Study Protocol Cover Page

Official Title: **Neurobehavioral Plasticity to Regular Sugar-Sweetened Beverage Intake: An fMRI Experiment**

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Study Protocol

A. Study Rationale

Half of Americans consume sugar-sweetened beverages (SSBs) on any given day[1]. Regular SSB intake is considered a contributing factor to excess energy intake, weight gain and obesity[2–4], which impacts 70% of Americans[5]. Preclinical and human studies indicate sugar is highly rewarding, as it elicits release of dopamine and opioids in the striatum[6]. Multiple brain-based models of food reward-driven obesity have been proposed, largely focusing on striatal response and dopaminergic functioning[7–14]. While these models have elucidated neural correlates of obesity, data supporting these models rely heavily on observational and cross-sectional studies in small samples. Without rigorous, experimental evidence, there are fundamental gaps in our knowledge about the critical initial period of habit formation as an individual begins to regularly consume a high sugar food. Further, current research frequently utilizes singular methodologies, limiting the understanding of the interrelationships among neural responses, implicit behavior, and the perception of foods. To address these gaps, our team and others have shown that brain response during food intake and food cue exposure are, in part, a function of eating behavior patterns independent of weight status[15–25]. These observational results dovetail with previous reports examining the impact of weight status providing convergent validity. To better examine the temporal precedence of these effects, we completed a small-randomized controlled trial that assigned daily consumption of SSBs over 3 weeks. Critically, results supported the hypothesis that regular SSB intake causes specific neurobehavioral adaptions that may represent habit formation, which, in theory, would serve to perpetuate consumption. We posit that an improved understanding of the strength, specificity, and persistence of neurobehavioral adaptions that occur in the critical, initial period of SSB consumption are imperative to elucidate the impact of sugar on regulation of intake.

To confirm and extend our preliminary evidence, we propose a rigorous approach that bridges neural, behavioral, and perceptual assessments to evaluate the impact of regular SSB intake. In the proposed randomized controlled trial, 230 young adults (18-28 years old, BMI 18-34) will be assigned to consume branded versions of either an SSB or unsweetened, similarly flavored control beverage daily for 3 weeks. Through this multimodal approach, the proposed experiment will be the first to provide relevant data on strength and specificity of neurobehavioral adaptations associated with regular SSB intake, and the individual factors that predict the degree of these adaptions. The central goals of this proposal are: 1) to determine whether daily intake of SSB results in differential neurobehavioral adaptions compared to baseline response and unsweetened, flavored control beverages, and examine the flavor specificity of these effects; 2) to test whether individual factors previously implicated in obesity moderate neurobehavioral adaptions

B. Study Objectives

Aim 1: Test the neurobehavioral adaptions in response to repeated intake of branded SSBs relative to unsweetened, flavored control beverages (USB).

We hypothesize that daily SSB intake will lead to:

a. increases in parietal/occipital brain response during exposure to the SSB brand;
b. decreased dorsal prefrontal and hippocampal response to the SSB brand;
c. reduced striatal response during receipt of the assigned SSB,

relative to baseline and to those who are assigned to consumed the control beverage.

Aim 2: Test whether BMI mediates the neurobehavioral response patterns to the consumed beverages as a function of daily SSB intake relative to baseline and to those who are assigned to consume USB.
We hypothesize that there will be no significant interaction, such that those individuals with elevated BMI will show no difference than those at a lower BMI in the brain adaptions described in Aim 1.

Aim 3: Test the impact of repeated consumption of SSBs on behavioral responses (reaction time and response inhibition) to the beverage brands measured by the stop sign task (SST).
We hypothesize that mean reaction time to Go trials will result in a significant interaction of group assignment (sugar vs. control) by pre-/post- daily consumption. Specifically, we hypothesize that the sugar group will show a decreased reaction time to Go trials, representing faster responses relative to the control group and baseline.

Aim 4: Test the impact of repeated consumption of sugar-sweetened beverage on perceptual hedonic and taste ratings.
We hypothesize that daily beverage intake will lead to:

a. *no change in pleasantness and desire ratings as a function of repeated consumption of the assigned beverages.*
b. *an assignment (sugar vs. control) by time (pre-/post- daily consumption) interaction for desire ratings of the non-assigned beverages. Specifically, we hypothesize that there will be a decrease in desire ratings of the control beverage after having consumed a SSB daily. We expect no change in pleasantness.*

