Cover Page

Official Title: **A Multimodel Examination of Bromocriptine on Homeostatic and Hedonic Mechanisms of Food Intake in Individuals at High Risk for Type 2 Diabetes**

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Study Protocol

A. Study Rationale

Twenty-nine million Americans suffered from type 2 diabetes (T2DM) in 2012 (2014 National Diabetes Report), with fewer than half able to meet treatment goals and considerably more are at risk for development of T2DM (1). Implementation of healthy eating behavior has been identified as a barrier to T2DM treatment and efficacy (2). The determinants of eating behavior and weight regulation involve a complex interaction among individual-level homeostatic, hedonic, and genetic systems, and the external food environment (3,4). The high prevalence of obesity and T2DM suggests hedonic motivation to consume food overrides homeostatic satiation signaling, resulting in excess food intake. Elevated intake increases body mass and promotes T2DM incidence via dysregulation of GLP1, amylin, and adiponectin, which in turn can negatively impact T2DM treatment options. Use of a pharmaceutical, such as bromocriptine, to aid in behavioral change is a novel method for treating and ameliorating T2DM and warrants investigation given that previous work has shown reward response to food images mediates T2DM control (5). Use of fMRI techniques to predict and evaluate hedonically-motivated eating behavior can be used to measure sensitivity to reward, and the role it plays in developing obesity (6,7), and is therefore an excellent tool to examine the associations among bromocriptine, satiety hormones, reward sensitivity and eating behavior. Moreover, since 20 35% of the population carries the DRD2 TaqIA A1 allele (8), and 65% of the population is overweight or obese and at high risk for T2DM development or currently diagnosed, as much as 23% of the population may greatly benefit from dopamine agonist treatment (9). Despite the possibility that bromocriptine may have robust impact on T2DM treatment or as prevention therapy in those that are genetically predisposed, few data are available that directly examine the three systems (homeostatic, hedonic, genetic) available to assess whether a genetically-informed, personalized T2DM treatment is viable.

B. Study Objectives

Aim 1: To test the hypothesis that acute bromocriptine administration will alter neural and perceptual hedonic drivers of eating behavior (Visual analog scales), both contributing to a decrease in palatable food intake in those at high risk for T2DM. We expect that bromocriptine will increase BOLD response during palatable food intake in dopaminergic brain regions thought to encode reward and increase perceptual hedonic food ratings. We also expect that bromocriptine will result in decreased ad lib palatable food intake.

Aim 2: Test whether the A1 variant of the DRD2 TaqIA polymorphism, which is associated with reduced dopamine-D2 receptor density and dopamine signaling, moderates the impact of bromocriptine on neural and perceptual hedonic drivers of eating behavior. By testing the bromocriptine by TaqIA allele status interaction, we expect that the effects described in aim 1 will be pronounced in those with at least 1 A1 variant of the TaqIA polymorphism.

Exploratory Aim 1: To test the hypothesis that acute bromocriptine administration will alter the homeostatic mechanisms of satiation (meal termination). We expect bromocriptine to modify endocrine-mediated satiation signaling via suppressed prolactin, augmented adiponectin, amylin, glucagon like peptide-1 (GLP1), and decrease postprandial plasma glucose and insulin.

C. Study Design

This within-subject pilot study will look at 180 overweight/obese (25 < BMI < 35) adults ages 18-35 years of age. All participants will be screened at the first visit for 50 eligible participants who will complete the other visits. 25 participants will have the DRD2 TaqIA A1 allele and 25 will have the A2/A2 variant. The study will be completed over two testing visits with a two-week washout period in between. Following published reports of the effect of acute administration of bromocriptine (10), participants will be given a 1.6mg dose of either bromocriptine-QR (Cycloset) or a placebo after a 6-8 hour fast, paralleling the recommended dosage and time of administration (11). Order of agonist/placebo will be counterbalanced across the two visits. At both visits, the participant will have a fasting blood draw, anthropometric measurements, complete visual analogue scales (VAS) for hunger, and satiety and surveys. Once bromocriptine/placebo is metabolically active (~60 mins) subjects will undergo a functional MRI with our milkshake receipt paradigm and a resting state MRI to assess functional connectivity. The Biomedical Research Imaging Center (BRIC) is located on the UNC-CH campus and 7-10 min walk from our laboratory (Neuropsychology of Ingestive Behavior Laboratory). Post-MRI, subjects will consume a fixed portion of milkshake (12 fl oz) and perform VAS hedonic ratings; will complete a test of reaction time and behavioral impulsivity, and two postprandial blood draws (30 & 60mins post milkshake ingestion). Finally, subjects will perform perceptual hedonic assessments of palatable foods and given the opportunity for ad lib consumption.

