. Steward, T, Mestre-Bach, G, Vintro-Alcaraz, C, Aguera, Z, Jimenez-Murcia, S, Granero, R, and Fernandez-Aranda, F. Delay Discounting of Reward and Impulsivity in Eating Disorders: From Anorexia Nervosa to Binge Eating Disorder. Eur Eat Disord Rev. 2017;25(6):601-606.
22. Smith, KE, Mason, TB, Johnson, JS, Lavender, JM, and Wonderlich, SA. A systematic review of reviews of neurocognitive functioning in eating disorders: The state-of-the-literature and future directions. Int J Eat Disord. 2018;51(8):798-821.
23. Wu, M, Hartmann, M, Skunde, M, Herzog, W, and Friederich, HC. Inhibitory control in bulimic-type eating disorders: a systematic review and meta-analysis. PLoS One. 2013;8(12):e83412.
24. Merlotti, E, Mucci, A, Volpe, U, Montefusco, V, Monteleone, P, Bucci, P, and Galderisi, S. Impulsiveness in patients with bulimia nervosa: electrophysiological evidence of reduced inhibitory control. Neuropsychobiology. 2013;68(2):116-123.
25. Rosval, L, Steiger, H, Bruce, K, Israel, M, Richardson, J, and Aubut, M. Impulsivity in women with eating disorders: problem of response inhibition, planning, or attention? Int J Eat Disord. 2006;39(7):590-593.
26. Jimerson, DC, Lesem, MD, Kaye, WH, and Brewerton, TD. Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. Arch Gen Psychiatry. 1992;49(2):132-138.
27. Broft, A, Shingleton, R, Kaufman, J, Liu, F, Kumar, D, Slifstein, M, Abi-Dargham, A, Schebendach, J, Van Heertum, R, Attia, E, Martinez, D, and Walsh, BT. Striatal dopamine in bulimia nervosa: a PET imaging study. Int J Eat Disord. 2012;45(5):648-656.
28. Kaye, WH, Wierenga, CE, Bailer, UF, Simmons, AN, Wagner, A, and Bischoff-Grethe, A. Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? Biol Psychiatry. 2013;73(9):836-842.
29. Frank, GK. Advances from neuroimaging studies in eating disorders. CNS spectrums. 2015;20(4):391-400.
30. Coffee, AL, Kuehl, TJ, Willis, S, and Sulak, PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. American journal of obstetrics and gynecology. 2006;195(5):1311-1319.
31. Freeman, EW. Evaluation of a unique oral contraceptive (Yasmin) in the management of premenstrual dysphoric disorder. Eur J Contracept Reprod Health Care. 2002;7 Suppl 3:27-34; discussion 42-23.
32. Stewart, M and Black, K. Choosing a combined oral contraceptive pill. Aust Prescr. 2015;38(1):6-11.
33. Andrist, LC, Arias, RD, Nucatola, D, Kaunitz, AM, Musselman, BL, Reiter, S, Boulanger, J, Dominguez, L, and Emmert, S. Women's and providers' attitudes toward menstrual suppression with extended use of oral contraceptives. Contraception. 2004;70(5):359-363.
34. Edelman, A, Micks, E, Gallo, MF, Jensen, JT, and Grimes, DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane database of systematic reviews (Online). 2014(7):CD004695.
35. Dinger, JC, Heinemann, LA, and Kuhl-Habich, D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception. 2007;75(5):344-354.
36. Dinger, J, Assmann, A, Mohner, S, and Minh, TD. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care. 2010;36(3):123-129.

