Evaluating Motivation and Reward Mechanisms and Brain Substrates in Adults with Obesity: Further evidence that obesity affects physical and mental health

Roger S. McIntyre

Professor of Psychiatry and Pharmacology, University of Toronto, Toronto, Canada
Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF), Toronto, Canada
Director, Depression and Bipolar Support Alliance (DBSA), Chicago, USA
Head, Mood Disorders Psychopharmacology Unit
http://www.mdpu.ca/
Professor and Nanshan Scholar, Guangzhou Medical University, Guangzhou, China
Adjunct Professor College of Medicine, Korea University, Seoul, Republic of Korea

Mailing Address:
73 Mathersfield Drive
Toronto, ON M3W 3W4
Canada
Telephone: 416-669-5279
Fax: 416-603-5368
Email: roger.mcintyre@uhn.ca

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Study Synopsis:

Anhedonia and abnormalities in reward behavior are core features of overweight/obesity (OW), a highly prevalent condition within MDD populations and is independently associated with reward disturbances. We therefore aimed to investigate the brain substrates subserving reward and motivation in adults with overweight/obesity. Herein, we are primarily interested in three overlapping, yet distinct aspects, of anhedonia. We are primarily interested in motivation, reward valuation, and reward learning towards addressing the measurement of each of these respective subdomains, eligible participants will complete validated gold standard measures (i.e. the Effort Expenditure for Rewards Task (EEfRT) (reward valuation), Probabilistic Reward Task (PRT) (reward learning), and the Monetary Incentive Delay (MID) task (reward anticipation)).

Twenty adults with overweight/obesity will complete all tasks at a single visit with two of the tasks being completed prior to MRI and one of the tasks (i.e. EEfRT) will be completed during MRI acquisition.

The **primary aim** of this pilot study is to determine whether associations exist between obesity and decreased performance on the respective motivation/reward paradigms. In addition, associations between performance on reward tasks and functional connectivity, as measured by MRI and DTI, a secondary objective is to ascertain whether associations exist between performance on the motivation reward tasks and gold standard measures of food intake (i.e. food diary) and energy expenditure (i.e. calorimetry).

Introduction

Anhedonia is a significant complaint and psychopathology in OW. Anhedonia is defined as markedly diminished interest or pleasure in all, or almost all, activities for an extended period of time. Anhedonia is a core criterion item for the diagnosis of MDD and OW, and is a robust predictor of poor longitudinal course of symptoms[1-4]. Existing psychological and pharmacological treatments are relatively ineffective for treating anhedonia, as they have little effect, and in some cases may even worsen anhedonic symptoms[2,5]. As a result, anhedonia is one of the most prevalent residual symptoms following treatment with antidepressants in individuals with MDD and OW[2,6,7].

Anhedonia includes elements of multiple reward processes[8-10]. Reward systems are primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, and reward/habit learning[8-10]. Evidence indicates that individuals with mood disorders exhibit abnormalities in multiple subcomponents of reward[13-17]. One of the main reward sub-constructs of interest in MDD is reward valuation, which includes the measurement of value and/or incentive salience of a prospective outcome and the willingness to work for it (i.e. effort)[11,12]. A consistent finding in MDD has been a decrease in the willingness to expend effort for rewards[13-16,18]. Individuals with depression display reduced motivation on effort-based decision making[14-16], a dissociation between liking a reward and the willingness to exert effort for it[13], and an increased subjective feeling of having exerted more effort[16].

Replicated evidence indicates that OW is highly prevalent in MDD populations. Meta-analytical studies have estimated the prevalence of obesity in MDD between 30 and 70%[19-22]. Conversely, OW has been consistently associated with motivational deficits, to both food and non-food rewards[23]. Evidence indicates that in obesity the anticipatory reward response seems to be increased[24,25], whereas, similar to MDD, the willingness to invest effort is diminished[26,27].

Within MDD populations, obesity, and its metabolic correlates (e.g. insulin resistance), have been associated with increased self-reported anhedonia[28,29]. As a result, anhedonia has been proposed as a key clinical mediator between MDD and metabolic comorbidities[30,31].