D. Study Duration, Enrollment and Number of Subjects

For each participant, the study will include three visits on three separate days.

Total study duration will be approximately two years.

We will recruit and screen 180, 18-35-year-old overweight/obese individuals in order to enroll 50 participants with and without the presence of the DRD2 TaqIA A1 allele, and at high risk for T2DM by virtue of HbA1c. The n=42 represents the number of participants who will provide usable data and accounts for possible attrition and negative side effects of the bromocriptine (based on previous repeated measures fMRI studies and reports of bromocriptine, expected attrition is 4%-7%).

E. Study Population

50 overweight/obese (25 < BMI < 35) adults ages 18-35 years of age. We will screen for enrollment such that 25 participants will have the DRD2 TaqIA A1 allele and 25 will have the A2/A2 variant. We will exclude participants who report current: a) contraindications of fMRI (e.g., metal implants, braces, or serious medical problems [e.g., known diabetes, CVD, recent stroke]), b) any previous habitual use of cigarettes or illicit drugs, or c) current major psychiatric disorders (depression, bipolar disorder, panic disorder, generalized anxiety disorder), d) pregnancy or breastfeeding e) current weight loss dieting and/or weight fluctuations great than 10 lbs in the previous 6 weeks. f) do not consume dairy e) allergy to bromocriptine, dairy, and nuts. Diabetes status will be assessed via self-report.

F. Study Procedures

1. <u>Screening Visit</u>

At the screening visit, following consent, the potential participant will be weighed and height will be measured to ensure they are overweight (25 < BMI < 35). A brief screener for identifying MRI contraindications will be administered before inviting subjects to join the MRI portion of the

study, as done in prior fMRI studies. If participants satisfy inclusion and exclusion criteria during the screen, they will be scheduled for the testing assessments. Female participants will be asked to self-report the date of their last menstruation to ensure they are in the follicular phase and are not pregnant (pregnancy test will be offered). Saliva (genotyping) and blood glucose values (mg/dL) will be collected from consented participants at the initial screening appointment. (30 minutes)

2. Testing Visits – Outline

- At the Neuropsychology of Ingestive Behavior Lab

Baseline: Fasting blood draw, fasting drug or placebo administration

Baseline-60 minutes: Visual analogues scales (VAS) hunger and satiety, height and weight measurement, demographic and psychological surveys, waiting for drug to become active

60 minutes: Walk to Biomedical Research Imaging Center

- At the Biomedical Research Imaging Center

90 minutes - 150 minutes: VAS hunger and satiety, MRI assessment, taste administration, resting state, anatomical scans

- At the Neuropsychology of Ingestive Behavior Lab

150 minutes-180 minutes: VAS hunger and satiety, fixed milkshake consumption

180 minutes: Blood draw

180 minutes-210 minutes: Behavioral impulsivity, surveys

210 minutes: Blood draw

210-240 minutes: VAS ratings, hedonic ratings, ad libitum food intake

The testing visit will last approximately 4 hours.

Testing visit occurs twice for each participant.

G. Study Evaluations and Measurements

Bromocriptine/placebo administration

Participants will be given either bromocriptine (1.6mg Cycloset) or placebo at each testing visit. Order of bromocriptine/placebo will be counterbalanced across the participants. The researcher and participant will be blinded to the treatment given. Dr. Burger, Dr. Klett, and IDS will have the randomization key. The research assistant will pick up the Cycloset or placebo from IDS. He or she will be blinded to the contents (whether placebo or Cycloset) and will give the participant the capsule to take orally. To allow the drug to reach maximum plasma concentration, participants will be scanned approximately 90 minutes following drug administration. The placebo will be developed by IDS and will come in a capsule which will look identical to the capsule the Cycloset is in.

