BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009347
Article Type:	Protocol
Date Submitted by the Author:	08-Jul-2015
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Surgery, Diagnostics, Nutrition and metabolism
Keywords:	PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Eating disorders < PSYCHIATRY, Magnetic resonance imaging < RADIOLOGY & IMAGING, SURGERY

Word Count: 4410

The effect of obesity on cognition in adults with and without a mood disorder: study design and methods

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Abstract

Introduction: Obesity is a common medical illness that is increasingly recognized as conferring risk of decline in cognitive performance, independent of other comorbid medical conditions. Individuals with mood disorders (Bipolar Disorder [BD] or Major Depressive Disorder [MDD]) display an increased prevalence of both obesity and risk factors for cardiovascular diseases. Moreover, BD and MDD are associated with impairment in cognitive functioning across multiple domains. The independent contribution of obesity to cognitive decline in this population has not been explored. This study examines the impact of obesity on cognition by comparing neuropsychological performance in obese individuals, with or without a mood disorder before and after undergoing bariatric surgery.

Methods and Analysis: This study compares measures of declarative memory, executive functioning and attention in obese individuals (BMI > 35 kg/m^2) with BD or MDD, and two control populations (obese individuals without a psychiatric illness and healthy non-obese controls) prior to and following bariatric surgery. Subjects (ages 18 – 60) receive a psychiatric diagnosis via the Structured Clinical Interview for the DSM-IV (SCID). Mood ratings, physical measurements, nutritional and health questionnaires are also administered. A standardized battery of neuropsychological tests aimed at establishing performance in areas of declarative memory, executive functioning and attention is administered. Warrington's *Recognition Memory Task* (RMT) and an N-Back task are performed in a 3T functional magnetic resonance imaging (fMRI) scanner to determine if cognitive performance is associated with specific patterns of neural activation. Additionally,

anatomical MRI data is obtained to investigate potential changes in neural structures. Baseline data will be analyzed for between-group differences and later compared to post-surgical data to investigate cognitive change.

Ethics and Dissemination: This study has been approved by the Hamilton Integrated Research Ethics Board (09-3254). Results will be available in peer-reviewed scientific publications and scientific meetings presentations, and released in lay form to media.

Strengths and limitations

Strengths:

- Only known study to follow use fMRI to study memory/higher order cognitive changes before and after a significant weight status change
- Extensive characterization and well-controlled design of population comorbdities
- Quantitative complimentary and comprehensive cognitive data collection methodologies (standarized neuropsychological measures, fMRI neural activation investigation, and MRI neural structure measurements)

Limitations:

- study entry limited by physical MRI restrictions (may capture limited portion of bariatric surgery population)

Keywords

Obesity, Cognition, Bariatric Surgery, Mood Disorder, Imaging

Background

Obesity and Cognition

Cognitive functions are frequently divided into the domains of perception, attention, memory and executive function, with executive function including a diverse range of higher-order processes such as planning, regulation and goal-oriented behaviour [1]. Each of these general categories can then be divided further into specific subtypes of cognitive function; memory, for example, is commonly divided into implicit or procedural memory (skill-based memory), semantic memory (fact-based memory) and episodic memory (memory related to biographical events). These distinctions are not merely theoretical in nature, but also represent distinct neuroanatomical circuits coordinating different aspects of memory and cognition more broadly [2].

The pathways through which obesity negatively affects cognition are not well elucidated. Although a number of medical conditions have been shown individually to adversely affect cognition, recent research suggests that adiposity itself may have a negative association with cognitive performance [3 4]. Research focused solely on the relation between obesity (in absence of comorbid medical health conditions) and cognition is slowly emerging. In a previous meta-analysis completed by van den Berg et al. (2009), only 6 studies investigating the association between obesity and cognition were identified [3]. One out of 3 cross-sectional and 2 out of 3 longitudinal studies reported a significant negative association between obesity and cognitive performance, with this association differing across individual cognitive domains. In

a more recent review, Smith et al. (2011) found that 14 out of 15 cross-sectional studies in human adult subjects reported a negative association between obesity and cognition [5]. Interestingly, executive functioning was the cognitive domain most often affected (11 out of 15 studies reported an association). There were only 4 prospective studies examining the impact of obesity and naturalistic weight changes on cognitive performance and later life outcome; the results from these 4 studies were inconsistent. While much of the prospective data showed that a higher BMI or waist-to-hip ratio was associated with poorer performance on tests of memory, Gunstand et al. (2010) found that waist circumference and BMI were associated with faster performance on a neuropsychological measure of processing speed [6]. To our knowledge, there have been at least 2 further studies published since this time also investigating the relation between obesity and cognition [4 7]. Discrepancies among the reported results in studies of cognition and obesity may be due to the lack of consistency in study design, including heterogeneity in inclusionary baseline BMI, age of subjects, present comorbidities, type of weight change (increase/decrease over time) and type of intervention applied (for example, level of dietary restriction, surgical intervention or changes in physical activity levels).

In addition, the majority of the literature examining the relation between cognition and obesity did not differentiate between the effects of obesity itself and its related comorbidities. For example, the large prospective Framingham Heart Study by Elias et al. [8] had 1,423 community subjects complete tests involving IQ, verbal memory and verbal fluency; after adjusting for potential confounders of age, education,

occupation, alcohol and smoking use, dyslipidemia and diabetes, significant effects of hypertension and obesity were observed on tests of learning, memory and intellectual functioning in men only. The effects of hypertension and obesity were interdependent (both resulted in diminished cognitive performance, but alone were insignificant). By contrast, Kuo et al.'s (2006) study of 2,684 normal-weight, overweight and obese subjects included completion of the Mini-Mental State Examination (MMSE), verbal learning, memory and reasoning tasks, and performance measures [9]. After age, race, sex, intervention type, education, and cardiovascular (CV) comorbidities were controlled for, overweight subjects had better overall cognitive performance on measures of verbal reasoning and processing speed. Cleary, there is an urgent need for well-designed and controlled weight loss-intervention studies that can adequately assess changes in cognition following significant, maintained weight-loss and monitored health changes in overweight and obese individuals.

Obesity and Mood Disorders

There is an estimated 12-month 9.5% prevalence of mood disorders (BD and MDD) in the general population and the lifetime prevalence of mood disorders is more than double this at 20.8% [10 11]. Individuals with mood disorders have a greater prevalence of risk factors for CV disease, including Type II Diabetes Mellitus (TDII), smoking and hypertension (BD is also associated with an increased risk factor for hypertriglyceridemia) [12]. This may be in part explained by the higher proportion of individuals with obesity in mood disorder populations. The National Comorbidity

Survey-Replication (NCS-R) reported odds ratios for obesity of 1.47 for lifetime BD and 1.21 for MDD [13].

It has been well documented by a wide body of research that both MDD and BD are associated with impairment in cognitive functioning across multiple frontal-temporally mediated cognitive domains, including executive functioning, attention memory [14-17]. Impairment on tests involving the conscious recollection of facts or events is among the most consistent deficit reported in patients with a mood disorder. Further, this declarative memory deficit may be most severe in patients with long-term illness duration or recurrent mood episodes [18]. Studies also indicate executive function impairment on tasks involving the selection, timing, monitoring and interpretation of behavior, including working memory and selective attention [19 20]. Although these cognitive deficits persist into the euthymic state in many patients [21], their implications for daily functioning are not fully understood [22]. Critically, the presence of cognitive impairments, in particular, deficits in executive functioning and in verbal memory, has been associated with poor functional outcomes (e.g., vocational) in patients with mood disorders [23-30].

Cognitive dysfunction is not always saliently present at the time of illness onset in mood disorders, often emerging over the course of illness and worsening with illness duration [14]. Fortunately, there is evidence that it may be amenable to strategies aimed at preventing or reducing functional impairment [31]. For example, psychotropic medication use has been associated with cognitive improvement [19]. Similarly, recent studies suggest that cognitive remediation approaches (e.g.,

computerized skills training) may improve cognitive functioning in patients with mood disorders [32 33]. However, residual cognitive symptoms often persist in euthymic patients [21]. Unfortunately, many medications used in treating mood disorders are also associated with increased weight gain and related metabolic comorbidities; this weight gain and metabolic dysregulation can be quite severe with use of certain medication classes (such as atypical antipsychotics). Moreover, these metabolic changes may themselves be associated with cognitive impairment in areas of memory and executive function [34]. Thus, it may be that the cognitive improvement expected in medicated or treated mood disorder patients is lost over time, and may actually be seen as a cognitive decline, as a consequence of this associated weight gain [34 35]. Given that a strong association between cognitive impairment and poor psychosocial functional outcomes has been established, understanding the interaction between medication use, weight, and cognition is of great concern to treating practitioners [15].

