Changing how the brain responds when making decisions: Translating neuroscience to population health

Sponsor: NA

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I. CONFIDENTIALITY

These materials contain confidential information belonging to the University of Kansas Medical Center (KUMC).

II. DESCRIPTION OF THE RESEARCH PROJECT

1. *Purpose of this research study:*

Our long-term goal is to understand how the interaction between positive associations and thinking about future rewards may influence healthy decision-making across multiple health behaviors (e.g. eating, exercise, smoking). The objective of the current study is to empirically test the combined effects of positive affect and positive episodic future thinking on brain activation and behavioral indices of TD and healthy food choices. Our central hypothesis is that positive affect and episodic future thinking will interact to increase brain activation in regulation brain regions (dlPFC) to regulate reward responses to unhealthy foods and increase brain activation in reward brain regions (vmPFC) to healthy foods and translate to healthier choices.

To address our objective and test our central hypothesis we will pursue the following specific aims in 20 overweight to obese participants:

Aim 1: Examine the effect of positive affect and episodic future thinking guided imagery on brain activation in regulation and reward regions. We hypothesize that positive affect/episodic future thinking will lead to increased regulation related activation when evaluating and making food decisions and increased vmPFC activation when evaluating and making healthy compared to unhealthy food decisions.

Aim 2: Examine the effect of positive affect and episodic future thinking guided imagery on healthy food choice and healthy food demand. We hypothesize that positive affect/positive episodic future thinking will lead to increased healthy food choices in the scanner and the lab, as well as, increased demand for healthy foods.

Aim 3: Examine correlations between changes in brain activation and food choices and food demand. We hypothesize that greater changes in regulation regions will correlate with more healthy food choices in the scanner and the lab.

2. *Background/Significance of this research study:*

Obesity is a complex condition arising from a combination of genetic, physiological, environmental, behavioral, social and psychological factors [1]. Homeostatic processes motivate us to seek out food when we are hungry [2], however we also eat for pleasure [3-6]. Despite extensive basic research on food reward in nonhuman animals and cross-sectional [7-12] and prospective studies [13-18] of food reward in humans, the extent to which these systems can be modified with brief and scalable interventions is unclear. Cognitive neuroscience offers a non-invasive approach to examine neural targets associated with eating behaviors, decision-making and obesity by increasing understanding of how people respond to food rewards (e.g. food cues) and make decisions to eat healthy or unhealthy foods. *The scientific premise for the proposed study is grounded theories of food reward in obesity and previous neuroimaging studies (conducted by Dr. Martin at KUMC and in other labs).* Functional neuroimaging studies of food decision-making indicate that the vmPFC drives choices related to tastiness of food, whereas, the dlPFC drives choices related to healthiness of food [19, 20]. Current theories of overeating and obesity are supported by prospective studies of weight change [21, 22]. All of these theories share a common theme that overeating is associated with increased reward sensitivity which is sometimes combined with decreased inhibitory responses or regulation to food, which can lead to overeating and eventual weight gain if energy balance is not achieved. The interplay between reward and inhibitory control or regulation have also been outlined in dual-system models that summarize the neural systems related to health behaviors into the regulation network referred to as the “executive” [23], “deliberative” [24], or “reflective” system [25] and the reward network referred to as the “impulsive” [23, 25] or “automatic” [24] system. The regulation network

