# COGNITION, OBESITY AND MOOD DISORDERS

# THE EFFECT OF OBESITY ON COGNITION IN ADULTS WITH AND WITHOUT A MOOD DISORDER

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## ABSTRACT

Obesity is a common medical illness that is known to confer risk for a large number of medical illnesses, such as Type II Diabetes, hypertension, cancer, and late-life dementia. More recently, the relation between obesity and decline in cognitive performance, independent of other comorbid medical conditions, has begun to be examined. Individuals with mood disorders (Bipolar Disorder [BD] or Major Depressive Disorder [MDD]) display an increased prevalence of both obesity and risk factors for cardiovascular disease. Moreover, BD and MDD are associated with impairment in cognitive functioning across multiple domains. The contribution of obesity to cognitive decline in this population has not been explored. This thesis begins with a systematic review of the literature examining the impact of obesity on cognition, providing a thorough background of this relation. The following chapter introduces a prospective cohort study designed to comprehensively explore the relation between obesity and cognition in individuals both with, or without, a mood disorder. The first of set of results from this study are presented in the remaining chapters. The neuropsychological study findings indicate that MDD and obesity may have an additive effect on cognition, resulting in significant cognitive decline in obese adults with MDD. Moreover, we show that different neural activation patterns are seen during a cognitive magnetic resonance imaging (MRI) task in obese versus obese MDD patients. Collectively, this provides strong evidence that populations already at risk for cognitive impairment, such as mood disorder populations, are susceptible to further cognitive changes due to increased weight.

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# LIST OF ABBREVIATIONS

ANOVA: Analysis of Variance

ASMR: Altman Self-Rating Scale for Mania

BC: Bariatric Control

BDI: Beck Depression Inventory

BMI: Body Mass Index

BVMT-R: Brief Visuospatial Measure Test – Revised

CFQ: Cognitive Failure Questionnaire

COWAT: Controlled Oral Word Association Test

CTT: Color Trails Test

CV: Cardiovascular

CVD: Cardiovascular disease

CVLT: California Verbal Learning Task

CTQ: Childhood Trauma Questionnaire

ECT: Electro-Convulsive Therapy

FDR: False-Discovery Rate

FFQ: Food Frequency Questionnaire

FSIQ: Full Scale Intelligence Quotient

HAMD-17: Hamilton Rating Scale for Depression – 17 Items

HC: Healthy Control

IFG: Inferior Frontal Gyrus

MDD: Major Depressive Disorder

MFG: Medial Frontal Gryus

OSA: Obstructive Sleep Apnea

PASAT: Paced Auditory Serial Addition Task

SCID: Structured Clinician Interview for DSM-IV

TDII: Type 2 Diabetes Mellitus

WASI: Wechsler Abbreviated Scale of Intelligence

WCST: Wisconsin Card Sorting Test

WMS-LM: Wechsler Memory Scale – Logical Memory

WTAR: Wechsler Test of Adult Reading;

YSRM: Young Self-Rating Scale for Mania

# DECLARATION OF ACADEMIC ACHIEVEMENT

**Chapter 2:** Restivo, M.R., Jones, H., Nashed, M., & Taylor, V.H. The effect of obesity on cognition: a systematic review. Prepared for submission to the journal *Obesity Reviews*.

- M.R. Restivo - Responsible for review design and procedures. Performed literature search, abstract screening and data extraction. Primary manuscript author.
- H. Jones and M. Nashed – replicated literature search. Acted as second raters for abstract screening and data extraction.
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- M. R. Restivo - Contributed to study design. Responsible for study implementation. Primary manuscript author.
- M.C. McKinnon - Contributed to cognitive and statistical study design.
- B.N. Frey – Contributed imaging study design. Local clinical supervision of patient interactions.
- G.B. – Contributed to imaging study design.
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- M. R. Restivo - Contributed to study design. Responsible for study implementation. Performed all subject screening, recruitment, and data collection. Supervised data entry and completed data cleaning and coding. Completed data analysis. Primary manuscript author.
- M.C. McKinnon - Contributed to neuropsychological aspects of study design. Provided consultation on cognitive data collection and analysis.
- B.N. Frey – Local clinical supervision of patient interactions. Provided feedback on results.
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- W. Syed – Assisted with data scoring, coding, and cleaning.
- V. H. Taylor – Responsible for original study design. Provided supervision and advice.