Blood Draws

Each blood draw will occur in either the antecubital vein in the arm or in the cephalic vein in the hand. 6 mL of blood will be drawn three times. For each visit, the first blood draw (fasting) will occur at the start of the visit and the second and third will occur 30mins and 60mins after the fixed milkshake portion (after fMRI scan; see Fig 1). This will allow us to assess fasted

circulating hormone levels and gives us the ability to examine satiation hormone fluctuation over two time points that encompass the entirety of the previously characterized GLP1 peak in serum. A trained phlebotomist will perform the blood draws. The phlebotomist will try no more than 3 times unless the participant consents to further attempt. Blood samples for satiety hormones will be assayed using Bio-Plex Pro Human Diabetes 7-plex Assay (Bio-rad, Hercules, CA). This kit analyzes adiponectin, amylin, and GLP1. Additionally, a custom Human Cancer Panel 1 with only prolactin will be used to analyze prolactin concentrations (Bio-rad, Hercules, CA) using a Millipore Luminex (Darmstadt, Germany). All samples will be kept at -80° until processed. Our team is well versed in blood processing procedures and Luminex operation.

Height and Weight

Height and weight will be measured without shoes or heavy clothing.

Visual Analogue Scale

Visual Analogue Scales will be used to assess hunger, fullness, thirst, and nausea periodically throughout the testing visits. These will be distributed via iPad on Qualtrics software.

Neuroimaging Paradigms

Participants will complete 2 functional MRI paradigms: milkshake receipt paradigm and resting state paradigm, in addition to an anatomical scan. These paradigms examine different aspects of neural functioning. First, the milkshake receipt paradigm allows us to examine how the brain responds during exposure to a primary reward (receipt of highly palatable taste) and a tasteless control. Second, the steady state paradigm will allow for functional connectivity analyses to examine reward and behavioral differences in the brain at ‘rest’.

Milkshake receipt fMRI paradigm

The paradigm is controlled by in-house Python scripts. Each trial in the paradigm starts with the presentation of a cue (duration: 1s) signaling the impending delivery of either 3 mL of highly palatable milkshake or a control water solution over a period of 6s. Taste delivery is followed by a 1s wait period and 2s rinse (tasteless solution). The next trial begins after a 1-9s jitter. Order of milkshake and water trials is pseudo randomized. In total, there are 32 trials per run for a total of 2 8-minute runs. This paradigm allows us to assess brain response to a receipt of primary reward (milkshake) and control (water solution) as well as in vivo neuroadaptations over repeated exposures.

Resting state functional connectivity

We will use resting state fMRI data for functional connectivity analyses to provide data about brain functioning and connectivity. Functional connectivity is assessed by examining the correlation of fluctuations of BOLD signals in different regions of the “resting” brain and is thought to provide a measure of its functional organization Steady-state fMRI data will be acquired in one run of 5 minutes; participants will be asked to remain still and relaxed and stay awake during the scanning. This paradigm allows us to assess the brain’s functional connectivity. We hypothesize that connectivity from the hypothalamus will be significantly altered by bromocriptine.

Total scan time will be approximately 50 minutes.

Behavioral impulsivity task

We will use a basic stop-signal task that assesses behavioral inhibitory control in response to palatable food images, adapted from Batterink and colleagues (12) and in current use in our lab. This task requires subjects to respond to “go” signals and occasionally inhibit responses to “no-go” signals. It measures the ability to inhibit a pre-potent tendency to respond. The task consists of 80 trials, evenly split between left-button responses (the letter A) and right-button responses (the letter Z). 16 total stop trials are presented (the stop signal is the letter X). The stop signal delay begins at 200ms, and increments by one screen refresh period depending on trial performance. The number of responses to stop signal stimuli (commission errors) will be used to provide a behavioral measure of inhibition failure.

