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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 recognised 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 (body mass index >35 kg/m^2) with BD or MDD, and 2 control populations (obese individuals without a psychiatric illness and healthy non-obese controls) prior to and following bariatric surgery. Participants (ages 18–60) receive a psychiatric diagnosis via the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; SCID). Mood ratings, physical measurements, nutritional and health questionnaires are also administered. A standardised 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 3 T functional MRI to investigate patterns of neural activation during cognitive performance. Additionally, anatomical MRI data are obtained to investigate potential changes in neural structures. Baseline data will be analysed for between-group differences and later compared with postsurgical 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 of this study

- Only known study to follow use of functional MRI (fMRI) to study memory/higher order cognitive changes before and after a significant weight status change.
- Extensive characterisation and well-controlled design of population comorbidities.
- Quantitative complimentary and comprehensive cognitive data collection methodologies (standardised neuropsychological measures, fMRI neural activation investigation and MRI neural structure measurements).
- Study entry limited by physical MRI restrictions (may capture limited portion of bariatric surgery population).

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*,[3] only six studies investigating the association between obesity and cognition were identified.[3] One out of three cross-sectional and two out of three longitudinal studies reported a significant negative association between obesity and cognitive performance, with this association differing across individual cognitive domains. In a recent review, Smith *et al*[5] found that 14 out of 15 cross-sectional studies in human adult participants reported a negative association between obesity and cognition. Interestingly, executive functioning was the cognitive domain most often affected (11 out of 15 studies reported an association). There were only four prospective studies examining the impact of obesity and naturalistic weight changes on cognitive performance and later life outcome; the results from these four studies were inconsistent. While much of the prospective data showed that a higher body mass index (BMI) or waist-to-hip ratio was associated with poorer performance on tests of memory, Gunstad *et al*[6] found that waist circumference and BMI were associated with faster performance on a neuropsychological measure of processing speed. To our knowledge, there have been two 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 participants, present comorbidities, type of weight change (increase/decrease over time) and type of intervention applied (eg, 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 1423 community participants complete tests involving IQ, verbal memory and verbal fluency. After adjusting for potential confounders of age, education, occupation, alcohol and smoking use, dyslipidaemia 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[9] study of 2684 normal weight, overweight and obese participants included completion of the Mini-Mental State Examination (MMSE), verbal learning, memory and reasoning tasks, and performance measures. After age, race, sex, intervention type, education, and cardiovascular (CV) comorbidities were controlled for, overweight participants 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 (bipolar disorder (BD) and major depressive disorder (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 hypertriglyceridaemia),[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 ORs 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 behaviour, 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 (eg, 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 stabiliser, 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 (eg, computerised skills training) may improve cognitive functioning in patients with mood disorders.[35 36] However, residual cognitive symptoms often persist in patients with euthymia.[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 12–39% of presurgical body weight, providing an effective intervention with which to assess cognitive change.[40] We have also worked with engineers to modify our MRI 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 with 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 standardised 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 standardised 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 postintervention, all surgery-treated groups will show a significant improvement in cognitive performance measures (and related neural investigations) following expected (12–39% presurgical 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 participants are seen 2–4 times during the study. Prior to surgery, participants 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 functional MRI (fMRI) session 1 year after surgical intervention (or 13 months following baseline visits for healthy control participants). Self-report questionnaires, psychiatric assessments and anthropomorphic measures are administered at the presurgical and postsurgical time points as well.

Participants: recruitment, screening and enrolment

Bariatric participants are recruited from the St. Joseph's Healthcare Hamilton programme 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, participants 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 participants from a departmental consent-to-contact phone list are contacted via telephone and administered parallel screening and enrolment procedures. In addition, recruitment also occurs via advertisements placed on hospital notice boards, and from healthcare provider referrals. Bariatric participants can be enrolled in the study during any stage following the orientation class of their presurgical process. The surgical candidacy process (and estimate time intervals between candidacy stages) can be found in figure 1.

Study participants 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 are 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 and 24.9 (normal range). *Exclusion criteria* include the presence of a current or pre-existing neurological condition (eg, epilepsy, severe head trauma) or unstable and/or severe medical condition (eg, 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 (eg, attention deficit hyperactivity disorder) or a Full Scale IQ (FSIQ) <70, an inability to complete the testing (eg, due to a hearing or vision impediment), and the presence of alcohol or substance abuse within the past 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 electroconvulsive therapy within the past 24 months is an exclusion criterion 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, Canada). Participants who are unable to complete MRI testing but have completed all other testing remain enrolled in the study. The first study participant was enrolled on 22 September 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 two.[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