Study Objective:

The goal of this study is to examine the impact of obesity on memory, executive function and attention in patients with and without a mood disorder (MDD or BD) by assessing cognitive performance prior to, and after, a significant 1-year weight loss following bariatric surgery. Changes in cognition associated with weight loss have been difficult to investigate primarily because most weight loss interventions do not result in a significant weight change [36]. We are uniquely positioned to investigate this, however, as we have designed an assessment paradigm that focuses

on bariatric surgery patients. Bariatric surgery results in a weight loss range of 12% to 39% of pre-surgical body weight, providing an effective intervention with which to assess cognitive change [37]. We have also worked with engineers to modify our magnetic resonance imaging (MRI) scanner to accommodate physical restrictions associated with cognitive testing in this population, allowing us to examine some of the brain correlates behind this association. The specific aims and hypotheses of the study are:

Aim 1: Determine the effect of obesity (and additional interactive effect of a mood disorder diagnosis) on cognitive performance.

Hypothesis 1a: Compared to a healthy BMI weight non-psychiatric control population, the obese (bariatric) non-psychiatric control population will show greater cognitive impairment, as assessed by the outcome of a standardized cognitive battery, prior to bariatric surgery.

Hypothesis 1b: Obese (bariatric) patients with a BD or MDD diagnosis will show greater impairment than both (healthy BMI and obese [bariatric]) control populations, as assessed by the outcome of a standardized cognitive battery, prior to bariatric surgery.

Aim 2: Examine whether structural or functional brain differences can be seen (either in neural activation patterns during cognitive tasks or structurally) in obese patients with or without a mood disorder

Hypothesis 2: Prior to surgery, bariatric groups will show dysregulation relative to the healthy BMI weight control group in neural activation during declarative memory and executive functioning tasks. This dysregulation will be seen in neural structures important to memory and executive function, such as, the prefrontal cortex and hippocampus.

Aim 3: Investigate whether any differences seen and associated with obesity (in cognitive performance tasks, neural activation patterns, or neural structures) can be diminished following significant weight loss

Hypothesis 3: At 1-year post intervention, all surgery-treated groups will show a significant improvement in cognitive performance measures (and related neural investigations) following expected (12% to 39% pre-surgical body weight [37]) weight-loss and overall health improvement.

Methods

Study Design and Timeline:

This is a prospective cohort study. Study subjects are seen 2 - 4 times during the study. Prior to surgery, subjects are seen once to complete cognitive testing and once to complete the brain imaging session; alternatively, some subjects may choose to complete all testing in one visit (due to travel or schedule restrictions). Subjects are required to return for an additional cognitive testing session and brain imaging session 1-year following surgical intervention (or 13-months following baseline

visits for healthy control subjects). Self-report questionnaires, psychiatric assessments and anthropomorphic measures are administered at the pre- and post-surgical time points as well.

Subjects: Recruitment, Screening and Enrollment

Bariatric subjects are recruited from the St. Joseph's Healthcare Hamilton program for Bariatric Surgery (an Ontario Centre for Surgical Excellence). All patient charts on file were manually screened for potential eligibility in an initial recruitment stage; potential eligibility was based on reported patient height and weight measurements, age and whether the patient was still awaiting surgery. Newly received referral patients continue to be screened on an ongoing basis. Patients deemed potentially eligible are first reached via telephone. The study is introduced and procedures are explained during this initial telephone contact; if interested, subjects then undergo a telephone screen to determine if they meet study inclusion/exclusion criteria. Those who meet criteria are then scheduled for baseline study appointments and written informed consent is obtained at the initial appointment prior to data collection. Healthy control subjects from a departmental consent-to-contact phone list are contacted via telephone and administered parallel screening and enrollment procedures. In addition, recruitment also occurs via advertisements placed on hospital notice boards, and from health care provider referrals. Bariatric subjects can be enrolled in the study during any stage following the orientation class of their pre-surgical process. The surgical candidacy process (and estimate time intervals between candidacy stages) can be found in Figure 1.

Study subjects are recruited into four groups: obese (bariatric) patients with BD, obese (bariatric) patients with MDD, obese (bariatric) patient without a psychiatric disorder (past or present), and healthy weight (non-surgical) controls without a psychiatric disorder (past or present). *Inclusion criteria* for all groups is as follows: age 18 – 60 years, ability to provide informed consent, and native English speaker (or having learned English by age 6). Additionally, healthy controls are required to have a BMI between 18.5 – 24.9 (normal range). *Exclusion Criteria* includes the presence of a current or pre-existing neurological condition (e.g., epilepsy, severe head trauma) or unstable and/or severe medical condition (e.g., cancer, severe heart attacks), contraindications to MRI (deemed unsafe to complete an MRI via safety screening questionnaire), left-handedness (confirmed via Edinburgh Handedness Inventory) [38], having been administered any of the cognitive study measures within the past 12 months, a history of a confirmed learning disorder or developmental disability diagnosis (e.g., attention deficit hyperactivity disorder) or a Full Scale Intelligence Quotient (FSIQ) < 70, an inability to complete the testing (e.g. due to a hearing or vision impediment), and the presence of alcohol or substance abuse within the last 6 months or lifetime dependency (those in the BD group will not be excluded due to lifetime dependency if in sustained full remission). In addition, presence of a past or current psychiatric condition is an exclusion criteria for both healthy BMI weight and bariatric (obese) non-psychiatric control groups while having been administered electro-convulsive therapy (ECT) within the last 24 months is an exclusion criteria for both BD and MDD bariatric patient groups. MRI eligibility screening is independently performed by MRI technicians at

the Imaging Research Centre (St. Joseph's Healthcare Hamilton, Ontario). Subjects who are unable to complete MRI testing but have completed all other testing remain enrolled in the study. The first study subject was enrolled September 22, 2010.

Surgical Intervention

Currently in Ontario there are 150,000 individuals eligible for bariatric surgery and over 3000 individuals actively pursuing bariatric surgery. As of 2014, the Bariatric Surgery Program at St. Joseph's Healthcare Hamilton completed approximately 600 surgeries per year [39]. Traditionally, all bariatric surgeries have been thought to cause weight loss through the processes of malabsorption (of nutrients or calories), caloric restriction, or a combination of the two. [37].

The most common gastric procedures performed are Laparoscopic Adjustable Gastric Banding (LAGB) and Roux-en-Y Gastric Bypass (RYGB) [40]. In Ontario, RYGB is the most routinely performed and is covered financially (for those with a BMI exceeding 40 or 35 with significant medical comorbidities) by the Ontario Health Insurance Program. Alternatively, the LAGB is rarely performed in public health settings due to its diminished rate of long-term weight loss success and the higher likelihood for additional follow-up surgical procedures; it is, however, readily available through private healthcare providers. Due to the presence of certain medical comorbidities, conditions, or gastrointestinal irregularities, a bariatric surgery team may opt to perform a laparoscopic vertical sleeve gastrectomy (VSG) or biliopancreatic diversion (BPD) with duodenal switch. [41].

Data Collection

Subjects complete baseline measures over the course of 1 – 2 study visits. Those who undergo an MRI at baseline are re-assessed for scan eligibility at their follow-up visit. All assessment measures are re-administered at follow-up with the exception of the Structured Clinical Interview for DSM-IV (SCID) (which is replaced by the Mini International Neuropsychiatric Interview [MINI] at follow-up). A double-entry system with independent research personnel is utilized for all cognitive and behavioural data and inconsistencies are checked and resolved by an additional assessor.

Psychiatric (and Mood) Assessment

Subjects are diagnosed via administration of the SCID at baseline. Current psychiatric status is reassessed at follow-up via the MINI. Mood ratings are also monitored at baseline and end visits via the Hamilton Rating Scale for Depression (HAMD-17) and the Young Mania Rating Scale (YMRS)[42 43]. In addition, the Beck Depression Inventory (BDI) and Altman Self-Rating Scale for Mania (ASRM) are also administered [44 45]. In circumstances where baseline visits are 2 or more weeks apart, the BDI and ASRM are administered separately at each of these visits to account for possible changes in mood state. As high rates of trauma exposure have been reported in both mood disorder and obese populations [46] [47], the Childhood Trauma Questionnaire (CTQ) is also administered [48].

Neuropsychological Assessment

A standardized battery of neuropsychological tests aimed at establishing pre- and post-intervention performance on tests of declarative memory, executive

functioning and attention is administered. These cognitive domains have been shown to be susceptible to impairment in metabolically dysregulated populations [38]. Tests were chosen with 2 objectives in mind: 1) to investigate different aspects of both declarative memory and executive functioning in order to provide an exhaustive overview of these composite areas, and; 2) with redundant overlap between areas and skills tested (to minimize the likelihood of spurious test results in any one sub-domain). Additional information regarding individual neuropsychological tests administered is also summarized in Table 1.