Nevertheless, few studies have used objective methods to assess reward deficits in populations with MDD and obesity. Herein, we aim to explore the role of OW in effort-based decision making in overweight/obese adults with varying levels of body mass index (BMI) above 30kg/m^2. We primarily aim to investigate the effects of OW correlation with effort for rewards, as measured by the Effort Expenditure for Rewards Task (EEfRT). The secondary aim is to examine the associations between effort-based decision-making as measured by EEfRT, with MRI/DTI measured alterations in reciprocity between reward and cognitive control circuits.

We **hypothesize** that obesity is associated with deficits in each of the reward paradigms we have selected. We also **hypothesize** that the foregoing disturbances correlate with functional disconnectivity within reward/cognitive control networks.

Methodology

Participants

Participants will be identified at the Brain and Cognition Discovery Foundation (BCDF). Twenty subjects with obesity, will be enrolled. All patients will be assessed for concurrent psychiatric disorders (e.g. mood disorders). Eligibility criteria are as follows: inclusion criteria: (a) 18-65 years of age; (b) meeting DSM-V criteria for: (i) major depressive disorder (symptomatic or asymptomatic in any phase of the illness) or (ii) bipolar disorder I/II (symptomatic or asymptomatic in any phase of the illness); (c) ability to provide written and informed consent; (d) obesity 30 kg/m^2; (e) weight under 440lbs; (f) shoulder-to-shoulder width under 60 cm; Exclusion criteria are as follows: (a) age below 18 or above 65; (b) use of benzodiazepines or consumption of alcohol within 12 hours of assessments; (c) abuse of marijuana; (d) physical,

cognitive, or language impairments sufficient to adversely affect data derived from assessments; (e) diagnosed reading disability or dyslexia; (f) clinically significant learning disorder by history; (g) history of moderate or severe traumatic brain injury; (h) other neurological disorders, or unstable systemic medical diseases; and (i) pregnancy and post-partum period (j) presence of any contra-indications for MRI; (k) weight above 440lbs; (l) shoulder-to-shoulder width greater than 60 cm. All subjects will be consented prior to initiating the study; (m) >45 BMI; (n) suicidality as determined by clinical discretion.

Measurements Obtained at Single Visit

1. Sociodemographic:
    a. Age
    b. Sex
    c. Education
    d. Employment Status
    e. Education Attainment
    f. Marital Status
    g. Ethnicity and Race
2. Illness Measurements:
    a. Severity of depression will be assessed with the Quick Inventory of Depressive Symptomatology (QUIDS)
    b. Measurement of anhedonia composite (SHAPS)
    c. Self-rated cognitive measurement (PDQ-5) Perceived Deficit Questionnaire 5
    d. Objective cognitive measurement (TMTA/B)
    e. Digit Symbol Substitution Test (DSST)
    f. UCLA Loneliness Scale

g. Food Diary
h. Calorimetry
i. Anxiety Measurement (Hamilton Anxiety Scale) (HAMD)
j. Age of onset
k. Number of episodes
l. Number of hospitalizations
m. Duration of current episode
n. Psychiatric comorbidity
o. Number of treatments

3. Medical Assessment:
    a. Weight
    b. Height
    c. Waist circumference
4. Laboratory Measures:
    a. Blood glucose
    b. Cholesterol and fractionation (E.g. HDL, LDL and triglycerides)
    c. Insulin levels
    d. Interleukin 1, interleukin 6, interleukin 10, tumor nercosis factor alpha, c reactive peptide, adiponectin, leptin, gherlin, DPP-IV
    e. Oxidative stress markers (e.g. TBARS)
5. Effort Expenditure for Rewards Task (EEfRT)
6. Monetary Incentive Delay (MID) task
7. Probabilistic Reward Task (PRT)
8. MRI Scan

All assessments and scan will be done on the same day.