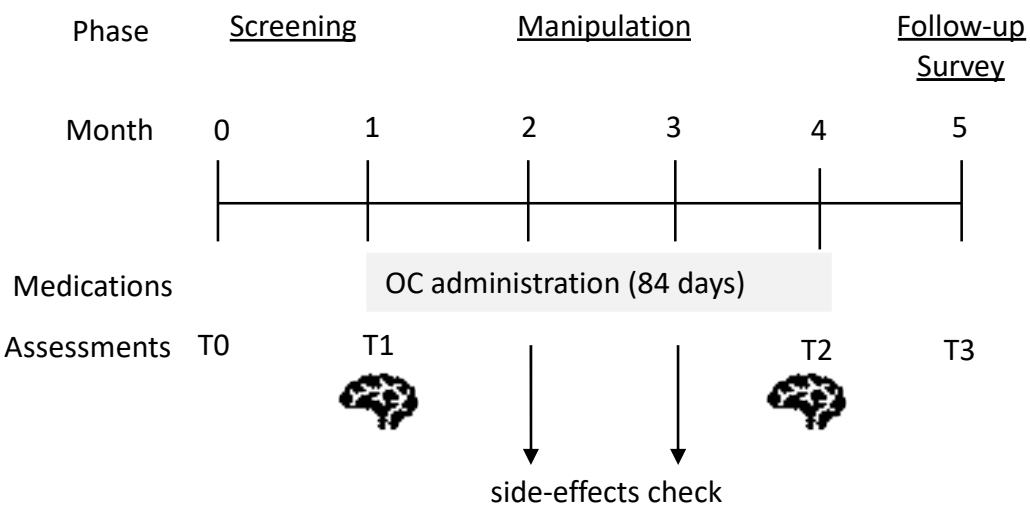
37. Seeger, JD, Loughlin, J, Eng, PM, Clifford, CR, Cutone, J, and Walker, AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstet Gynecol. 2007;110(3):587-593.
38. Vinogradova, Y, Coupland, C, and Hippisley-Cox, J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2015;350:h2135.
39. Zerwas, SC, Watson, HJ, Hofmeier, SM, Levine, MD, Hamer, RM, Crosby, RD, Runfola, CD, Peat, CM, Shapiro, JR, Zimmer, B, Moessner, M, Kordy, H, Marcus, MD, and Bulik, CM. CBT4BN: A Randomized Controlled Trial of Online Chat and Face-to-Face Group Therapy for Bulimia Nervosa. Psychotherapy and psychosomatics. 2017;86(1):47-53.
40. Thornton, LM, Munn-Chernoff, MA, Baker, JH, Jureus, A, Parker, R, Henders, AK, Larsen, JT, Petersen, L, Watson, HJ, Yilmaz, Z, Kirk, KM, Gordon, S, Leppa, VM, Martin, FC, Whiteman, DC, Olsen, CM, Werge, TM, Pedersen, NL, Kaye, W, Bergen, AW, Halmi, KA, Strober, M, Kaplan, AS, Woodside, DB, Mitchell, J, Johnson, CL, Brandt, H, Crawford, S, Horwood, LJ, Boden, JM, Pearson, JF, Duncan, LE, Grove, J, Mattheisen, M, Jordan, J, Kennedy, MA, Birgegard, A, Lichtenstein, P, Norring, C, Wade, TD, Montgomery, GW, Martin, NG, Landen, M, Mortensen, PB, Sullivan, PF, and Bulik, CM. The Anorexia Nervosa Genetics Initiative (ANGI): Overview and methods. Contemp Clin Trials. 2018;74:61-69.
41. Baker, JH, Eisenlohr-moul, TA, Bulik, CM, Schiller, CE, and Girdler, SS, *Impact of Estrogen and Progesterone on Changes in Eating Disorder Symptoms During the Menopause Transition*, in *International Conference on Eating Disorders*2018: Chicago, IL.
42. First, MB, Williams, JBW, Karg, RS, and Spitzer, RL, *Structured Clinical Interview for DSM-5: Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV)*2015, Arlington, VA: American Psychiatric Association.
43. Gordon, JL, Rubinow, DR, Eisenlohr-Moul, TA, Leserman, J, and Girdler, SS. Estradiol variability, stressful life events, and the emergence of depressive symptomatology during the menopausal transition. Menopause (New York, N.Y. 2016;23(3):257-266.
44. Whiteside, SP and Lynam, D. The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. Personality and Individual Differences. 2001;30(4):669-689.
45. Watson, D, O'Hara, MW, Simms, LJ, Kotov, R, Chmielewski, M, McDade-Montez, EA, Gamez, W, and Stuart, S. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). Psychol Assess. 2007;19(3):253-268.
46. Fairburn, C and Cooper, Z, *The Eating Disorders Examination (12th Edition)*, in *Binge-Eating: Nature, Assessment and Treatment*, C. Fairburn and G. Wilson, Editors. 1993, Guilford Press: New York. p. 317-360.
47. Stunkard, A and Messick, S. Three-factor eating questionnaire to measure dietary restraint, disinhibition, and hunger. J Psychosom Res. 1985;29:71-83.
48. Carver, CS and White, TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. Journal of Personality and Social Psychology. 1994;67:319-333.
49. Torrubia, R, Avila, C, Molto, J, and Caseras, X. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Personality and Individual Differences. 2001;31(6):837-862.
50. Gray, JC, Amlung, MT, Palmer, AA, and MacKillop, J. Syntax for calculation of discounting indices from the monetary choice questionnaire and probability discounting questionnaire. J Exp Anal Behav. 2016;106(2):156-163.
51. Knutson, B and Greer, SM. Anticipatory affect: neural correlates and consequences for choice. Philos Trans R Soc Lond B Biol Sci. 2008;363(1511):3771-3786.