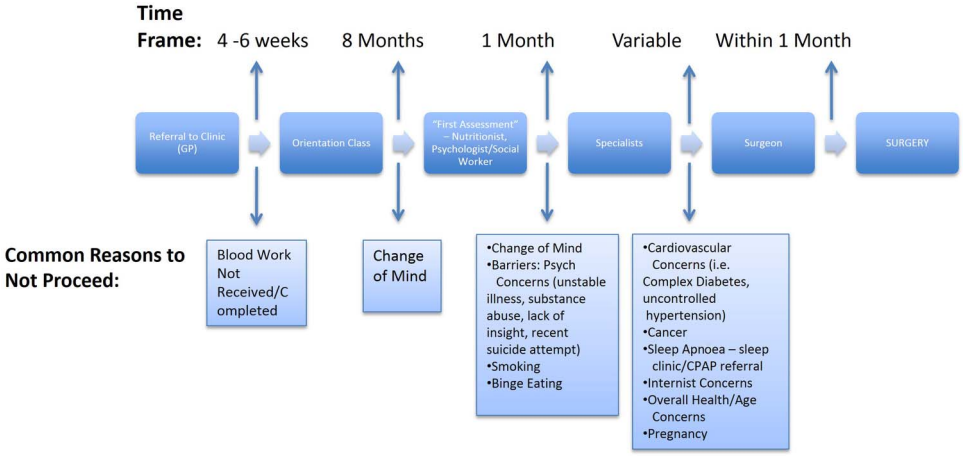

Figure 1 The surgical candidacy process and estimate time intervals between candidacy stages. CPAP, continuous positive airway pressure; GP, general practitioner.

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. Owing to the presence of certain medical comorbidities, conditions or gastrointestinal irregularities, a bariatric surgery team may opt to perform a laparoscopic vertical sleeve gastrectomy or biliopancreatic diversion with duodenal switch.[44]

Data collection

Participants complete baseline measures over the course of 1–2 study visits. Those who undergo MRI at baseline are reassessed for scan eligibility at their follow-up visit. All assessment measures are readministered at follow-up with the exception of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (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 utilised 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. To accommodate patient schedule restrictions, study visits 1 and 2 (presurgical baseline), and study visits 3 and 4 (postsurgical 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.

Psychiatric (and mood) assessment

Participants 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 practitioner 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 inter-rater 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 standardised battery of neuropsychological tests aimed at establishing preintervention and postintervention 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 two 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 minimise the likelihood of spurious test results in any one subdomain). Additional information regarding individual neuropsychological tests administered is also summarised 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).

Declarative memory function battery:

1. 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]
2. 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]
3. Brief Visuospatial Memory Test—Revised: a nonverbal test of visuospatial memory under explicit encoding conditions.[66]

Executive functioning and attention battery:

1. Controlled Oral Word Association Task (COWAT): this task taps phonemic and semantic (animals) fluency.[67]
2. Stroop Colour and Word Test (Golden version): this task taps sensitivity to suppress a habitual response in favour of a less familiar one.[68]
3. Wisconsin Card Sorting Task (64-item version): this task taps the ability to form and shift concepts based on feedback.[69]
4. Colour Trails Test Part A and B: whereas Part A assesses processing speed, Part B taps the ability to sequence two stimulus sets while alternating between them.[70]
5. 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]

Premorbid IQ

Participants complete one subtest of the performance (matrix reasoning) and verbal (vocabulary) indices of

Table 1 Study visit schedule

	First visit (baseline/ screening, presurgical)	Second visit (presurgical)	Third visit (1 year following surgery)	Fourth visit (follow-up, postsurgical)
SCID (DSM-IV-TR)	X			
MINI			X	
HAMD-17	X		X	
YMRS	X		X	
BDI	X		X	
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 and 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 participants during their first visit at both time points to be completed and returned by their next study visit.
ASRM, Altman Self-Rating Scale for Mania; BDI, Beck Depression Inventory; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; fMRI, functional MRI; HAMD, Hamilton Rating Scale for Depression; MINI, Mini International Neuropsychiatric Interview; SCID, Structured Clinical Interview for DSM-IV; YMRS, Young Mania Rating Scale.

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 premorbid intellectual functioning in participants.[73] This test consists of 50 words, listed in order of difficulty. Participants 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 participant's buttocks.