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- G.B. – Contributed to study design. Provided feedback and consultation on imaging data collection and analysis.
- B.N. Frey – Contributed to study design. Local clinical supervision of patient interactions.
- M.C. McKinnon – Contributed to study design. Provided feedback on results.
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# CHAPTER 1:INTRODUCTION

**Overview of Obesity**

Obesity, the accumulation of excess adipose tissue, has quickly become characterized as a global pandemic and is now widely recognized as a disease state by clinicians and scientists alike (Ng et al., 2013). In Canada, the rate of obesity in adults has significantly increased in recent decades from a baseline of 10% in 1970-72 to 26% in 2009-2011 (Janssen, 2013). As a result, the associated healthcare burden associated with obesity has also risen dramatically; using information from the 2011 Obesity in Canada report (from the Public Health Agency of Canada and Canadian Institute for Health Information), the total cost of obesity was estimated to be between 4.7 and 7.1 billion dollars (Education, 2011). The higher estimation included both direct and indirect healthcare costs associated with 18 obesity-associated chronic diseases (such as hypertension). Obesity (particularly, visceral or central obesity) is often associated with widespread and negative health consequences, due to the increased risk it confers for other medical co-morbidities (Jarolimova, Tagoni, & Stern, 2013). Moreover, the 2011 Obesity in Canada report did not account for healthcare costs resulting from the cognitive impairment, and resultant disability burden, associated with obesity. Cognitive impairment has been associated with decreased rates of return to work in patients experiencing both mood and metabolic dysfunction (R. S. McIntyre, Liauw, & Taylor, 2011).

Obesity is considered an energy regulation disorder that results in a chronic state of excess energy, with the excess energy ultimately being converted into adipose tissue (Hussain & Bloom, 2011). The traditional treatment approach to obesity has been to

increase physical activity (energy expenditure) and decrease caloric intake (energy intake). However, this approach rarely leads to sustained long-term weight loss and two-thirds of people who lose weight will regain it within 12 months. Almost all of the remaining individuals will regain the lost weight within 5 years (Wadden, 1993). A multitude of biological factors are now recognized as contributing to an individual's energy regulation system including (but not limited to): genetic determinants, sex, aging, neuroendocrine (hormonal) factors, sarcopenia (degenerative loss of muscle mass), and amounts of various subtypes of adipose tissue (brown versus white adipose) (Garaulet, Ordovas, & Madrid, 2010; MacDonald, 2000). Additionally, many behavioural factors, such as previous weight reduction, hyperphagia (over-eating), co-morbid psychological conditions, neurological deficits, current medications and barriers to increased physical activity must all be addressed in order to achieve and maintain successful weight-loss (Sharma & Padwal, 2010)

**Weight Loss Interventions**

In addition to the factors mentioned above, weight treatment and management plans must take current Body Mass Index (BMI) class into consideration. For those in the overweight and class I obesity classes (25.0-29.9 and 30.0-34.9 respectively), treatment options usually consist solely of lifestyle and diet modifications. Even though this usually results in only a modest percent loss of total body weight, this difference is enough to greatly lower cardiovascular (CV) risk and provides numerous health benefits (Ames et al., 2005; Campbell et al., 1999; Casey & Mechanick, 2014; Wadden, 1993). However,