C. Study Design

We propose to use a randomized control trial design and recruit 230 18-28 year old men and women over a 42-month period to address the proposed aims. Participants will be randomly assigned to an experimental condition (sugar-sweetened beverage [SSB] or unsweetened, flavored control [USB]) and then to one of two flavors within their experimental condition. This results in 4 cells: two flavors high-sugar beverages (n=115; 58/57 for each flavor of SSB) and the same two flavors of unsweetened control beverages (n=115; 58/57 for each flavor of control). The two-tiered randomization process allows for a fully powered test of the effects of SSB consumption (n=115) versus unsweetened control (n=115; Aim 1) and individual difference factors (Aims 2-4). Participants will complete the pre-intervention assessments (see **Table 1** & **Study Procedures**), then begin the intervention which will include the daily consumption of their flavored beverage for 21 days. Following the intervention, participants will come back in the lab to complete the post-intervention assessments (see **Study Procedures**).

D. Study Duration, Enrollment and Number of Subjects

For each participant, the study will include 2 pre-intervention visits, 2 post-intervention visits, and 9 in-lab assessments during the 21-day intervention period. Total study duration will be approximately two years. We will recruit 230, 18-28-year-old healthy individuals. Stratified randomization techniques will be used to distribute: 1) male & females, 2) those with a BMI > 26.1 & those with a BMI < 26.1 equally across the 2 experimental conditions (SSB vs. unsweetened beverage) and then to the two flavors within each experimental condition. BMI of 26.0 was selected as it is the midpoint of inclusion criteria 18 < BMI < 34. Experimental and flavor conditions will be blinded to those performing analyses.

E. Study Population

To best capture the local population, we will require that participants have BMI between 18-34 kg/m^2. Following our previous studies, we will exclude young adults who report current: a) contraindications of fMRI (e.g., metal implants), b) serious medical problems (e.g., diabetes) assessed using a standard review form, c) any previous treatment for eating disorders or drug or alcohol abuse/addiction, d) current major psychiatric disorders (e.g., depression, generalized anxiety disorder), e) current dieting, f) regular smoking, and g) dietary practices that do not allow intake of intervention beverages. We will provide samples of the beverages during the consent process to ensure all the participants are willing to adhere to protocols.

Table 1. Assessments	**Pre-intervention (2 separate visits)**	**Intervention (21 days)**	**Post-intervention (2 separate visits)**
fMRI scan	●		●
Fasting blood draw	●		●
Ad lib sugary food intake	●		●
Daily beverage intake		●	
Height/Weight	●		●
Behavioral tasks (incl. SST)	●		●
Explicit perceptual & hedonic ratings	●	X	●
Intake & activity patterns	●		●

X = assigned beverage only

F. Study Procedures - Outline

1. Pre-intervention Behavioral Visit

Occurs: 1-3 days prior to the pre-intervention scan visit.
Location: Neuropsychology of Ingestive Behavior Lab
Duration: 1.5 hours
Compensation: $40
Study Session Flow:

- Consent
- FMRI screening sheet
- Height and weight
- Internal state ratings (hunger/fullness/thirst/nausea) using visual analog scales (VAS)
- Taste test & hedonic VAS
- Surveys: FFQ, BIS-15, FCI, DEBQ, IPAQ, Handedness, SPSRQ, YFAS, BIS/BAS, PFS, Demographics
- Stop signal task
- Saliva sample
- Compensation

2. Pre-intervention Scan Visit

Occurs: 1-3 days after the pre-intervention behavioral visit.
Location: Biomedical Research Imaging Center (BRIC)
Duration: 1.5 hours
Compensation: $60

Study Session Flow:

- Pre-Scan:
  - Weight
  - Blood glucose and hba1c
  - FMRI screening sheet
  - Internal state ratings (hunger/fullness/thirst/nausea) using VAS
  - Surveys: how long since last meal, menstrual cycle (if biologically female), sleep quality rating for past 2 days
- fMRI scan
- Post-Scan:
  - Taste test & hedonic VAS
  - Compensation

3. Intervention: Daily Beverage Consumption (21 days)

Occurs: every Monday, Wednesday, and Friday starting after their pre-intervention scan visit date for 9 occurrences
Location: Neuropsychology of Ingestive Behavior Lab
Duration: 5-15 minutes
Compensation: $20 at every third visit ($60 total)
Study Session Flow:

- Internal state ratings (hunger/fullness/thirst/nausea) using VAS
- Begin drinking the 10oz bottle of assigned beverage
- Taste test (of assigned beverage only) & hedonic VAS
- Collection of returned empty bottles
- Distribution of next day's (or weekend's) bottles
- Compensation

4. Post-intervention Scan Visit

Occurs: 2-5 days after the end of the intervention
Location: Biomedical Research Imaging Center (BRIC)
Duration: 2 hours
Compensation: $80
Study Session Flow:

- Pre-Scan:
  - Weight
  - Blood glucose and hba1c
  - FMRI screening sheet
  - Internal state ratings (hunger/fullness/thirst/nausea) using VAS
  - Surveys: how long since last meal, menstrual cycle (if biologically female), sleep quality rating for past 2 days
- fMRI scan
- Post-Scan:
  - Taste test & hedonic VAS
  - Compensation

5. Post-intervention Behavioral Visit

Occurs: 1-3 days after the post-intervention scan visit.
Location: Neuropsychology of Ingestive Behavior Lab
Duration: 1 hours
Compensation: $60

Study Session Flow:

- Weight
- Internal state ratings (hunger/fullness/thirst/nausea) using visual analog scales (VAS)
- Taste test & hedonic VAS
- Ad libitum beverage distribution
- Surveys: FFQ, YFAS, BIS-15, FCI, PFS, DEBQ, IPAQ
- Stop signal task
- Compensation

G. Study Evaluations and Measurements

Demographics and Anthropometrics. Self-ported gender, race, and ethnicity were recorded. Height was measured to the nearest mm using a stadiometer. Weight was assessed to the nearest 0.1 kg using digital scales, with participants wearing light clothing without shoes at each assessment. BMI (kg/m^2) was then calculated.

Intervention beverages & logos. To optimally test the hypothesized sugar-contingent neuroadaptations, the active SSB condition contained 111 kcals and 27g of sugar/10 fl oz (equivalent to the caloric and sugar density of soft drinks), and the unsweetened control beverages used in the study were similarly flavored to SSBs. In a preliminary study, we performed an evaluation of 6 differently mixed fruit flavors of beverages presented in the SSB and unsweetened versions to ensure that the selected beverages are equal in palatability and novelty across flavors. For the pilot, young adults meeting the inclusion criteria proposed here (n=27; $\bar{x}$ BMI = 23.3 ± 3.5) rated the mixed fruit strawberry lemonade and mixed fruit cherry orange flavors as equally palatable across flavors, and equally willing to consume daily for 3 weeks in both the SSB and unsweetened versions (*p's=0.77-0.99*). These ratings were not significant impacted by gender or BMI (*p's=0.46-0.99*). Beverages did not include high fructose corn syrup or artificial sweeteners, or preservatives; they are caffeine- and texture-free and generally novel in flavor. Beverages were presented in 10 fl oz bottles (295 mL). To mimic the branding of the beverages, logos were placed on the beverages that correspond with flavors. Logos were selected to be novel, of similar visual complexity, in black and white, and convey no information beyond a unique symbol, and yet be easily distinguishable from one another.

Explicit hedonic, taste and internal state ratings assessed via visual analog scales (VAS). Explicit hedonic scales were used to evaluate characteristics of the beverages, including pleasantness, desire, sweetness, bitterness, intensity, and familiarity insight into alterations the perceptual hedonic value of the beverages. Measures of internal state: hunger, fullness, thirst, and nausea were also collected. For perceptual hedonic assessments, labeled hedonic scales and generalized labeled magnitude scales provide a ratio-like data with the ability to compare individual differences in a more sensitive way than traditional scales. The participant consumed a small amount of the beverage and completed the associated scale (e.g., pleasantness). Additionally, similar internal state scales were assessed via 200mm cross-modal visual analog scales at all assessments. Scales of all beverages (SSB, USB; both flavors) were collected on the pre- and post-intervention behavioral visits. Scales for assigned beverages only were also collected on the pre- and post-intervention scan visits.

Stop signal task (SST). The Stop-Signal Task measures motor response time, accuracy, and response inhibition. The task was performed on an iPad app where participants underwent 6 total runs at the pre-intervention behavioral visit and at the post-intervention behavioral visit. Three of these runs were of their assigned condition, where the logo of their assigned beverage

was presented and the other three runs presented the logo of the unassigned beverage (of the same flavor). The order of assigned vs. unassigned was randomized across the sample. Within each run of this task, 64 (20 “go”) trials were presented, and participants were instructed to make a speeded response to a “go” stimulus except trials when an additional “stop” signal occurs (an X presented over the logo), in which case participants were instructed to withhold their response. The beverage logos (used as the “go” stimuli) were presented in two colors, indicating that the participant was to press the right or left of the screen. This speeded reaction time establishes a prepotency to respond to the logos. There were also trials where the “go” stimulus was followed, after a variable delay, by the stop-signal where the participants were instructed to withhold their response. The onset of the stop-signal, or stop-signal delay (SSD), varied and depended on the participant’s performance, such that it is decreased after a previous failure to inhibit and increased after a previous inhibition (resulting in SSD staircases across the course of the task). Participants were instructed to react quickly but also inhibit responses on trials where the stop-signal appeared as correctly responding and inhibiting were equally important.