52. Watson, DC, LA. Tellegen, A. Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of Personality & Social Psychology. 1988;54(6):1063-1070.
53. SAS Institute Inc, *SAS/STAT® Software: Version 9*2004, Cary, NC: SAS Institute, Inc.

12 Appendices

Appendix A. Study Procedures Flow Chart

Figure 2



Appendix B. COVID Procedures

Due to the COVID-19 pandemic, this study as described above will be modified as described below. These procedures are only in response to the COVID-19 pandemic. If we are able to begin recruitment, enrollment, and study visits 'as usual' when it is safe, study procedures will resume as described.

All remote portions of study visits will be conducted via WebEx calls. All scheduled WebEx visits will be password protected and only those with the password can enter the call. WebEx has been approved by the UNC ITS as secure programs for PHI and sensitive information and the School of Medicine specifically recommends the use of WebEx for research study visits. WebEx is HIPAA complaint, ISO/IEC 27001:2013 certified, and approved for the transmission of PHI. Visits will be password protected and only those with the password can enter the study visit. Although Internet access is not a specific inclusion/exclusion criteria, because COVID19 requires converting many aspects of this study to virtual visits, we acknowledge participants will need to have access to the Internet.

Overview:

This updated addendum (Date 7.29.20) includes our plans to begin enrolling participants and the updated measures to prevent against the spread of SARS-CoV-2. We have altered our study activities to make portions of the procedures remote. Due to the nature of the study, two visits will require the participant to travel to the UNC BRIC for an fMRI scan and other visits will require brief interactions with the participants, at their homes if possible, to draw blood for labs or to drop off study medications or other materials.

When contact is essential for certain activities, we follow required and established procedures to protect participants and our study team. We are limiting the number of study personnel that conduct in-person visits to two individuals. Both will be dressed in personal protective equipment (PPE) and will follow procedures to prevent the opportunity of transmission.

PPE. During all interactions with participants, participants will be given a surgical mask and the study personnel will wear scrubs, gloves, and a surgical mask. Eye protection will be worn during any blood draws completed by the study coordinator. All items will be immediately removed as soon as possible after the study visit and washed or thrown away.

COVID screening. A COVID health screen will be completed with all participants 24 hours prior to an in-person study visit. If this is not completed, the study visit will not occur. In addition, a CEED-specific Qualtrics survey will be completed by research personnel prior to any study visits or interactions with human subjects, regardless of the location.

Social distancing. Distance will be maintained between people any time closer contact is not absolutely required (e.g., blood draws). As much as possible, study visits will be scheduled as in-home. If a subject prefers to come to the hospital for a study visit, this request will be considered. As much of a study visit that can be completed without being in person will occur remotely in order to decrease interaction with subjects.