Procedures for Participants

Visit 1

The single visit entails the provision of detailed study information to participant and obtainment of informed written consent, as well as completion of all questionnaires, activities, MRI, and participant compensation. The psychiatrists will assess participants' eligibility based on inclusion/exclusion criteria and confirm a diagnosis of MDD or BD based on their scheduled appointment visit. Demographics including date of birth, sex, and race will be recorded. Years of education will be recorded as well. Psychiatric and medical history, number of psychotropic medications received according to participant self-report/clinical chart review, as well as anthropometrics (including height, weight and waist circumference) will be measured. Participants will complete a series of questionnaires to assess their illness. These include: Quick Inventory of Depressive Symptomatology (QIDS), Snaith-Hamilton Pleasure Scale (SHAPS), Perceived Deficits Questionnaire for Depression (PDQ-5-D), Hamilton Depression Rating Scale (HAMD). Participants will also have loneliness assessed by participating in the UCLA Loneliness Scale. All self-reports will be administered by a member of the study team. Participants will record their food intake via a Food Diary, and will have a Calorimetry test taken. Participants will also complete cognitive measures including the Trail Making Test A/B (TMT A/B), and the Digit Symbol Substitution Test (DSST). Participants will then complete the Monetary Incentive Delay (MID) task, as well as the Probabilistic Reward Task (PRT). All study procedures will take place in a quiet setting. Fasting (12-hours) clinical and research bloodwork will also be collected. Participants will be escorted by a study member to the MRI facility where they will complete the MRI and the Effort Expenditure for Rewards Task (EEfRT). Upon completion of the MRI, participants will receive the reimbursement fee for their participation in the study.

Adverse Events

Definitions:

Adverse event: An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An

undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event: A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s). Note that SAEs that could be associated with any study procedure should also be reported. For such events the casual relationship is implied as "yes".

Recording of Adverse Events

AEs will be collected during each visit. At each visit, subjects will be asked if they have had any health problems since the previous visit. All AEs will be recorded appropriately, whether or not considered related to the investigational product. This will include AEs spontaneously reported by the patient and/or observed by the staff as well as AEs reported in response to a direct question e.g. “Have you had any health problems since your last visit?”

For each AE, the following parameters be described:

- start and stop date
- action taken with regards to investigational product
- outcome
- if the AE caused the patient to discontinue
- a statement if the AE fulfils the criteria for a SAE or not

- the investigator's assessment of the causal relationship between the event and the investigational product

- intensity of the AE

  - mild (awareness of sign or symptom, but easily tolerated)

  - moderate (discomfort sufficient to cause interference with normal activities)

  - severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Symptoms associated with overdose should be reported as AEs. For further information regarding overdose, see section.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Follow-up of adverse events should be based upon the clinical judgement of the investigator.

Reporting of Serious Adverse Events

Reporting of SAEs to regulatory authorities will be done by the investigator in accordance with local regulations. A copy of the report will also be sent to the manufacturer of the investigational product.

Risks Related to Being in the Study

This study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about that have not been seen in study participants to date. Some can be managed. Please call the study doctor if you have any side effects even if you do not think they have anything to do with this study. The risks we know of are:

a) MRI risks: There are few potential risks of having an MRI scan, as it is a non-invasive procedure and does not involve any radiation. The main potential risk comes from loose metal objects, which, if taken near the scanner, could be dangerous. The combination of the noise of the scanner and confined space can also be stressful for people who feel uncomfortable in closed spaces.

b) Blood draw risks: Drawing blood may cause very mild pain, bruising, redness, and rarely infection at the needle stick.
c) Other risks: In addition to medical risks, being in this study may make you feel uncomfortable. You will be asked personal questions about your psychiatric and medical history. You may refuse to answer questions or stop the interview at any time if there is any discomfort. Administering the cognitive testing may sometimes be frustrating particularly if you are not performing as well as you think you should, and may also lead to mild mental and physical fatigue.

Benefits to Being in the Study

You may or may not receive any direct benefit from being in this study. Information learned from this study may help other people with mood disorders in the future.

Timeline

It is estimated that it will require approximately 3-5 months to recruit.

Primary and Secondary Outcome Measures

The **primary outcome measure** in this study will be the association between performance on the EEfRT, MID, and PRT. Anthropometric data will be obtained from all participants at the day of the EEfRT assessment. Body mass index (BMI) will be measured using the formula BMI = weight (Kg) / height (meters)^2. The **secondary outcome** will be the association between the EEfRT/ MID/PRT and function reciprocity of the reward circuit/cognitive control network as measured by MRI/DTI. All participants will also have whole blood samples collected after a 12 hour fast. Metabolic parameters will be measured immediately in a single laboratory with the same assay. Insulin resistance and beta-cell function (i.e. insulin secretion) in basal state will be calculated from fasting plasma glucose and fasting insulin using the HOMA2 calculator (http://www.dtu.ox.ac.uk)[33].