Eating Attitudes

The Dutch Eating Behavior Questionnaire (DEBQ; 26) 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 (27). This scale has shown internal consistency (α= .93), 2-week test-retest reliability (r = .86), and sensitivity to detecting change.

Hedonic Impact of Food Environment

The Power of Food scale assesses reported appetitive drive, food reward responsivity, sensitivity to food cues in the environment, and the frequency of food-related thoughts (35). The 21-item scale prompts subjects to rate how much they agree with statements about hedonic hunger on a 5-point scale, where 1=do not agree at all, 2=agree a little, 3=agree somewhat, 4=agree, and 5=strongly agree. The scale has strong internal consistent (Cronbach’s alpha = 0.91) and an adequate four-month test-retest reliability (r = .77).

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 (28). This scale has shown internal consistency (α=.81), 2-week test-retest reliability (r =.88), and discriminates between psychiatric patients and controls.

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 (29) to measure habitual dietary intake. Food frequency questionnaires are the most practical and economical method for collecting dietary intake data in large studies (30). Block FFQ values correlated (r = .57) with 4-day food record estimates for energy and most

nutrients (31). 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; (32)). Participants will also complete a modified version of the Pittsburgh Sleep Quality Index, which will ask about sleep quality over the past week (33), 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 (34).

fMRI scan paradigms. The participants will complete 2 types of functional MRI paradigms, a task-based paradigm and a resting-state paradigm.
The task-based paradigm will assess evoked blood oxygen level dependent (BOLD) response to receipt of study beverages (SSB and unsweetened) and a water solution, and logo-elicited anticipation of both SSB and unsweetened beverages and water solution. The paradigm is controlled by in-house scripts written in PsychoPy software. The visual stimuli are two beverage logos, a water logo, and a fixation cross. The logos served as branding for the beverages. Each logo (1 second) signals impending delivery of 3 mL of the associated beverage/water over 6 seconds, with the fixation cross otherwise presented. A jitter ranging from 5 to 13 ($\bar{x}$ =8) seconds follows each trial. In total, the participants are presented 24 repeats of the events of interest over four 7-min runs. Each participant is exposed to the SSB and USB logos of their assigned flavor independent of their intervention assignment.

The resting-state scan will assess functional connectivity by examining the correlation of fluctuations of BOLD signals in different regions of the "resting" brain and will provide a measure of its functional organization. Resting-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.

H. Study Intervention

- During the 3-week (21 days) intervention period all participants will come to our lab at a consistent time Monday, Wednesday, and Friday to: 1) consume that day's beverage in lab; 2) complete hedonic ratings (described above); 3) pick up the following day(s) beverage; and 4) return the empty bottles from the previous day(s). On Fridays, participants will be given two bottles to take home and instructed to consume one per day.
- Empty bottles will be returned to increase compliance. In the case the participant is unable to attend an intervention assessment and cannot acquire their beverage, they will return the following day to resume. To remain in the study, the participants may not miss consuming the beverage for three consecutive days, and must consume the beverage >17 occasions.
- Following current protocols, the behavioral and scan sessions will be scheduled at approximately the same time in the day for each assessment (within-subject) and will occur after a 4-6 hour fast. Participants will be reminded of the day before and number of hours since last eaten will be recorded at assessment.
- During the intervention we will ask participants to consume their beverage 1 hour outside of a meal, as not to confound beverage with postprandial meal effects, and maintain their typical dietary patterns as to best mimic a real-world setting in which they elected to consume a new-to-market beverage daily.

I. 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, finger sticks, 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.

J. 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 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.

K. Recruitment Strategy

Recruitment flyers will be placed on the UNC campus, in community centers, and restaurants in local Chapel Hill/Durham area. Additionally, we will use 'Join the Conquest', an online study listing and engagement site intended to improve transparency and awareness of research at UNC. Those interested in participating will be directed to fill a screening questionnaire, which will be used to determine participant eligibility. Eligible 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 study assessments.

L. Consent Process

The consent will be emailed to the subject for review prior to enrollment. Study staff will be available to answer any questions prior to scheduling/meeting with subjects for the first assessment. Consent will be confirmed by trained research staff. Consent will be reviewed and confirmed and all answers regarding study expectations will be answered by trained staff on the pre-intervention behavioral visit.

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