Visit Schedule Changes

Eligibility. Previously we would offer the option to screen in an in-person interview. During COVID-19, all individuals will be screened remotely as described in the original protocol. For those that complete the Qualtrics eligibility screener, a brief phone call will be scheduled to confirm eligibility before the T0 visit is scheduled. In

the event study activities need to be suspended again due to COVID19, we will continue to screen individuals, and, with their verbal permission, we will add them to a waitlist to be re-contacted once the study is able to resume. This waitlist is a password-protected document that contains the potential subjects' name, temporary ID, and contact information. For the time being, since we are able to complete study activities, we will not use the waitlist.

Screening (T0). Previously, this visit was completed entirely in-person. During COVID-19, this visit will be broken up into two visits (T0a and T0b). These will be scheduled for different days.

T0a.
Two copies of the main study informed consent documents will be mailed to the participant's home and will be reviewed remotely via Webex, signed on the physical copy, and that copy will be mailed back and the other will be retained as a personal copy for the participant to keep. The remote consent will function in a virtually identical manner to in-person consent: we will walk the participant through the consent forms, verbatim, allowing ample opportunity for questions. We will also review the COVID information sheet during this WebEx call. Prior to signing the informed consent, the participant will be asked the questions on the informed consent quiz to ensure understanding. If the participant agrees to participate in the study, they will be instructed to sign the study consent form and HIPAA authorization form and to mail them back to study staff using the pre-paid postage envelope provided.

T0b.
Once the informed consent documents are received, the second portion of the T0b screening visit will be scheduled and conducted. This includes the clinical interview and clinical health screen. This will be completed remotely to examine inclusion/exclusion criteria. Self-report questionnaires will be completed via Qualtrics. For those participants who initially appear eligible, the study coordinator will schedule a time to visit the participant's home to draw blood for labs.

Once eligibility for the study is confirmed, the research coordinator will schedule a time to drop off an ovulation test kit to use at home as previously planned. Alternatively, this may be mailed directly to the participant's home in an unidentified package or the participant can meet the coordinator in front of the hospital and do a drive-by to pick it up themselves. This will be decided based upon participant preference.

Baseline (T1). This visit will be scheduled during the mid-luteal phase of the subject's menstrual cycle based on their ovulation test kit results. Within 24 hours of coming to the Biomedical Research Imaging Center (BRIC), they will complete the COVID wellness check and asked to complete a baseline assessment including self-report questionnaires. When they arrive, the coordinator will give them a mask and will accompany them into Marsico Hall. All COVID procedures as outlined by BRIC will be followed. The study personnel will speak with BRIC staff before entering the building. Once inside, they will complete next steps following BRIC's Human Imaging Core Facility COVID-19 safety plan. This will include a second wellness screen and waiting in designated areas until the reserved fMRI room is available and clean.

End-of-OC administration (T2). During the last two weeks of medication administration, participants will be scheduled for a second visit to the BRIC for an fMRI scan. Before arriving at the facility, within 24 hours of the visit, they will complete the wellness check. All study procedures at T1 will be repeated.

Side Effects and Safety. Two partially remote monthly check-ins with study staff (Table 1: monthly visits) will occur during the 84-day medication administration period—approximately 4-weeks after medication begins and approximately 8-weeks after medication administration begins (i.e., monthly). During these check-ins, side

effects and protocol adherence will be monitored via questionnaires and interviews remotely and during the first monthly check-in, a blood draw will occur during a brief in-person visit at the participants' home for labs.

The side effects and adherence interview will be conducted through WebEx. Participants responses to the daily surveys will continue to be monitored daily and participants endorsing any concerning symptoms will be followed up with by the PI (as outlined in the original protocol).

Follow-up (T3). One month after study completion, a brief online follow-up assessment. At the completion of the study and after T3, subjects will be given the option to virtually meet with the study PI and receive a detailed report about how the medication affected them.