Ad lib taste test

After the fMRI scan and fixed consumption of milkshake, participants undergo the postprandial blood draw and perform a taste test which includes perceptual hedonic ratings of a variety of foods and an ad lib intake challenge. Participants first perform a taste test of 1g of each of the 4 foods (M&Ms, Skittles, Doritos, cheddar popcorn). These foods were selected as they are generally considered highly palatable and represent a variety of flavors, mouth feels and nutrient contents (e.g., sugar, fat, salt). Participants complete perceptual hedonic ratings of the pleasantness, sweetness, taste intensity, and desire to consume on generalized, labeled magnitude scales of each of the foods. After the taste test, participants will be told that they are free to eat as many snacks as they like, as we have to discard them after each participant (they will not be allowed to have backpacks, purses, or bags, so they do not take snacks from the room). Participants will be left alone during the tasting to minimize demand characteristics. Food will be pre- and post-weighed to determine ad lib intake. Total caloric intake will be calculated and translated to % of calorie needs using gender-specific formulas (NAS, 2005). We currently use these techniques (NORC5-34387, HHSN275201300015C).

Eating Attitudes

The Dutch Eating Behavior Questionnaire (DEBQ; 13) is a 46-item questionnaire with three subscales measuring restrained, external, and emotional eating. Responses are recorded on a 5-point Likert scale. These three scales demonstrated strong internal consistency (Cronbach’s alpha = 0.80 – 0.95), interrelationships between scales, and factorial validity.

Food Craving

The Food Craving Inventory (FCI) will assess the degree of craving for high- and low-fat/sugar foods (14). This scale has shown internal consistency (α= .93), 2-week test-retest reliability (r = .86), and sensitivity to detecting change.

Self-report Impulsivity

The Barratt Impulsivity Scale (BIS-15) is a 15-item self-report assessment that will measure attentional, motor, and non-planning impulsivity (15). This scale has shown internal consistency (α=.81), 2-week test-retest reliability (r =.88), and discriminates between psychiatric patients and controls (56).

Acute and Habitual Dietary Intake

Participants will complete our adapted version of the Block Food Frequency Questionnaire (Block FFQ) which inquiries about the frequency of consumption of 60 specific foods over the

past 2 weeks (16) to measure habitual dietary intake. Food frequency questionnaires are the most practical and economical method for collecting dietary intake data in large studies (17). Block FFQ values correlated (r = .57) with 4-day food record estimates for energy and most nutrients (18). We have successfully used this version in previous studies (NORC5-34387, HHSN275201300015C) and published results.

Additional Surveys

We will administer the Short-Form International Physical Activity Questionnaire (IPAQ), which queries about physical activity over the previous days and has shown strong reliability (r = .80; (19)). Participants will also complete a modified version of the Pittsburgh Sleep Quality Index, which will ask about sleep quality over the past week (20), which we can determine the previous night's sleep. Lastly, participants will complete the Edinburgh Handedness Inventory, which is a continuous measure of hand dominance (21).

All Surveys will be administered via an iPad using Qualtrics software and applications.

H. Study Intervention

- Bromocriptine-QR cycloset; 1.6mg; once; oral
- Placebo; 2 capsules; once; oral

Participants will be administered two placebo pills at one testing visit and a two 0.8mg dose of bromocriptine at the other visit. Bromocriptine dose agrees with optimal dose according to clinical trials (22,10). Adverse effects related to bromocriptine include nausea, dizziness, fatigue, headache, diarrhea, and constipation (11). However, adverse events (AEs) are generally not severe; according to Scranton & Cincotta, 17% subjects on bromocriptine reported adverse drugs experiences as severe, while 14% on placebo reported AEs as severe (22). Moreover, the most commonly reported adverse event, nausea, was not reported as severe (22). To prevent any potential adverse interactions with bromocriptine, participants will be asked to abstain from any drugs for 12 hours before the assessment including over the counter pharmaceuticals such as (ex. Advil, aspirin, Benadryl), and for the remainder of the day after the session. Participants will be asked to avoid consuming alcohol for 24 hours after bromocriptine administration to prevent increased risk of drowsiness. Bromocriptine may decrease the effectiveness of oral contraceptives, female participants taking oral contraceptives will be asked to refrain from intercourse for 24 hours or to use an additional form of birth control. Because the half-life for bromocriptine is 6 hours after 24 hours the amount of active drug in the participant's system will have decreased 98%.

I. Study Intervention Administration

This is a within subjects designed experiment, so all subjects will receive the Cycloset and placebo. The administration will be blinded to subject and the research. Dr. Burger will oversee the blinding procedure. The order of the drug and placebo will be counterbalanced across the two visits, and Dr. Burger will see to the drug/placebo administration schedule. Because the screening visit is before the testing visit and randomization we are confident in the participant's eligibility.