Effort Expenditure for Rewards Task (EEfRT), Probabilistic Rewards Task (PRT), and Monetary Incentive Delay (MID) task

The EEfRT measures participants' willingness to make efforts to obtain a monetary reward under different conditions of reward probability and magnitude[14,18]. In each EEfRT trial, participants are given an opportunity to choose between two tasks with different levels of difficulty: "hard task" and "easy task." Successful completion of the easy task trials requires 30 button presses using the dominant index finger within 7 seconds, whereas the hard task trials requires 100 button presses using the non-dominant little finger within 21 seconds. Participants will be informed that successful trial completion does not guarantee winning the monetary reward. Before making a choice, participants are provided with information that varies from trial to trial regarding: (1) the probability (12%, 50%, or 88%) of winning the money; and (2) the magnitude of reward for successfully completing the hard task. The reward magnitude will be set at $1.00 for easy tasks and higher amounts that will vary per trial within a range of $1.24-$4.30 for hard tasks. Probability levels will always be applied to both the hard task and easy task, and there will be equal proportions of each probability level across the experiment. Participants are given 20 minutes to perform the task; thus, the number of trials will vary across the participants. The Probabilistic Rewards Task (PRT) measures response bias and sensitivity to reward under variable conditions. The Monetary Incentive Delay (MID) task assesses the basis of anticipation and consumption of reward and punishment. Each test takes approximately 20 minutes to administer.

Statistical Analysis

Graph theoretical analysis (GTA) will be used to assess functional connectivity of the default mode network, cognitive control network, affect network and reward network. This is a

preliminary exploratory analysis, descriptive statistics will be conducted on the sociodemographic, clinical and metabolic parameters. Associations between obesity and alterations in functional connectivity will be the primary outcome of interest and additional coprimary outcome is the association between obesity and reward motivation as indexed by the EEfRT/MID/PRT task. Laboratory parameters will be used to explore potential mediational relationships between obesity and brain connectivity measurements, as well as reward performance.

For each variable, distribution normality will be assessed with one-sample Kolmogorov-Smirnov tests. Comparisons between groups will be conducted using independent samples t-tests and Mann-Whitney U (for normally and non-normally distributed variables, respectively). Participants are given 20 minutes to complete the EEfRT, and the number of trials completed during that time will vary among them (Table 1). Consistently with previous studies, only the first 50 trials will be used[18]. Similar to previous studies using the EEfRT, we will use generalized estimating equation (GEE) models to test the effects of groups, reward magnitude and probability on the willingness to expend effort for rewards (i.e. percentage of trials on which the 'hard' task was selected). We will use an independent matrix, which best fit our data, and a binary logistic distribution to model the dichotomous outcome of choosing the hard versus the easy task. All GEE models will include reward magnitude, probability, and expected value (EV, defined as the interaction between reward probability and magnitude). In addition, each model will include a trial number as a covariate to control for possible effects of fatigue over the course of the task. Reward magnitude will be categorized in three groups: low (<$2.30), medium ($2.31-$3.29), and high (>$3.30). To assess associations between EEfRT and clinical and metabolic data, we will calculate the mean proportions of hard-task choices for all subjects.

Stepwise linear regression will then be used to identify significant predictors. MRI/DTI will be attained for all subjects.

Data Handeling

Personal Data Protection

All data collection material will be de-identified. Participant records will be distinguished using participant identification (PID) numbers.

Data Retention

Records and documents pertaining to the conduct of the study as well as all data collected as part of the study will be retained in a secure place for 25 years in accordance with Health Canada regulations. All data collected throughout the study will be kept with membership of the BCDF for 25 years.

Participant Protection

Participants will not be placed at any risk as a result of the study. Information obtained will be maintained in a secure and confidential fashion. No participant will be coerced and/or placed under duress to complete study procedures.

Implications

We believe our results will comport with the notion that obesity [31] is subserved by disturbances in reward circuits and cognitive control networks. We believe that alterations in reward and motivation are fundamental brain disturbances due to obesity[34-36],[37-39]. The Research Domain Criteria (RDoC) construct of reward is a core domain for the overlap between mood and metabolic disorders. We believe our results will show that obesity moderates and as a consequence of disturbance in reward and motivation and functional disconnectivity.

Mechanistically, a recent genetic study identified multiple genes that are shared between mood and metabolic disorders; and revealed an over-representation of genes involved in

dopamine signaling, which plays a crucial role in anhedonia and reward processing[40]. In addition, obesity and MDD have a shared biosignature, with well-documented involvement of inflammatory mechanisms, hypothalamic–pituitary–adrenal (HPA) dysregulation, and oxidative/mitochondrial stress[41-43]. Replicated neuroimaging studies have reported specific morphological alterations of the MDD and obesity comorbidity, implicating mainly medial prefrontal areas[39,44]. Conversely, these areas are an important hub of reward valuation, and are known to be affected by, for example, inflammatory and metabolic mediators[45-48].