includes brain regions associated with cognitive control, emotion regulation, and goal directed behavior [e.g. dorsolateral (dlPFC), dorsomedial (dmPFC), ventrolateral prefrontal cortices (vlPFC)]. The reward network includes brain regions associated with evaluating, anticipating and processing rewards [e.g. ventromedial (vmPFC), medial prefrontal cortices (MPFC), and striatal regions. In obesity, the regulation network is often considered underactive and the reward network is considered overactive [26]. When there is an imbalance between these networks, the reward network can override the regulation network leading to overeating, weight gain, and eventually obesity [26]. A critical implication of this model is that effective treatments target one or both of these systems to improve treatment outcomes [24, 25]. In obesity, the regulation and reward networks can be measured using functional magnetic resonance imaging (fMRI) while obese individuals view food cues [8, 27-30] or make decisions [19, 20]. Neuroimaging studies suggest a disruption in the balance between the regulation and reward networks in obese compared to healthy weight individuals. Moreover, when overweight and obese individuals are provided with real-time feedback during fMRI scanning they can learn to increase the functional connectivity between reward and regulation regions [31]. Behaviors that have been associated with activity in the regulation network such as temporal discounting (TD) can serve as a behavioral index of regulation. Neuroimaging studies of delay discounting show activation in regulation regions when participants make decisions involving delayed rewards and activation in reward regions when participants make decisions involving immediately available rewards [32]. Obesity is associated with greater discounting [33, 34]. Episodic future thinking is a technique in which individuals are asked to picture themselves in the future and has been shown to reduce preferences for immediate compared to delayed rewards (i.e. temporal discounting) in obese and overweight individuals [35] and smokers [36]. The contribution of the proposed research is to identify distinct neural targets for interventions to promote and improve healthy decision-making and behaviors. Specifically, focusing on what happens in the brain and behaviors before and after a positive affect and episodic future thinking guided imagery exercise. *This is significant because it will systematically examine reward/regulation activation during food evaluation and decision-making in the scanner and test real-world food decisions outside the scanner.* The benefits of this approach will be to engage neural targets of reward and regulation to increase healthy decision making. Finally, this proposal adds neuroimaging assays to our Cancer Research United Kingdom (CRUK) pilot project.

3. *Review of the Scientific Merit*

Despite well-described models of overeating and neuroimaging studies of food reward and regulation in obesity there is a disconnect between these models that focus predominately on the contribution of reward in the development of obesity and behavioral weight loss interventions that focus on creating an energy deficit by reducing energy intake and increasing energy expenditure through diet and exercise. Although an energy deficit is essential for weight loss, research is limited in terms of developing and testing interventions specifically designed to engage the reward and regulation brain regions described in neuroscience models of eating behaviors. To realize the benefits of the significant advances that have been made in understanding the neural mechanisms underlying obesity it is vital to integrate cognitive neuroscience models and intervention development. *The research proposed in this application is innovative, in our opinion, because obesity is a complex condition arising from several factors including the interplay between brain regions associated with reward and regulation and this study will examine the impact of a novel intervention designed to increase reward for healthy foods and increase regulation for unhealthy foods, where food reward and regulation occurs; in the brain*. The long-term benefits of this approach could be the development of a scalable eating behavior intervention that could be delivered online or through a mobile app to complement a comprehensive lifestyle intervention for weight loss or other health behavior interventions (e.g. smoking).

4. *Location of where the study is to be conducted*

This study will be conducted at the Hoglund Brain Imaging Center at the University of Kansas Medical Center (KUMC).

III. STUDY INCLUSION AND EXCLUSION CRITERIA, RECRUITMENT PROCEDURES

1. *Subjects enrolled*

Approximately 20 overweight and obese participants will be recruited from the Kansas City metropolitan area using recruitment methods used that have been successful in Dr. Martin's previous obesity related studies, including internet (e.g., Craigslist), flyers and the Pioneers Registry. Individuals who are eligible and interested in participating will be scheduled to complete two appointments. Subjects will be recruited from informational flyers posted on the KUMC campus and surrounding establishments (e.g., restaurants, shops, bars, apartment buildings), from e-mail alerts through the myKUMC website, and from advertisements posted on www.craigslist.org. All flyers and advertisements will be approved by the Human Subjects Committee.

2. *Inclusion/Exclusion Criteria*

Inclusion: Individuals are eligible if they meet the following criteria: 1) body mass index (BMI) 25 to 55 kg/m^2, will 2) 18-55 years of age, 3) right-handed, and 4) not currently dieting or attempting to lose weight.

Exclusion: Individuals may be ineligible if they report any of the following: 1) serious medical illness unsuitable for the MR scanner based on best clinical judgment; 2) any neurologic or current psychiatric diagnosis; 3) currently taking anti-seizure medication; 4) history of concussion; 5) left-handedness 6) risk for hazard due to magnetic fields such as metal in the body surgically or accidentally (e.g., pacemaker, cochlear implants, aneurysm clips, intravascular stents or coils, spinal shunt, injury involving bullets, shrapnel or metal implanted in their body, etc); 7) pregnancy. Final eligibility will be at the discretion of the PI.