Table 1. Summary and Psychometric Properties of Neuropsychological Test Measures and fMRI Behavioural Tasks [49]

Test	Administration Time (Minutes)	Age Range (Years)	Measure and Purpose
Brief Visuospatial Memory Test – Revised (BVMT-R)	15 (40 with delay interval)	18 – 79	Multiple-trial figure-learning paradigm assessing visual learning and memory
California Verbal Learning Test – II (CVLT-II)	35 – 40	16 – 89	Multiple-trial list-learning paradigm assessing verbal learning and memory

Color-Trails Test	5 – 10	18 – 89	Manual drawing task assessing speed of attention, sequencing, mental flexibility, visual search, and motor function
N-Back Task	22 (fMRI version)	Not defined	Continuous performance task assessing attention and short-term memory
Paced Auditory Serial Addition Task (Computerized Version)	15 – 20	16 – 74	Serial-addition task assessing working memory, divided attention, and information processing speed
Stroop (Golden Version)	5	5 – 90	Reading task assessing cognitive control, goal maintenance, and suppression of a habitual response in favour of a less familiar one
Warrington's Recognition Memory Task (Words Subtest	8 (fMRI Version)	18 – 70	Assesses recognition memory for printed words

Only)			
Wechsler Abbreviated Scale of Intelligence (WASI)	15	6 – 89	Brief intelligence measure
Wechsler Test of Adult Reading	10	16- 89	Reading task assessing pre-morbid functioning
Wisconsin Sorting Card Task	15 – 30	5 – 89	Card-sorting task assessing ability to form abstract concepts, shift and maintain set, and utilize feedback

Declarative memory function battery:

i) California Verbal Learning Test II (standard and alternate forms): this word list learning task provides indices of immediate and delayed memory performance, interference learning, and recognition [50].

ii) Wechsler Memory Scale III - Logical Memory subtest: this contextually-based memory task provides indices of learning slope, immediate and delayed memory performance, retention, and recognition [51]

iii) Brief Visuospatial Memory Test – Revised: a nonverbal test of visuospatial memory under explicit encoding conditions [52]

Executive functioning and attention battery:

i) Controlled Oral Word Association Task: this task taps phonemic (FAS) and semantic (animals) fluency [53]

ii) Stroop Colour and Word Test (Golden version): this task taps sensitivity to suppress a habitual response in favor of a less familiar one [54]

iii) Wisconsin Card Sorting Task (64-item version): this task taps the ability to form and shift concepts based on feedback [55]

iv) Colour Trails Test Part A & B: whereas Part A assesses processing speed, Part B taps the ability to sequence two stimulus sets while alternating between them [56]

v) Paced Auditory Serial Attention Test (Victoria Computerized Adaptation): this task assesses capacity and rate of information processing as well as sustained and divided attention [57]

Pre-morbid IQ

Subjects complete one subtest of the performance (Matrix Reasoning) and verbal (Vocabulary) indices of the Wechsler Abbreviated Scale of Intelligence in order to estimate current intellectual functioning via FSIQ [58]. The Wechsler Test of Adult

Reading is also administered to estimate pre-morbid intellectual functioning in subjects [59]. This test consists of 50 words, listed in order of difficulty. Subjects are presented with the word list and instructed to read each word aloud. Total number of correct pronunciations comprises the final score.

Anthropometric Measures

A glucose measurement is obtained on the day of cognitive testing both at baseline and end visits via a 'finger prick' glucometer reading. Height, weight, waist and hip circumferences, systolic and diastolic blood pressure, and heart rate measurements are measured for non-bariatric controls at baseline and end visits. Waist circumference was measured according to the WHO STEPS protocol that instructs that the measurement is made approximately between the lower margin of the last palpable rib and the top of the iliac crest [60]. Hip circumference was measured around the widest portion of the subject's buttocks.

For bariatric surgery subjects, these measurements are obtained via manual data extraction by study personnel from subjects' medical record charts containing doctor, nurse and dietician visit notes and summary. Nurses and dieticians review and record relevant blood-work that must be completed and available by a bariatric surgery program patient's first clinic visit, as well as capture the anthropomotric measures listed earlier (such as blood pressure, weight, and waist circumference) during this first visit. Glucose, HbA1C and lipid assessment profiles contained in the subjects' medical record for bariatric subjects are also obtained via data extraction by study personnel from laboratory result reports.

Demographics and Medical Health

Age, gender, education, job status, family psychiatric history, and medical health/illness information is collected during the initial telephone screen questionnaire. As part of the bariatric surgery process, clinic doctors and nurses capture extensive information regarding the patient's past and current medical condition diagnoses during the patient's initial clinic visit (following referral by a family doctor and completion of an orientation class). Study personnel extract data recorded from clinic doctor and nurse encounters available in each subject's medical chart in order to confirm the presence or absence of comorbidities often seen in obese populations (including, type II diabetes or glucose dysregulation, hypertension, dyslipidemia, and sleep apnea). Given that different surgical procedures are associated with different rates and mechanisms of weight loss, the type of bariatric surgery completed by each subject is also recorded. Additional information concerning living arrangements, previous education details, marital/relationship status, number of children, smoking behaviour and previous medication history is collected in the general demographics questionnaire administered during the study.

All subjects are also asked to provide a complete listing of current medications, vitamins, and herbal supplements (including dosage and indication). The Berlin Sleep Questionnaire [61] ,which assesses the risk level for current Obstructive Sleep Apnea (OSA) or sleep disordered breathing is also completed. It is administered as part of the study self-report package for non-bariatric subjects, while bariatric

subjects complete this questionnaire through the bariatric surgery clinic as part of their surgical candidacy process.

Nutrition

Nutritional intake is assessed via a non-consecutive 3-day dietary record (Food Frequency Questionnaire), with one day being a weekend day [62]. This 3-day method has been demonstrated to estimate habitual energy intake within 10% of the actual values in groups as small as 13 subjects [63]. In addition to overall caloric intake, diet component analysis will also be completed. Specifically, total and percent intake of proteins, carbohydrates, fat, cholesterol, fibre, sugar and sodium is calculated per subject for future analysis.

Disability and Self-reported Cognitive Measures

The Sheehan Disability Scale (SDS) [64] is administered to provide a quick measure of the impact of the subject's disability (obesity and/or mood disorder) across various life domains. The Cognitive Failure Questionnaire [65] is a measure of self-reported failures in perception, memory and motor function and is used to assay subjective feelings of cognitive dysfunction.

Imaging

Each subject also undergoes a one-hour MRI session at baseline and follow-up time points. A high-resolution axial 3D anatomical T1-weighted scan with full brain coverage is performed to obtain relevant neuroanatomical data (including hippocampus volume). Following this, two tasks tapping declarative memory

function (Warrington's Recognition Memory Task, or RMT) [66] and executive functioning (N-Back Task) are performed (additional information regarding Warrington's RMT the N-Back Task is available in Table 1). Regional activation patterns will be compared and contrasted across groups. Behavioural data, such as reaction time, correct number of responses on N-Back subtests, and correct number of recognition hits on the RMT, is also collected. As part of the subject's orientation and training, practice trials of each task are administered outside of the MRI on the day of the actual MRI session.

Data Analysis

R Statistical Software [67] and the Statistical Package for Social Sciences (SPSS) statistics will be used [68] for data analysis. MRI imaging analyses will be completed using Statistical Parametric Mapping (SPM), Matlab [69] and FreeSurfer [70].

Cognitive performance on neuropsychological measures at both baseline and end visits will be compared across groups (bariatric MDD, bariatric BD, bariatric controls and healthy matched controls). The primary outcome variable at follow-up will be cognitive change at 12 months following surgery. We chose group sample sizes of 20 minimum in order to have enough power to adequately examine neuroimaging differences between groups [71]. Based on work by Woods (1996), we will also have enough power for use of individual contrast images in second-level random effects models that will allow us to investigate target regional responses at the group level [72].

Neuropsychological measures will be examined independently and may be integrated into an executive function/attention composite and declarative memory composite. Composite score may be obtained by converting individual scale scores across to z-scores and then averaging across independent measures.

Exploratory analyses using descriptive statistics will be used to present demographic and medical data (such as comorbidity presence, age, etc.). Initial one-way between-group univariate analyses of variance will be run to identify potential confounding covariates in any effects found at baseline. The impact of related comorbidities (such as TDII and hypertension) will also be examined. Although our primary interest is the effect of obesity alone on cognition, additional cardiovascular comorbidities are likely to have an additive effect on cognitive performance and their effect contribution will be explored via hierarchal regression model analysis. Bariatric surgery is known to normalize blood glucose and reverse TDII status in surgery patients even without significant weight loss [37]. This potential effect on overall cognitive performance differences will be explored in post-surgical group analyses.