One of the key subcomponents of metabolic dysfunction in obesity is insulin resistance[49]. Insulin resistance has been associated with depressive symptoms in epidemiological studies[50] and, in clinical populations, with anhedonia specifically[28]. Indeed, we observed a strong correlation between insulin resistance and willingness to expend effort in the MDD subgroup. Multiple brain regions that are relevant to reward systems have relatively increased expression of insulin receptors[51,52]. Specifically, midbrain dopamine neurons, one of the main hubs of reward neurocircutiry[53,54], widely express insulin receptors[55]. Imaging studies have reported that, in healthy individuals, insulin modulates brain activity in the hypothalamus, hippocampus and prefrontal cortex[56-58]. A recent gene expression analysis reported that the differential expression of dopamine-related molecules in individuals with mood and psychotic disorders was related to altered expression of insulin signaling genes; an effect that was moderated by obesity in a region-specific manner (Mansur et al., 2018). As a result, peripheral insulin sensitivity has been shown to modulate reward behavior in humans. In obese adults, insulin resistance was associated with a stronger preference for immediately receiving a smaller, but certain, monetary reward over delaying the receipt of a larger, but less certain one (i.e. greater delay discounting)[59].

In humans, insulin resistance is associated with less endogenous dopamine at D2/3 receptors in the ventral striatum and nucleus accumbens, in both obese and non-obese adults[60,61]. Another study documented that weight loss following bariatric surgery was associated with an increase in D2 receptor availability[62]. In effort-based decision-making, evidence indicates that dopamine responsivity, particularly in the striatum and ventromedial prefrontal cortex, is strongest for low probability trials[63,64]. Conversely, we observed a stronger effect of overweight/obesity in the low reward trials. If overweight/obesity and the peripheral measures of insulin resistance used herein do indeed reflect and/or are associated with brain insulin resistance, it could be posited that disturbances in central insulin signaling lead to decreased dopamine sensitivity, resulting in an increased likelihood to choose low-effort options. This hypothesis, however, has two principle outstanding questions. First, it relies on the assumption that peripheral and brain insulin sensitivity are correlated (or that peripheral measures are reliable indicators of central processes), which is insufficiently characterized[65,66]. Direct measurements of brain insulin sensitivity, and its relationship to dopamine signaling and effort-based decision-making, are necessary.

Second, it assumes that disturbances in insulin signaling are the principle mediators of the changes in dopamine function; an idea that does have support in the literature[67,68], but cannot be fully ascertained in a cross-sectional study. Moreover, recent evidence has indicated that the brain is also as an important regulator of systemic glucose and energy metabolism[69,70]. For example, bromocriptine, a potent dopamine D2 receptor agonist, has been shown to improve glucose metabolism in humans[71]. Dopamine release in the striatum might enhance whole-body insulin sensitivity, whereas inhibition of dopamine activity might reduce it[70]. Therefore, individuals predisposed to lower central dopamine activity may be more susceptible to the development of obesity and insulin resistance states. Disturbances in reward behavior,

particularly effort, might also affect peripheral metabolism indirectly, through lower levels of physical activity and changes in dietary quality and/or patterns[72,73]. In addition, other important factors might confound and/or mediate the association between obesity and effort in MDD, such as the use of psychotropic medications. There is a need for longitudinal studies, with carefully selected and described samples, to answer these questions.

There is, however, evidence indicating that circadian rhythms can affect reward behavior[75,76], dopamine signaling[77,78] and glucose/insulin metabolism[79-81]; and are as well a prominent component of the overlap between mood and metabolic disorders[40,82,83]. The potential effects of circadian rhythms should be directly explored and/or accounted for in future work in the area.

In conclusion, we believe that obesity is a result of, and induces, disturbances in reward/motivation and cognitive control. There is a need to parse the substrates that subserve motivation/reward disturbance in adults with obesity. There is an additional need to evaluate the disturbance in reward/motivation with a rigorous paradigm i.e. EEfRT. The results of this proposal will also reinforce the brain and body consequences of obesity.

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