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

Table 2 Summary and psychometric properties of neuropsychological test measures and functional MRI (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 (computerised 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 only)	8 (fMRI version)	18–70	Assesses recognition memory for printed words
Wechsler Memory Scale—III (WMS-III; Logical Memory I and II subtests)	35–45 min 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 premorbid functioning
Wisconsin Sorting Card Task (WSCT)	15–30	5–89	Card-sorting task assessing ability to form abstract concepts, shift and maintain set, and utilise feedback

Many of the measures chosen, namely the COWAT, CVLT-II, Stroop, WASI, WSCT, 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]

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 anthropometric measures described earlier (such as blood pressure, weight and waist circumference) during this first visit. Glucose, glycated haemoglobin and lipid assessment profiles contained in the participants' medical record for bariatric participants 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 participants 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 participant 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.

Participants 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 apnoea (OSA) or sleep-disordered breathing is also completed. It is administered as part of the study self-report package for non-bariatric participants, while bariatric participants complete this questionnaire through the bariatric surgery clinic as part of their surgical candidacy process. OSA will be analysed 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 presurgically and postsurgically).

Increasing levels of physical activity has been associated with positive cognitive outcomes and increased hippocampal size.[34 76 77] Although not a standardised, 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 (eg, 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 1 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 participants.[79] In addition to overall caloric intake, diet component analysis will also be completed. Specifically, total and per cent intake of proteins, carbohydrates, fat, cholesterol, fibre, sugar and sodium is calculated per participant 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 participant'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 participant also undergoes a 1 h MRI session at baseline and follow-up time points. A high-resolution axial three-dimensional (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 (eg, 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, are also collected. As part of the participant'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 (R: A Language and Environment for Statistical Computing (program). Vienna, Austria: R Foundation for Statistical Computing, 2014) and the Statistical Package for Social Sciences (SPSS) statistics will be used (IBM SPSS Statistics. V.22 (program), 2013) for data analysis. MRI analyses will be completed using Statistical Parametric Mapping (SPM), Matlab (MATLAB and Statistics Toolbox Release 2012b (program). Natick, Massachusetts, USA2012) and FreeSurfer (FreeSurfer V.1.0 (program). Boston, Massachusetts, USA, 2011).

Cognitive performance on neuropsychological measures at both baseline and end visits will be compared across four 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.[84] Based on work by Woods,[85] 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.

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 CV 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 normalise 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 postsurgical group analyses.

Both structural and functional imaging scans will be run at baseline and follow-up using the same 3 T General Electric (General Electric, Milwaukee, Wisconsin, USA) system at the Imaging Research Centre (St. Joseph's Healthcare Hamilton, Ontario, Cannada). fMRI tasks will be displayed using E-Prime software (http://www.pstnet.com) (E-Prime 2.0 Software (program). Pittsburgh, Pennsylvania, USA, 2012). Hippocampal volume (and change in volume over time) will be measured using FreeSurfer (FreeSurfer V.1.0 (program). Boston, Massachusetts, USA, 2011). Acquired functional images will be processed and analysed using Statistical Parametric Mapping (SPM) and Matlab software (MATLAB and Statistics Toolbox Release 2012b (program). Natick, Massachusetts, USA, 2012). Collected

data will be slice-time corrected, 3D motion corrected and realigned to the fifth volume in the first series collected, and normalised to Montreal Neurological Institute space. High-resolution T1-weighted 3D anatomical MRI data collected for each participant will be used for co-registration with functional data. Anatomical data sets will be averaged across healthy control participants 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 participant to examine neural activation patterns for each group. Activation contrasts will be examined using participant group as a between-participants factor.

Ethics and dissemination

Written informed consent is obtained from each participant after study information is provided and before study entry. Participants are informed that all data collected are de-identified and that identifying consent forms are kept separately from other collected data. Collected data are 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 hypothesise that weight status will have a significant effect on cognition, a conclusion that may influence the way mental healthcare 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 enrolment for all but one participant group (bariatric BD). Numbers of participants that have been enrolled and fully completed testing in each arm of the study are available in table 3 below.

Table 3 Current participant enrolment

Group	Neuropsychology arm	MRI arm
Healthy controls	20	20
Bariatric controls	25	20
Bariatric MDDs	21	23
Bariatric BDs	11	4

BD, bipolar disorder; MDD, major depressive disorder.

Contributors MCM, MRR and VHT designed the study protocol. MRR completed study participant 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 MRR prior to start of patient testing. MCM provided feedback and consultation on cognitive data collection and analysis. GBH and BNF designed aspects of the study related to the MRI and provided feedback and consultation on MRI data collection and analysis. MRR will analyse data under the supervision of VHT and in consultation with a statistician at the Sunnybrook Health Sciences Centre (Dr Alex Kiss). MRR drafted the manuscript. All authors contributed to and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Hamilton Integrated Research Ethics Board of St. Joseph's Healthcare Hamilton Hospital and Hamilton Health Sciences Centre (09-3254).

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