Both structural and functional imaging scans will be run at baseline and follow-up using the same 3 Tesla General Electric (General Electric, Milwaukee, WI) system at the Imaging Research Centre (St. Joseph's Healthcare Hamilton, Ontario). Functional MRI tasks will be displayed using E-Prime software (www.pstnet.com) [73]. Hippocampal volume (and change in volume over time) will be measured using FreeSurfer [70]. Acquired functional images will be processed and analyzed using

Statistical Parametric Mapping (SPM) and Matlab software [69]. Collected data will be slice-time corrected, 3D motion corrected and realigned to the fifth volume in the first series collected, and normalized to Talairach space. High-resolution T1-weighted 3D anatomical MRI data collected for each subject will be used for co-registration with functional data. Anatomical data sets will be averaged across subjects to generate a composite image onto which the functional activation results are projected. General Linear Models will be created for both tasks and overlaid for each subject to examine neural activation patterns for each group. Activation contrasts will be examined using subject group as a between-subjects factor.

Ethics and Dissemination

This study has been approved by the Hamilton Integrated Research Ethics Board of St. Joseph's Healthcare Hamilton Hospital and Hamilton Health Sciences Centre (09-3254). Written informed consent is obtained from each subject after study information is provided and before study entry. Subjects are informed that all data collected is de-identified and that identifying consent forms are kept separately from other collected data. Collected data is stored securely in both electronic and paper forms. Only approved research personnel and study investigators have access to the data. Results will be available in peer-reviewed scientific publications and scientific meetings presentations, and released in lay form to media outlets.

Discussion

The goal of this project is to *quantify* cognitive impairment in patients with mood disorders and assess the impact of obesity on cognitive performance and brain activation by measuring each before and after an intervention that significantly alters weight. We speculate that changes in cognitive function associated with mood disorders are caused in part by weight status, thereby increasing the burden of illness associated with MDD and BD.

This study will be the first of its kind to investigate the impact of obesity on cognition via an intervention that results in significant and sustained weight loss in a population with a mood disorder. We hypothesize that weight status will have a significant effect on cognition, a conclusion that may influence the way mental health care is provided and have important ramifications for first-line recommendations with respect to medications. It will also improve our understanding of the neural pathways involved in cognitive processes, furthering our understanding of how mental illness develops and the additional risk conferred by obesity.

Study Status

The status of the study at the time of manuscript submission was completion of enrollment for all but one subject group (bariatric BD).

Abbreviations

ASMR: Altman Self-Rating Scale for Mania; BD: Bipolar Disorder; BDI: Beck Depression Inventory; BMI: Body Mass Index; BPD: Biliopancreatic Diversion; CTQ:

Childhood Trauma Questionnaire; CV: cardiovascular; fMRI: functional Magnetic Resonance Imaging; FSIQ: Full Scale Intelligence Quotient; HAMD-17: Hamilton Rating Scale for Depression – 17 Items; LAGB: Laparoscopic Adjustable Gastric Banding; MDD: Major Depressive Disorder; MINI: Mini International Neuropsychiatric Interview; MMSE: Mini-Mental State Examination; MRI: Magnetic Resonance Imaging; OSA: Obstructive Sleep Apnea; RYGB: Roux-en-Y Gastric Bypass; RMT: Recognition Memory Task; SCID: Structured Clinician Interview for DSM-IV; TDII: Type 2 Diabetes Mellitus; VSG: Vertical Sleeve Gastrectomy; YSRM: Young Self-Rating Scale for Mania

Competing Interests And Role of Funding Source

Dr. Valerie Taylor received an unrestricted educational grant from Bristol Myers Squibb to help fund this study. MR is a doctoral thesis candidate who has been supported by fellowships from the Canadian Institute of Health Research and Government of Ontario. The study sponsors play no role in study design, data collection, data analysis, data interpretation or report writing.

Authors' Contributions

MM, MR, and VT designed the study protocol. MR completed study subject screening and recruitment, all data collection (including data extraction from patient records), supervised data entry (completed by undergraduate students) and completed data cleaning and coding. Thorough training under a team of clinical neuropsychologists was provided to MR prior to commencement of patient testing. MM provided feedback and consultation on cognitive data collection and analysis. GH and BF

designed aspects of the study related to the MRI and provided feedback and consultation on MRI data collection and analysis. MR will analyze data under the supervision of VT and in consultation with a statistician at the Sunnybrook Health Sciences Centre (Dr. Alex Kiss). MR drafted the manuscript. All authors contributed to and approved the final manuscript.

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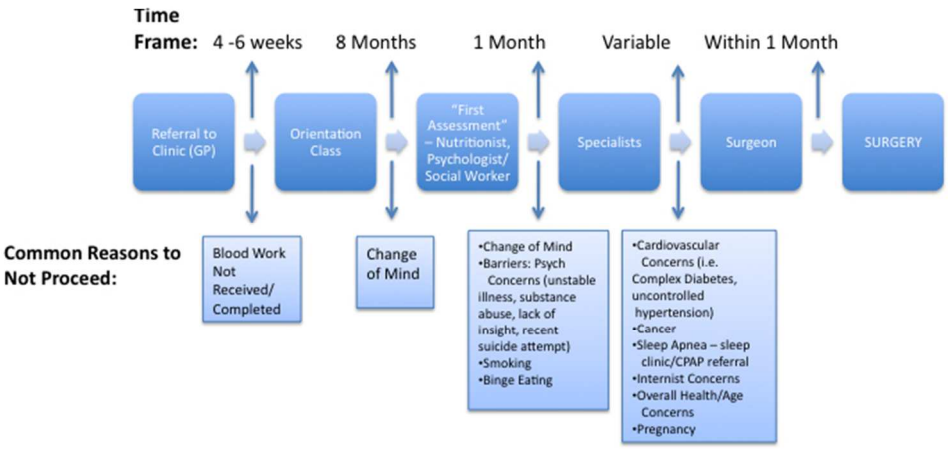

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BMJ Open

The effect of obesity on cognition in adults with and without a mood disorder: study design and methods

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009347.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Dec-2015
Complete List of Authors:	Restivo, Maria; McMaster University, McMaster Integrative Neuroscience Discovery and Study (MiNDS) McKinnon, Margaret; McMaster University, McMaster Integrative Neuroscience Discovery and Study (MiNDS); McMaster University, Department of Psychiatry and Behavioural Neuroscience Frey, Benicio; McMaster University, McMaster Integrative Neuroscience Discovery and Study (MiNDS); St. Joseph's Healthcare Hamilton, Mood Disorders Program Hall, Geoffrey; McMaster University, Department of Psychology, Neuroscience & Behaviour Taylor, Valerie; Women's College Hospital, Mental Health Department; McMaster University, McMaster Integrative Neuroscience Discovery and Study (MiNDS)
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Surgery, Diagnostics, Nutrition and metabolism
Keywords:	PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Eating disorders < PSYCHIATRY, Magnetic resonance imaging < RADIOLOGY & IMAGING, SURGERY

Word Count: 5487

The effect of obesity on cognition in adults with and without a mood disorder: study design and methods

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Abstract

Introduction: Obesity is a common medical illness that is increasingly recognized as conferring risk of decline in cognitive performance, independent of other comorbid medical conditions. Individuals with mood disorders (Bipolar Disorder [BD] or Major Depressive Disorder [MDD]) display an increased prevalence of both obesity and risk factors for cardiovascular diseases. Moreover, BD and MDD are associated with impairment in cognitive functioning across multiple domains. The independent contribution of obesity to cognitive decline in this population has not been explored. This study examines the impact of obesity on cognition by comparing neuropsychological performance in obese individuals, with or without a mood disorder before and after undergoing bariatric surgery.

Methods and Analysis: This study compares measures of declarative memory, executive functioning and attention in obese individuals (BMI > 35 kg/m^2) with BD or MDD, and two control populations (obese individuals without a psychiatric illness and healthy non-obese controls) prior to and following bariatric surgery. Subjects (ages 18 – 60) receive a psychiatric diagnosis via the Structured Clinical Interview for the DSM-IV (SCID). Mood ratings, physical measurements, nutritional and health questionnaires are also administered. A standardized battery of neuropsychological tests aimed at establishing performance in areas of declarative memory, executive functioning and attention are administered. Warrington's *Recognition Memory Task* (RMT) and an N-Back task are

performed in a 3T functional magnetic resonance imaging (fMRI) scanner to investigate patterns of neural activation during cognitive performance. Additionally, anatomical MRI data is obtained to investigate potential changes in neural structures. Baseline data will be analyzed for between-group differences and later compared to post-surgical data to investigate cognitive change.

Ethics and Dissemination: This study has been approved by the Hamilton Integrated Research Ethics Board (09-3254). Results will be available in peer-reviewed scientific publications and scientific meetings presentations, and released in lay form to media.