MRI safety screening will be completed during pre-screening as well as on the day of the MRI testing.

3. *Consenting of Subjects*

Participants will provide written consent in order to participate in the study.

IV. STUDY DESIGN AND PROCEDURES

1. *Study Summary*

The experimental study assesses the interactive effects of positive affect to increase positive associations with healthy food and episodic future thinking to increase regulation during food decision-making on measures of discounting, food demand, and food choice in and out of lab. During the study participants are randomized to receive a guided mental imagery scheme to increase positive affect and positive episodic future thinking. Measures of temporal discounting (TD), food demand, and food choices serve as dependent variables and are measured at Session 1 and Session 2 to assess immediate and lasting impact of guided imagery.

2. *Discussion of Study Design*

Careful consideration was given to the selection of the fMRI task for the proposed study. We chose to use a passive cue-reactivity paradigm as opposed to one that explicitly instructs participants to regulate their responses to food cues or other food decision-making tasks. This is because the goal of the proposed study is to examine how the brain changes in response to positive affect/episodic future thinking guided imagery, as opposed to changes resulting from instructions to regulate. We chose to focus on within subject changes related to only one of our guided imagery exercises as oppose to the 2 by 2 design due to budget and power considerations. This approach will allow us to test the within subject effects in the combined positive affect and episodic future thinking guided imagery in the

condition where we expect to see the greatest changes in our behavioral measures of TD, demand and food choice in a moderate neuroimaging sample size (n=20).

3. *Procedures by Visit*

Potential participants will contact the study team via telephone, e-mail, or by filling out an online eligibility survey. During the initial correspondence, the study will be explained briefly to assess interest and determine initial eligibility. If interested, a consent appointment will be scheduled for the participant. The appointment will take place at the Hoglund Brain Imaging Center. We will re-evaluate eligibility at each appointment.

Initial screening. Initial screening interviews will be conducted online (RedCap survey) or by phone. This screening will review inclusion/ exclusion criteria, and provide detailed information about study participation. Participants may be asked to fast for two hours before each appointment.

Study Activities

1) *Session 1 (Day 1):* Staff will review consent forms describing study goals, procedures, risks, and confidentiality. During the baseline session participants will complete: 1) a battery of questionnaires assessed in the CRUK project, 2) baseline assessment of TD for food and money, 3) baseline assessment of food demand, 4) baseline fMRI assessment of food cue-reactivity and decision-making, 5) combined positive affect/episodic future thinking guided imagery exercise (delivered in the scanner; See Appendix), 6) follow-up food cue-reactivity and decision-making task, 7) follow-up assessment of TD for food and money, 7) follow-up assessment of food demand, and 8) ad lib food choice. The entire testing session is expected to take approximately 2.5 hrs.

   Measures: A battery of measures assessing basic health status, psychological wellness, and health behavior habits including sleep, diet, physical activity, and alcohol, drug, and cigarette use. *TD tasks:* A computerized delay discounting task [37, 38] will be used to assess impulsive choice. The delay discounting task asks participants to choose between hypothetical smaller-sooner and larger-later rewards across a wide range of delays (1 day to 25 years). Participants will complete two versions of the task, each with a different reward type (money, food). *Food Demand Task:* A food demand task will be used to measure demand for healthy and unhealthy foods. In this task participants are asked how much food they would eat in a day across a wide range of hypothetical prices ($0.01 to $35). The resulting data will be modeled to yield a number of economic indicators related to demand including elasticity, intensity, breakpoint, and maximum expenditure. *fMRI food cue-reactivity task and MRI acquisition:* The experimental paradigm includes passive viewing of healthy and unhealthy food cues, followed by a decision of whether or not participants want to eat the item previously presented (1-5 scale). This paradigm allows us to look at brain activation to the food cues while participants evaluate the item and brain activation during the decision-making phase. A total of four fMRI runs, lasting approximately 6.5 minutes, will be completed before and after the guided imagery exercise. *Ad lib food decision:* Participants will be asked to fill out additional questionnaires in a room where snacks are available. Following participation researchers will see which and how much of the snacks were eaten.

   Guided imagery: Participants will listen to a ~8-minute guided imagery exercise in the scanner. The guided imagery exercise was developed through community and expert panels and asks participants to think about positive associations with healthy foods and imagine their future healthy selves (See Appendix).