lifestyle treatments must be maintained indefinitely and as a result, lead to high rates of recidivism (Hussain & Bloom, 2011). Physicians may also choose to augment lifestyle interventions with pharmaceutical treatments for individuals with class I obesity, increasing total loss of body weight by an additional 5-8% (Hainer, Toplak, & Mitrakou, 2008). Unfortunately, weight loss medication use is associated with several unwanted side effects and is primarily prescribed for short-term periods. For many with class III (morbid or severe) obesity, lifestyle and diet interventions alone do not result in the necessary change in weight to significantly lower CV risk factors. For those with class III obesity, bariatric (weight loss) surgery is considered the only treatment that offers sustained, long-term weight loss (Christou, 2009). Surgery has been shown to result in improvement or remission of many of the co-morbidities associated with obesity, including Type II Diabetes (T2D) (80%), hyperlipidemias (70%), hypertension (75%), and obstructive sleep apnea (OSA) (80%) (Henry Buchwald et al., 2004). Even more dramatically, in an investigation by Christou (2009) of the studies completed on the impact of surgery on overall survival, a 67% Excess Weight Loss (EWL) resulted in an 89% reduction in risk of death. Even the lowest EWL rate reported (34% in the Swedish Obesity Study) still resulted in a 24% reduction in risk (Christou, 2009).

**Overview of Bariatric Surgery**

During the period of April 2014 to March 2015, the Bariatric Surgery Program at St. Joseph's Healthcare Hamilton alone performed 309 surgeries (Anvari et al., 2015). During the same time period, 1,463 bariatric surgeries were performed in the province of

Ontario (with approximately 2,427 performed province-wide the previous year). Traditionally, all bariatric surgeries have thought to cause weight loss through the processes of malabsorption (of nutrient or calories), caloric restriction, or a combination of the two (H. Buchwald & Oien, 2013). However, recently the contributing role of changes in gastrointenstinal hormones (such as Glucagon-Like Peptide 1 and Grehlin secretion) has been recognized (Ionut & Bergman, 2011).

The most common gastric procedures performed are Laparoscopic Adjustable Gastric Banding (LAGB) and Roux-en-Y Gastric Bypass (RYGB) (H. Buchwald & Oien, 2013). In Ontario, RYGB is the most routinely performed and is covered financially (for those with a BMI exceeding 40) 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 higher likelihood for additional follow-up surgical procedures; it is however readily available through private healthcare providers.

Recently, there have been a growing number of research studies using bariatric surgery populations to investigate the effects of obesity (Alosco et al., 2014; Beth Spitznagel et al., 2013; Miller et al., 2013). Bariatric surgery allows for implementation of a unique intervention study design, whereby it is possible to compare changes prior to and following a significant and sustained weight loss (Henry Buchwald et al., 2004; Miller et al., 2013). This design has been utilized in the study of obesity on a number of health outcome measures, but has only recently been used to examine cognitive health outcomes pre- and post-surgical intervention (Alosco et al., 2014; Gunstad et al., 2011).

**The Relation between Obesity, Mood Disorders and Cognition**

Mood Disorders and obesity are amongst the leading causes of disability worldwide (Ferrari, 2013; Ng et al., 2013) and there is evidence suggesting that there may be a bidirectional association between the two (Rosenblat, Cha, Mansur, & McIntyre, 2014; Soczynska et al., 2011). The prevalence rates of obesity in individuals with Major Depressive Disorder (MDD) or Bipolar Disorder (BD) have been found to be almost double that of the general population (32% and 20% respectively) (Avila et al., 2015). Moreover, obesity has been reported to increase the risk of onset of clinical depressive symptoms and manic episodes (Mather, Cox, Enns, & Sareen, 2008; Luppino, de Wit, Bouvy, & et al., 2010). There is epidemiological, longitudinal and clinical evidence that mood disorders and obesity mutually influence each other with respect to trajectory and outcome (Mansur, Brietzke, & McIntyre, 2015), with some authors proposing that there may be a distinct illness subtype (i.e. "metabolic mood-syndrome") (Levitan et al., 2012; McIntyre et al., 2007).