Strengths and limitations

Strengths:

- Only known study to follow use fMRI to study memory/higher order cognitive changes before and after a significant weight status change
- Extensive characterization and well-controlled design of population comorbidities
- Quantitative complimentary and comprehensive cognitive data collection methodologies (standardized neuropsychological measures, fMRI neural activation investigation, and MRI neural structure measurements)

Limitations:

- study entry limited by physical MRI restrictions (may capture limited portion of bariatric surgery population)

Keywords

Obesity, Cognition, Bariatric Surgery, Mood Disorder, Imaging

Background

Obesity and Cognition

Cognitive functions are frequently divided into the domains of perception, attention, memory and executive function, with executive function including a diverse range of higher-order processes such as planning, regulation and goal-oriented behaviour [1]. Each of these general categories can then be divided further into specific subtypes of cognitive function; memory, for example, is commonly divided into implicit or procedural memory (skill-based memory), semantic memory (fact-based memory) and episodic memory (memory related to biographical events). These distinctions are not merely theoretical in nature, but also represent distinct neuroanatomical circuits coordinating different aspects of memory and cognition more broadly [2].

The pathways through which obesity negatively affects cognition are not well elucidated. Although a number of medical conditions have been shown individually to adversely affect cognition, recent research suggests that adiposity itself may have a negative association with cognitive performance [3 4]. Research focused solely on the relation between obesity (in absence of comorbid medical health conditions) and

cognition is slowly emerging. In a previous meta-analysis completed by van den Berg et al. (2009), only 6 studies investigating the association between obesity and cognition were identified [3]. One out of 3 cross-sectional and 2 out of 3 longitudinal studies reported a significant negative association between obesity and cognitive performance, with this association differing across individual cognitive domains. In a more recent review, Smith et al. (2011) found that 14 out of 15 cross-sectional studies in human adult subjects reported a negative association between obesity and cognition [5]. Interestingly, executive functioning was the cognitive domain most often affected (11 out of 15 studies reported an association). There were only 4 prospective studies examining the impact of obesity and naturalistic weight changes on cognitive performance and later life outcome; the results from these 4 studies were inconsistent. While much of the prospective data showed that a higher BMI or waist-to-hip ratio was associated with poorer performance on tests of memory, Gunstad et al. (2010) found that waist circumference and BMI were associated with faster performance on a neuropsychological measure of processing speed [6]. To our knowledge, there have been 2 further studies published since this time also investigating the relation between obesity and cognition [4 7]. Discrepancies among the reported results in studies of cognition and obesity may be due to the lack of consistency in study design, including heterogeneity in inclusionary baseline BMI, age of subjects, present comorbidities, type of weight change (increase/decrease over time) and type of intervention applied (for example, level of dietary restriction, surgical intervention or changes in physical activity levels).

In addition, the majority of the literature examining the relation between cognition and obesity did not differentiate between the effects of obesity itself and its related comorbidities. For example, the large prospective Framingham Heart Study by Elias et al. [8] had 1,423 community subjects complete tests involving IQ, verbal memory and verbal fluency. After adjusting for potential confounders of age, education, occupation, alcohol and smoking use, dyslipidemia and diabetes, significant effects of hypertension and obesity were observed on tests of learning, memory and intellectual functioning in men only. The effects of hypertension and obesity were interdependent (both resulted in diminished cognitive performance, but alone were insignificant). By contrast, Kuo et al.'s (2006) study of 2,684 normal-weight, overweight and obese subjects included completion of the Mini-Mental State Examination (MMSE), verbal learning, memory and reasoning tasks, and performance measures [9]. After age, race, sex, intervention type, education, and cardiovascular (CV) comorbidities were controlled for, overweight subjects had better overall cognitive performance on measures of verbal reasoning and processing speed. Clearly, there is an urgent need for well-designed and controlled weight loss-intervention studies that can adequately assess changes in cognition following significant, maintained weight-loss and monitored health changes in overweight and obese individuals.

Obesity and Mood Disorders

There is an estimated 12-month 9.5% prevalence of mood disorders (BD and MDD) in the general population and the lifetime prevalence of mood disorders is more than

double this at 20.8% [10 11]. Individuals with mood disorders have a greater prevalence of risk factors for CV disease, including type 2 diabetes (T2D), smoking and hypertension (BD is also associated with an increased risk factor for hypertriglyceridemia) [12], finding that may in part be explained by the high rates of obesity in this population. The National Comorbidity Survey-Replication (NCS-R) reported odds ratios for obesity of 1.47 for lifetime BD and 1.21 for MDD [13].

It has been well documented that both MDD and BD are associated with impairment in cognitive functioning across multiple frontal-temporally mediated cognitive domains, including executive functioning, attention memory [14-17]. Impairment on tests involving the conscious recollection of facts or events is among the most consistent deficit reported in patients with a mood disorder. Further, this declarative memory deficit may be most severe in patients with long-term illness duration or recurrent mood episodes [18]. Studies also indicate executive function impairment on tasks involving the selection, timing, monitoring and interpretation of behavior, including working memory and selective attention [19 20]. Although these cognitive deficits persist into the euthymic state in many patients [21], their implications for daily functioning are not fully understood [22]. Critically, the presence of cognitive impairments, in particular, deficits in executive functioning and in verbal memory, has been associated with poor functional outcomes (e.g., vocational) in patients with mood disorders [23-30].

Cognitive dysfunction is not always saliently present at the time of illness onset in mood disorders, often emerging over the course of illness and worsening with illness duration

[14]. This may be attributed, in part, to a combination of clinical and treatment variables. Antidepressants (especially antidepressants that target more than one receptor) for example, are associated with improvements in some aspects of cognition, while other areas may be more resistant [31]. Some psychotropic medications used in the treatment of BD have also been associated with cognitive improvement [19] and lithium, which is widely used as a mood stabilizer, has been shown to have a neuroprotective effect resulting in neurogenesis in the hippocampus (an important neural structure in memory processing) [32]. In contrast, however, the chronic effects of anticholinergic drugs have been shown to increase risk for permanent cognitive impairment [33]. Adding to this issue are clinical variables, as early onset MDD itself is associated with increased risk for Alzheimer's Disease [34].

Fortunately, there is evidence that cognition may be amenable to strategies aimed at preventing or reducing functional impairment. Recent studies suggest that cognitive remediation approaches (e.g., computerized skills training) may improve cognitive functioning in patients with mood disorders [35 36]. However, residual cognitive symptoms often persist in euthymic patients [21]. Also, many medications used in treating mood disorders are also associated with increased weight gain and related metabolic comorbidities; this weight gain and metabolic dysregulation can be quite severe with certain medication classes (such as atypical antipsychotics). Moreover, these metabolic changes may themselves be associated with cognitive impairment in areas of memory and executive function [37]. Thus, it may be that the cognitive improvement expected in medicated or treated mood disorder patients is negated over

time, and may ultimate manifest as cognitive decline, as a consequence of this associated weight gain [37 38]. Given that a strong association between cognitive impairment and poor psychosocial functional outcomes has been established, understanding the interaction between medication use, weight, and cognition is of great concern to treating practitioners [15].

Study Objective:

The goal of this study is to examine the impact of obesity on memory, executive function and attention in patients with and without a mood disorder (MDD or BD) by assessing cognitive performance prior to, and after, a significant 1-year weight loss following bariatric surgery. Changes in cognition associated with weight loss have been difficult to investigate primarily because most weight loss interventions do not result in a significant weight change [39]. We are uniquely positioned to investigate this, however, as we have designed an assessment paradigm that focuses on bariatric surgery patients. Bariatric surgery results in a weight loss range of 12% to 39% of pre-surgical body weight, providing an effective intervention with which to assess cognitive change [40]. We have also worked with engineers to modify our magnetic resonance imaging (MRI) scanner to accommodate physical restrictions associated with cognitive testing in this population, allowing us to examine some of the brain correlates behind this association. The specific aims and hypotheses of the study are:

Aim 1: Determine the effect of obesity (and additional interactive effect of a mood disorder diagnosis) on cognitive performance.

Hypothesis 1a: Compared to a healthy BMI weight non-psychiatric control population, the obese (bariatric) non-psychiatric control population will show worse cognitive performance, as assessed by the outcome of a standardized cognitive battery, prior to bariatric surgery.

Hypothesis 1b: Obese (bariatric) patients with a BD or MDD diagnosis will show worse cognitive performance than both (healthy BMI and obese [bariatric]) control populations, as assessed by the outcome of a standardized cognitive battery, prior to bariatric surgery.

Aim 2: Examine whether structural or functional brain differences can be seen (either in neural activation patterns during cognitive tasks or structurally) in obese patients with or without a mood disorder

Hypothesis 2: Prior to surgery, bariatric groups will show differences in regional pattern activations relative to the healthy BMI weight control group in neural activation during declarative memory and executive functioning tasks. These regional differences will be seen in neural structures important to memory (such as the hippocampus and precuneus) and executive function, such as, the dorsolateral prefrontal cortex.