2) *Food diaries (Days 2-6):* Collected daily through online forms (or paper forms, if needed) between Session 1 and Session 2.

3) *Session 2 (Day 7):* During the follow-up session participants will repeat Session 1 measures including: 1) a battery of questionnaires assessed in the CRUK project, 2) assessment of TD for food and money, 3) assessment of food demand, and 4) ad lib food choice. Participants will receive a debriefing form explaining the overall goal of this study at the end of the final appointment.The entire testing session is expected to take approximately 1 hour.

4. *Safety and Tolerability Parameters*

Written informed consent will be obtained from each subject. No subjects will have metallic implants or other contraindications for MRI. The MR imaging and physiological data collection procedures do not pose a significant risk to subjects meeting the entry criteria for this study.

5. *Efficacy Parameters*

This study is not assessing treatment efficacy and is safe; therefore, no efficacy parameters will be monitored.

6. *Laboratory Tests/Measurements*

Laboratory tests or measurements collected in this study will be the participants' self-report measures (described above), food diaries (described above), and the MR scanning of participants' brains,. These MR scans are not medically diagnostic and will not be read by a physician.

V. STUDY MEDICATION

There will be no medication used in this study.

VI. RISKS AND BENFITS OF THE RESEARCH STUDY

1. *Risk*

There is no known hazard associated with MR imaging. Nuclear magnetic resonance imaging does not involve ionizing radiation such as that associated with X-ray or radionuclide techniques. All studies will use radiofrequency power deposition and gradient switching which have been approved by the FDA. High speed echo planar imaging has been performed on hundreds of volunteers and patients across the US, with no adverse reactions reported. Although MR imaging is thought to be hazard free, some subjects may find the enclosed space of the MRI device to be physically uncomfortable or anxiety producing. Subjects will be able to converse with a staff member via a microphone and speaker system. Every effort will be made to reassure the patient and minimize any such discomforts. Noise from the MRI machine can also cause discomfort. Subjects will be offered earplugs and/or earphones to minimize this discomfort as well. Subjects can request that a study be stopped at any time. No risks due to the physiological data collection equipment are anticipated. There are no substantial risks associated with the questionnaires or other testing to be performed outside the scanner.

The potential for unanticipated problems will be monitored and reported to the appropriate individuals. Subjects' privacy will be protected by conducting the assessments in a private room. In addition, each participant will be assigned a subject number to ensure that all data is kept completely confidential.

2. *Benefits*

There will be no direct benefits to the participants of this study. The primary benefit to study participants will be their contribution to research. Results from this study will help us understand how people make food decisions and how guided imagery may support healthy food decisions.

VII. COST OF RESEARCH

Participants will be paid up to $115 for completing the study. Participants will be paid $30 for their first appointment and $55 for their second and $5 per day for each food diary completed. A larger payment is scheduled for the second appointment to encourage participants to return. Scan costs and participant reimbursements will be provided by Dr. Martin.

VIII. STUDY COMPLETITION/WITHDRAWAL

Participants will be informed that they are able to discontinue participation and withdraw from the study at any time with no penalty. Participants will be compensated a prorated amount based on what aspects of the study they have completed. Even after they have completed the assessment, they can opt to withdraw their data from the researcher's use at any time.

IX. STATISTICAL CONSIDERATIONS

As mentioned above, we will recruit approximately 20 participants. This sample will be more than sufficient to provide power for the statistical analyses. Statistical measures used will include standard descriptive statistics (mean, median, mode, standard deviation) for the rating task, as well as the generalized linear model for the functional MRI data.

Published estimates of sample size for fMRI experiments with typical activations, and a conservative random effects model, indicate that 80% power can be achieved using a threshold of .05 with approximately 10 participants, or .002 with approximately 20 participants [39]. Research suggests that even approximately 20 participants per group in fMRI studies yields group activation maps consistent with larger sample sizes [40].

X. STUDY RECORDS

Study records will be maintained in locked cabinets and password-protected databases (RedCap) within KUMC for the duration of the study. Participants will be assigned study ID numbers, and all data for publication or presentation will be deidentified.

XI. DISCLOSURE OF DATA

Only the study team members will have access to the raw data.

XI. REFERENCES

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