J. Safety Management

It is possible that the questionnaires may cause distress or embarrassment to the participants. One potential risk to participants is that it may be distressing to disclose information about

psychiatric difficulties. In our estimation, there is a low risk of this possibility and the effects would probably be short-lived. We have conducted several thousand of these types of interviews with no adverse events. We will take steps to minimize this risk by informing them that their data will be confidential. Additionally, it is possible someone maybe embarrassed to be weighed. The research staff will be trained to be highly professional for the entire study visit. Data will be obtained from participants through surveys, taste assessments, height and weight measurements, fMRI scans, blood draws, and saliva. There is a slight risk that these research records might be obtained by persons not authorized to do so. There is also a risk that participants may not understand the limits of confidentiality (i.e. that we will not keep certain information confidential, such as spontaneous disclosures on their part regarding suicidal ideation and child abuse [no measures inquire about sensitive topics such as these]). Data for all participants will be kept strictly confidential, except as mandated by law. All research files will be kept in locked file cabinets in a locked room in a locked building. Participants will be assigned a numerical code for identification in the files. Names and other identifiers will be kept in separate locked files and will never be recorded on any data forms. Statistical analyses will be performed on aggregate-level data; participants are never individually named. All entered data will be kept on the password protected, secured computers or networks at the research site. These data will be accessible only to research staff, using confidential usernames and passwords. All staff on this project will receive training in the ethical conduct of research with human participants prior to contact with data or research participants. Participants will be informed in detail about the limits of confidentiality, including disclosure of intentions to inflict harm to self or others and the possibility that we might break confidentiality to report suspected child or elder abuse. All participants will be told that participation is voluntary and that they may terminate their involvement at any time without any consequences. If, during any assessment, the project coordinator determines that a participant has developed a serious health problem, efforts will be made to help the participant access appropriate treatment as quickly as possible. In addition, any scans that suggest possible problems are sent to a radiologist for a consult. In the event of a potential problem, Dr. Burger will meet with the participant and the radiologist to discuss the findings, per protocol from the Biomedical Research Imaging Center.

K. Data Collection and Management

All paper data will be stored in a locked filing cabinet in a locked room. All digital data will be stored on servers which require passwords to access. Data will be saved as confidential, coded files. All blood data and genetic data will be de-identified and will be kept in secure freezers until it is assayed.

Only authorized project staff will have access to the information gathered for this project. We will follow established data handling procedures as follows: (a) data will be reported in aggregate form only; (b) all data will be kept in locked file cabinets and/or in password-protected computer files; and (c) all personnel interacting with participants and having access to data are trained in confidentiality procedures.

Any paper documents will be stored in locked files, behind locked doors at the laboratory on campus at UNC-CH. The key that links participant names to the identification numbers will be kept separate from the data, also in a locked file.

fMRI data collected at the BRIC is sent over a secured server (PACS), this data is attached to coded numbers. fMRI data is accessed through this password protected served and transferred to the lab's protected databases. Unprotected personal information of subjects is never sent over the web.

L. Recruitment Strategy

Recruitment posters will be placed on the UNC campus, in community centers, and restaurants in local Chapel Hill/Durham area. Additionally, we will use the 'UNC-Chapel Hill Biomedical Research Imaging Center (BRIC) Database' (UNC-CH IRB #13-0959) and the 'Join the Conquest' (UNC-CH IRB #13-1768) recruitment databases. These and similar approaches have been successfully used for recruitment in this sampling frame (e.g., R01DK092468, NORC5-34387). Those interested in participating will be directed to the screening website. Information needed to determine participant eligibility will be obtained via web, phone or in person (see attached prescreening material). The subjects will be contacted by research staff via the preferred method of the subject (phone, email, in person) to provide the consent for review and schedule the first assessment (if applicable).

M. Consent Process

If the potential participant is interested in the study they will be scheduled for a screening visit and a consent form will be mailed or emailed to them. At the screening visit, before an assessments, the consent form will be reviewed, all answers regarding study expectations will be answered, and consent will be confirmed by trained study staff (listed in the personnel section of the application). Consenting will be performed in a private room.

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