Aim 3: Investigate whether any differences seen and associated with obesity (in cognitive performance tasks, neural activation patterns, or neural structures) can be diminished following significant weight loss

Hypothesis 3: At 1-year post intervention, all surgery-treated groups will show a significant improvement in cognitive performance measures (and related neural investigations) following expected (12% to 39% pre-surgical body weight [40]) weight-loss and overall health improvement.

The overall goal of this project is to *quantify* cognitive impairment in patients with mood disorders and assess the impact of obesity on cognitive performance and brain activation by measuring these variables before and after an intervention that significantly alters weight. We speculate that changes in cognitive function associated with mood disorders are caused in part by weight status, thereby increasing the burden of illness associated with MDD and BD.

Methods

Study Design and Timeline:

This is a prospective cohort study. Study subjects are seen 2 - 4 times during the study. Prior to surgery, subjects are seen once to complete cognitive testing and once to complete the brain imaging session. They will be required to return for a second cognitive

testing and fMRI session 1-year after surgical intervention (or 13-months following baseline visits for healthy control subjects). Self-report questionnaires, psychiatric assessments and anthropomorphic measures are administered at the pre- and post-surgical time points as well.

Subjects: Recruitment, Screening and Enrollment

Bariatric subjects are recruited from the St. Joseph's Healthcare Hamilton program for Bariatric Surgery (an Ontario Centre for Surgical Excellence). All patient charts on file were manually screened for potential eligibility in an initial recruitment stage; potential eligibility was based on reported patient height and weight measurements, age and whether the patient was still awaiting surgery. Newly received referral patients continue to be screened on an ongoing basis. Patients deemed potentially eligible are first reached via telephone. The study is introduced and procedures are explained during this initial telephone contact; if interested, subjects then undergo a telephone screen to determine if they meet study inclusion/exclusion criteria. Those who meet criteria are then scheduled for baseline study appointments and written informed consent is obtained at the initial appointment prior to data collection. Healthy control subjects from a departmental consent-to-contact phone list are contacted via telephone and administered parallel screening and enrollment procedures. In addition, recruitment also occurs via advertisements placed on hospital notice boards, and from health care provider referrals. Bariatric subjects can be enrolled in the study during any stage following the orientation class of their pre-surgical process. The surgical candidacy

process (and estimate time intervals between candidacy stages) can be found in Figure 1.

Study subjects are recruited into 4 groups: obese (bariatric) patients with BD, obese (bariatric) patients with MDD, obese (bariatric) patient without a psychiatric disorder (past or present), and healthy weight (non-surgical) controls without a psychiatric disorder (past or present). *Inclusion criteria* for all groups is as follows: age 18 – 60 years, ability to provide informed consent, and native English speaker (or having learned English by age 6). Additionally, healthy controls are required to have a BMI between 18.5 – 24.9 (normal range). *Exclusion Criteria* includes the presence of a current or pre-existing neurological condition (e.g., epilepsy, severe head trauma) or unstable and/or severe medical condition (e.g., cancer, life-threatening myocardial infarction), contraindications to MRI (deemed unsafe to complete an MRI via safety screening questionnaire), left-handedness (confirmed via Edinburgh Handedness Inventory) [41], having been administered any of the cognitive study measures within the past 12 months, a history of a confirmed learning disorder or developmental disability diagnosis (e.g., attention deficit hyperactivity disorder) or a Full Scale Intelligence Quotient (FSIQ) < 70, an inability to complete the testing (e.g. due to a hearing or vision impediment), and the presence of alcohol or substance abuse within the last 6 months or lifetime dependency (those in the BD group will not be excluded due to lifetime dependency if in sustained full remission). In addition, presence of a past or current psychiatric condition is an exclusion criterion for both healthy BMI weight and bariatric (obese) non-psychiatric control groups while having been administered electro-convulsive therapy

(ECT) within the last 24 months is an exclusion criteria for both BD and MDD bariatric patient groups. MRI eligibility screening is independently performed by MRI technicians at the Imaging Research Centre (St. Joseph's Healthcare Hamilton, Ontario). Subjects who are unable to complete MRI testing but have completed all other testing remain enrolled in the study. The first study subject was enrolled September 22, 2010.

Surgical Intervention

Currently in Ontario there are 150,000 individuals eligible for bariatric surgery and over 3000 individuals actively pursuing bariatric surgery. As of 2014, the Bariatric Surgery Program at St. Joseph's Healthcare Hamilton completed approximately 600 surgeries per year [42]. Traditionally, all bariatric surgeries have been thought to cause weight loss through the processes of malabsorption (of nutrients or calories), caloric restriction, or a combination of the 2. [40].

The most common gastric procedures performed are Laparoscopic Adjustable Gastric Banding (LAGB) and Roux-en-Y Gastric Bypass (RYGB) [43]. In Ontario, RYGB is the most routinely performed and is covered financially (for those with a BMI exceeding 40 or 35 with significant medical comorbidities) by the Ontario Health Insurance Program. Alternatively, the LAGB is rarely performed in public health settings due to its diminished rate of long-term weight loss success and the higher likelihood for additional follow-up surgical procedures; it is, however, readily available through private healthcare providers. Due to the presence of certain medical comorbidities, conditions, or gastrointestinal irregularities, a bariatric surgery team may opt to perform a

laparoscopic vertical sleeve gastrectomy (VSG) or biliopancreatic diversion (BPD) with duodenal switch. [44].

Data Collection

Subjects complete baseline measures over the course of 1 – 2 study visits. Those who undergo an MRI at baseline are re-assessed for scan eligibility at their follow-up visit. All assessment measures are re-administered at follow-up with the exception of the Structured Clinical Interview for DSM-IV (SCID) (which is replaced by the Mini International Neuropsychiatric Interview [MINI] at that time point). A double-entry system with independent research personnel is utilized for all cognitive and behavioural data and inconsistencies are checked and resolved by an additional assessor. A summary of the test measures administered at each time point is found in Table 1 "Study Visit Schedule". To accommodate patient schedule restrictions, study visits 1 and 2 (pre-surgical baseline), and study visits 3 and 4 (post-surgical follow-up) may occasionally be collapsed into one visit. Similarly, self-report questionnaires and psychiatric measures may occasionally be administered on the same study visit to accommodate the patient.

Table 1. Study Visit Schedule

	1st Visit (Baseline/ screening, pre-surgical)	2nd Visit (Pre-surgical)	3rd Visit (1 year following surgery)	4th Visit. (Follow-up, post-surgical)

SCID (DSM-IV-TR)	X			
MINI			X	
Hamilton Rating Scale for Depression (HAMD-17)	X		X	
Young Mania Rating Scale (YMRS)	X		X	
the Beck Depression Inventory (BDI)	X		X	
Altman Self-Rating Scale for Mania (ASRM)	X		X	
Anthropomorphic, Glucose measures	X		X	
Wechsler Abbreviated Scale of Intelligence	X		X	
The Wechsler Test of Adult Reading	X		X	
fMRI		X		X
Practice Session		X		X
Warrington's Recognition Memory Task		X		X
executive functioning (N-Back Task)		X		X
Declarative memory function battery:				
California Verbal Learning Test II (standard and alternate forms)	X		X	
Wechsler Memory Scale III - Logical Memory subtest	X		X	
Brief Visuospatial Memory Test – Revised	X		X	
Executive functioning and attention battery:				

Controlled Oral Word Association Task	X		X	
Stroop Colour and Word Test (Golden version)	X		X	
Wisconsin Card Sorting Task (64-item version)	X		X	
Colour Trails Test Part A & B	X		X	
Paced Auditory Serial Attention Test	X		X	
Additional Self-Report Questionnaires				
Cognitive Failure Questionnaire		X		X
Sheehan Disability Questionnaire		X		X
Berlin Sleep Questionnaire (Healthy Controls only)		X		X
Childhood Trauma Questionnaire		X		X
Demographics Questionnaire		X		X
Food Frequency Questionnaire*	X		X	
Medications List Questionnaire*	X		X	

*Both these questionnaires require extensive information (with the Food Frequency Questionnaire requiring a minimum 3 –day recording of food intake). As such, they are given to study subjects during their first visit at both time-points to be completed and returned by their next study visit.

Psychiatric (and Mood) Assessment

Subjects are diagnosed via administration of the SCID at baseline. Current psychiatric status is reassessed at follow-up via the MINI. Both current and euthymic patients are included in the Bariatric BD and Bariatric MDD groups. As this is not an intervention

trial, patients are not assigned nor treated by a study psychiatrist. Patients currently being treated by a community or clinic mental health professional or general practioner will continue to do so. If patients indicate symptoms of current suicidality, they are referred to emergency psychiatric services. Mood ratings are also monitored at baseline and end visits via the Hamilton Rating Scale for Depression (HAMD-17) and the Young Mania Rating Scale (YMRS)[45 46]; both are assessed by the same study personnel to avoid issues of interrater reliability. In addition, the Beck Depression Inventory (BDI) and Altman Self-Rating Scale for Mania (ASRM) are also administered [47 48]. In circumstances where baseline visits are 2 or more weeks apart, the BDI and ASRM are administered separately at each of these visits to account for possible changes in mood state. As high rates of trauma exposure have been reported in both mood disorder and obese populations [49] [50], the Childhood Trauma Questionnaire (CTQ) is also administered [51].

Neuropsychological Assessment

A standardized battery of neuropsychological tests aimed at establishing pre- and post-intervention performance on tests of declarative memory, executive functioning and attention is administered. These cognitive domains have been shown to be susceptible to impairment in metabolically dysregulated populations [3 8]. Executive function is also shown to be the most robust cognitive domain susceptible to impairment in obese populations specifically [52], while there is also evidence indicating the areas of memory [53-55] and attention [6 56 57] may also be affected . Tests were chosen with 2 objectives in mind: 1) to investigate different aspects of both declarative memory and

executive functioning in order to provide an exhaustive overview of these composite areas, and; 2) with redundant overlap between areas and skills tested (to minimize the likelihood of spurious test results in any one sub-domain). Additional information regarding individual neuropsychological tests administered is also summarized in Table 2. A clinical neuroscience graduate student (MRR), trained in neuropsychological assessment and psychometric methodologies, administers the testing. She has received training and is supervised by a registered clinical neuropsychologist (MCM).

Table 2. Summary and Psychometric Properties of Neuropsychological Test Measures and fMRI Behavioural Tasks [58]

Test	Administration Time (Minutes)	Age Range (Years)	Measure and Purpose
Brief Visuospatial Memory Test – Revised (BVMT-R)	15 (40 with delay interval)	18 – 79	Multiple-trial figure-learning paradigm assessing visual learning and memory
California Verbal Learning Test – II (CVLT-II)	35 – 40	16 – 89	Multiple-trial list-learning paradigm assessing verbal learning and memory

Color-Trails Test (CTT)	5 – 10	18 – 89	Manual drawing task assessing speed of attention, sequencing, mental flexibility, visual search, and motor function
N-Back Task	22 (fMRI version)	Not defined	Continuous performance task assessing attention and short-term memory
Paced Auditory Serial Addition Task (Computerized Version)	15 – 20	16 – 74	Serial-addition task assessing working memory, divided attention, and information processing speed
Stroop (Golden Version)	5	5 – 90	Reading task assessing cognitive control, goal maintenance, and suppression of a habitual response in favour of a less familiar one
Warrington's Recognition	8 (fMRI Version)	18 – 70	Assesses recognition

Memory Task (Words Subtest Only)			memory for printed words
Wechsler Memory Scale – III (WMS-III) (Logical Memory I & II Subtests)	35 – 45 minutes with delay interval	18 -89	Assesses auditory declarative (verbal) memory and learning
Wechsler Abbreviated Scale of Intelligence (WASI)	15	6 – 89	Brief intelligence measure
Wechsler Test of Adult Reading (WTAR)	10	16- 89	Reading task assessing pre-morbid functioning
Wisconsin Sorting Card Task (WSCT)	15 – 30	5 – 89	Card-sorting task assessing ability to form abstract concepts, shift and maintain set, and utilize feedback

Many of the measures chosen, namely the COWAT, CVLT-II, Stroop, WASI, WCST ,WMS-II and the WTAR have been used in previous studies involving obese populations, allowing for better direct comparison of future study results with work that has been previously completed [7 53 59-63].

Declarative memory function battery:

i) California Verbal Learning Test II (standard and alternate forms): this word list learning task provides indices of immediate and delayed memory performance, interference learning, and recognition [64].

ii) Wechsler Memory Scale III - Logical Memory subtest: this contextually-based memory task provides indices of learning slope, immediate and delayed memory performance, retention, and recognition [65]

iii) Brief Visuospatial Memory Test – Revised: a nonverbal test of visuospatial memory under explicit encoding conditions [66]

Executive functioning and attention battery:

i) Controlled Oral Word Association Task: this task taps phonemic (FAS) and semantic (animals) fluency [67]

ii) Stroop Colour and Word Test (Golden version): this task taps sensitivity to suppress a habitual response in favor of a less familiar one [68]

iii) Wisconsin Card Sorting Task (64-item version): this task taps the ability to form and shift concepts based on feedback [69]

iv) Colour Trails Test Part A & B: whereas Part A assesses processing speed, Part B taps the ability to sequence two stimulus sets while alternating between them [70]

v) Paced Auditory Serial Attention Test (Victoria Computerized Adaptation): this task assesses capacity and rate of information processing as well as sustained and divided attention [71]

Pre-morbid IQ

Subjects complete one subtest of the performance (Matrix Reasoning) and verbal (Vocabulary) indices of the Wechsler Abbreviated Scale of Intelligence in order to estimate current intellectual functioning via FSIQ [72]. The Wechsler Test of Adult Reading is also administered to estimate pre-morbid intellectual functioning in subjects [73]. This test consists of 50 words, listed in order of difficulty. Subjects are presented with the word list and instructed to read each word aloud. Total number of correct pronunciations comprises the final score.

Anthropometric Measures

A glucose measurement is obtained on the day of cognitive testing both at baseline and end visits via a 'finger prick' glucometer reading. Height, weight, waist and hip circumferences, systolic and diastolic blood pressure, and heart rate measurements are measured for non-bariatric controls at baseline and end visits. Waist circumference is measured according to the WHO STEPS protocol that instructs that the measurement is made approximately between the lower margin of the last palpable rib and the top of the iliac crest [74]. Hip circumference is measured around the widest portion of the subject's buttocks.

For bariatric surgery subjects, these measurements are obtained via manual data extraction by study personnel from subjects' medical record charts containing doctor, nurse and dietician visit notes and summary. Nurses and dieticians review and record

relevant blood-work that must be completed and accessible by the patient's first clinical visit, and record the anthropomotric measures described earlier (such as blood pressure, weight, and waist circumference) during this first visit. Glucose, HbA1C and lipid assessment profiles contained in the subjects' medical record for bariatric subjects were obtained via data extraction by study personnel from laboratory reports.

Demographics and Medical Health

Age, gender, education, job status, family psychiatric history, and medical health/illness information is collected during the initial telephone screen questionnaire. As part of the bariatric surgery process, clinic staff capture extensive information regarding the patient's past and current medical diagnoses during the patient's initial clinic visit and study personnel extract data recorded during these encounters in order to confirm the presence or absence of comorbidities. It is expected that the vast majority of enrolled subjects will receive Roux X-en-Y gastric bypass, however, given that different surgical procedures are associated with different rates and mechanisms of weight loss and that a minority of patients may receive an alternate surgery, the type of bariatric surgery completed by each subject is also recorded. This will allow us to investigate the potential variation in outcomes for patients receiving different forms of surgery. Additional information concerning living arrangements, previous education details, marital/relationship status, number of children, smoking behaviour and previous medication history is collected in the general demographics questionnaire administered during the study.

Subjects are also asked to provide a complete listing of current medications, vitamins, and herbal supplements (including dosage and indication), at both baseline and follow-up time points. The Berlin Sleep Questionnaire [75] ,which assesses the risk level for current Obstructive Sleep Apnea (OSA) or sleep disordered breathing is also completed. It is administered as part of the study self-report package for non-bariatric subjects, while bariatric subjects complete this questionnaire through the bariatric surgery clinic as part of their surgical candidacy process. OSA will be analyzed as a categorical variable (present, current controlled through treatment, or absent). OSA status is reassessed at follow-up as well. Patients complete a self-report questionnaires regarding their current level of physical activity and mobility (both pre- and post-surgically). Increasing levels of physical activity has been associated with positive cognitive outcomes and increased hippocampal size [34 76 77]. Although not a standardized, quantitative questionnaire, this self-report may provide us with a qualitative assessment of current level of exercise that can be converted into a categorical variable representing general level of physical activity (e.g. sedentary, minimal, moderate or high) to be used in later exploratory analyses.

Nutrition

Nutritional intake is assessed via a non-consecutive 3-day dietary record (Food Frequency Questionnaire), with one day being a weekend day [78]. This 3-day method has been demonstrated to estimate habitual energy intake within 10% of the actual values in groups as small as 13 subjects [79]. In addition to overall caloric intake, diet

component analysis will also be completed. Specifically, total and percent intake of proteins, carbohydrates, fat, cholesterol, fibre, sugar and sodium is calculated per subject for future analysis.

Disability and Self-reported Cognitive Measures

The Sheehan Disability Scale (SDS) [80] is administered to provide a quick measure of the impact of the subject's disability (obesity and/or mood disorder) across various life domains. The Cognitive Failure Questionnaire [81], a measure of self-reported failures in perception, memory and motor function that has been used in comparable populations previously [82] is used to assay subjective feelings of cognitive dysfunction.

Imaging

Each subject also undergoes a one-hour MRI session at baseline and follow-up time points. A high-resolution axial 3D anatomical T1-weighted scan with full brain coverage is performed to obtain relevant neuroanatomical data (including hippocampus volume). Anatomical data collected will also allow for exploratory whole-brain analysis (e.g. global volume differences) to be completed. Following this, two tasks tapping declarative memory function (Warrington's Recognition Memory Task, or RMT) [83] and executive functioning (N-Back Task) are performed (additional information regarding Warrington's RMT the N-Back Task is available in Table 2). Regional activation patterns will be compared and contrasted across groups. Behavioural data, such as reaction time, correct number of responses on N-Back subtests, and correct number of recognition hits on the RMT, is also collected. As part of the subject's orientation and training, practice

trials of each task are administered outside of the MRI on the day of the actual MRI session.

Data Analysis

R Statistical Software [84] and the Statistical Package for Social Sciences (SPSS) statistics will be used [85] for data analysis. MRI imaging analyses will be completed using Statistical Parametric Mapping (SPM), Matlab [86] and FreeSurfer [87].

Cognitive performance on neuropsychological measures at both baseline and end visits will be compared across 4 groups (bariatric MDD, bariatric BD, bariatric controls and healthy matched controls). The primary outcome variable at follow-up will be cognitive change at 12 months following surgery. We chose group sample sizes of 20 minimum in order to have enough power to adequately examine neuroimaging differences between groups [88]. Based on work by Woods (1996), we will also have enough power for use of individual contrast images in second-level random effects models that will allow us to investigate target regional responses at the group level [89].

Neuropsychological measures will be examined independently and may be integrated into an executive function/attention composite and declarative memory composite. Composite score may be obtained by converting individual scale scores across to z-scores and then averaging across independent measures.

Exploratory analyses using descriptive statistics will be used to present demographic and medical data (such as comorbidity presence, age, physical activity, medication load,

etc.). Initial one-way between-group univariate analyses of variance will be run to identify potential confounding covariates in any effects found at baseline. The impact of related comorbidities (such as T2D and hypertension) will also be examined. Although our primary interest is the effect of obesity alone on cognition, additional cardiovascular comorbidities are likely to have an additive effect on cognitive performance and their effect contribution will be explored via hierarchal regression model analysis. Bariatric surgery is known to normalize blood glucose and reverse T2D status in surgery patients even without significant weight loss [40]. This potential effect on overall cognitive performance differences will be explored in post-surgical group analyses.

Both structural and functional imaging scans will be run at baseline and follow-up using the same 3 Tesla General Electric (General Electric, Milwaukee, WI) system at the Imaging Research Centre (St. Joseph's Healthcare Hamilton, Ontario). Functional MRI tasks will be displayed using E-Prime software (www.pstnet.com) [90]. Hippocampal volume (and change in volume over time) will be measured using FreeSurfer [87]. Acquired functional images will be processed and analyzed using Statistical Parametric Mapping (SPM) and Matlab software [86]. Collected data will be slice-time corrected, 3D motion corrected and realigned to the fifth volume in the first series collected, and normalized to MNI space. High-resolution T1-weighted 3D anatomical MRI data collected for each subject will be used for co-registration with functional data. Anatomical data sets will be averaged across healthy control subjects to generate a composite image onto which the functional activation results are projected. General Linear Models will be created for both tasks and overlaid for each subject to examine

neural activation patterns for each group. Activation contrasts will be examined using subject group as a between-subjects factor.

Ethics and Dissemination

This study has been approved by the Hamilton Integrated Research Ethics Board of St. Joseph's Healthcare Hamilton Hospital and Hamilton Health Sciences Centre (09-3254). Written informed consent is obtained from each subject after study information is provided and before study entry. Subjects are informed that all data collected is de-identified and that identifying consent forms are kept separately from other collected data. Collected data is stored securely in both electronic and paper forms. Only approved research personnel and study investigators have access to the data. Results will be available in peer-reviewed scientific publications and scientific meetings presentations, and released in lay form to media outlets.

Discussion

This study will be the first of its kind to investigate the impact of obesity on cognition via an intervention that results in significant and sustained weight loss in a population with a mood disorder. We hypothesize that weight status will have a significant effect on cognition, a conclusion that may influence the way mental health care is provided and have important ramifications for first-line recommendations with respect to medications. It will also improve our understanding of the neural pathways involved in

cognitive processes, furthering our understanding of how mental illness develops and the additional risk conferred by obesity.

Study Status

The status of the study at the time of manuscript submission was completion of enrollment for all but one subject group (bariatric BD). Numbers of subjects that have been enrolled and fully completed testing in each arm of the study are available in Table 3 below.

Table 3. Current Subject Enrollment

Group	Neuropsychology Arm	MRI Arm
Healthy Controls	20	20
Bariatric Controls	25	20
Bariatric MDDs	21	23
Bariatric BDs	11	4

Abbreviations

ASMR: Altman Self-Rating Scale for Mania; BD: Bipolar Disorder; BDI: Beck Depression Inventory; BMI: Body Mass Index; BPD: Biliopancreatic Diversion; CTQ: Childhood

Trauma Questionnaire; CV: cardiovascular; fMRI: functional Magnetic Resonance Imaging; FSIQ: Full Scale Intelligence Quotient; HAMD-17: Hamilton Rating Scale for Depression – 17 Items; LAGB: Laparoscopic Adjustable Gastric Banding; MDD: Major Depressive Disorder; MINI: Mini International Neuropsychiatric Interview; MMSE: Mini-Mental State Examination; MRI: Magnetic Resonance Imaging; OSA: Obstructive Sleep Apnea; RYGB: Roux-en-Y Gastric Bypass; RMT: Recognition Memory Task; SCID: Structured Clinician Interview for DSM-IV; TDII: Type 2 Diabetes Mellitus; VSG: Vertical Sleeve Gastrectomy; YSRM: Young Self-Rating Scale for Mania

Competing Interests And Role of Funding Source

Dr. Valerie Taylor received an unrestricted educational grant from Bristol Myers Squibb to help fund this study. MR is a doctoral thesis candidate who has been supported by fellowships from the Canadian Institute of Health Research and Government of Ontario. The study sponsors plays no role in study design, data collection, data analysis, data interpretation or report writing.

Authors' Contributions

MM, MR, and VT designed the study protocol. MR completed study subject screening and recruitment, all data collection (including data extraction from patient records), supervised data entry (completed by undergraduate students) and completed data cleaning and coding. Thorough training under a team of clinical neuropsychologists was provided to MR prior to commencement of patient testing. MM provided feedback and consultation on cognitive data collection and analysis. GH and BF designed aspects of

the study related to the MRI and provided feedback and consultation on MRI data collection and analysis. MR will analyze data under the supervision of VT and in consultation with a statistician at the Sunnybrook Health Sciences Centre (Dr. Alex Kiss). MR drafted the manuscript. All authors contributed to and approved the final manuscript.

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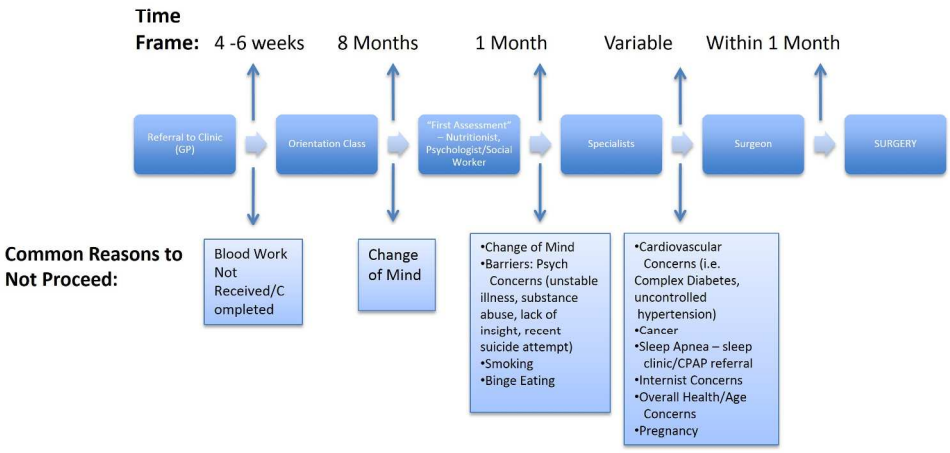

Figure 1. The surgical candidacy process and estimate time intervals between candidacy stages.
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