The underlying mechanisms linking the two disorders are not fully understood, but several overlapping risk factors have been proposed. Genetic studies have found overlap between risk factors for both disorders, such as the FTO (fat mass and obesity associated) gene (Chuang, Beason-Held, An, Resnick, & Thambisetty, 2013; Van Der Merwe, 2007). The association between this gene and obesity was shown to be moderated by depressive symptoms (Rivera et al., 2012; Samaan et al., 2013). There is also a great amount of overlap in environmental risk factors for both disorders. Early childhood trauma or life adversity has been shown to confer risk for both obesity and mood

disorders, with a high prevalence of childhood trauma being reported in both populations (McFarlane, 2010; Vieweg et al., 2006). Emerging research also indicates that the prenatal environment can confer risk for later development of metabolic conditions, such as obesity and Type II Diabetes (T2D) (Bliddal et al., 2013; Casas et al., 2013) and psychiatric illness during pregnancy has been associated with increased risk of depression during adolescence, as well as increased BMI in childhood (Goodman & Gotlib, 1999; Grigoriadis et al., 2013). Lastly, several overlapping neuroendocrine disturbances common to both conditions have been identified. These disturbances include dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, chronic elevation of pro-inflammatory markers, disruption of neural networks subsuming emotion regulation, reward processing and executive function, and dysregulation of dopaminergic transmission (Bond et al., 2011; Golden, 2007; Liu, Carvalho, & McIntyre, 2014; Malt, 2012; Raber, 1998; Rosenblat et al., 2014; Soczynska et al., 2011; van Tol et al.).

Given the numerous converging mechanisms impacting the etiology of both mood disorders and obesity, it follows that they also share vulnerabilities for the development of similar comorbid conditions as well. While the link between mood disorders and cognitive impairment has been well-established (Benas & Gibb, 2011; Bora, Harrison, Yücel, & Pantelis, 2013), research on the relation between obesity and cognition has only begun to largely emerge in the last decade. Traditionally, the association between obesity and cognitive dysfunction has been attributed to the indirect impact of medical comorbidities common to obesity (such as hypertension and T2D). However, more recent research suggests that adiposity itself may have a direct impact on cognitive performance

(van den Berg et al., 2009; Smith, Hay, Campbell, & Trollor, 2011). Even less investigated is the role of obesity on cognition in mood disorders populations. Cognitive impairment is a common complaint in mood disorder populations (McIntyre et al., 2013). In particular, executive functioning, attention and memory have been shown to be associated with poor psychosocial and functional outcomes in mood disorders populations (Gildengers et al., 2011; Mora et al., 2013). In parallel, certain classes of psychotropic medication have been shown to have detrimental metabolic side effects, including increased weight gain (thought to be partially responsible for the high prevalence rates of overweight and obesity in mood disorders patients) (Ananth & Kolli, 2005; Balt, Galloway et al., 2011; Correll, 2008; Fiedorowicz et al., 2012). This endocrine disruption can, therefore, via obesity, worsen cognitive symptoms already seen in this population. Better understanding of the impact of obesity on cognition, as well as its unique impact within mood disorder population would help guide treatment in this already vulnerable population. The directionality and nature of the interaction (e.g., whether an additive effect is seen) between obesity and mood disorders on cognitive outcomes is not yet fully understood. Given the economic burden and high impact of obesity and mood disorders on public health, there is an urgent need to improve the characterization of this relation.

**Overview of Study and Thesis Outline**

We set out to better characterize and quantify the interactions between obesity, and cognitive impairment, especially within the context of a mood disorder population.

Although the cognitive deficits linked with MDD and BD have been well-established (Bora et al., 2013; Chen et al., 2011; McDermott & Ebmeier, 2009; Robinson et al., 2006), research focusing on the effect of obesity has only recently gained traction in the last decade. We begin in Chapter 2 by performing a systematic review of the current literature to date reporting on cognitive effects attributed to obesity. In Chapter 3, we present the study design and detailed methodology for a prospective cohort study we designed to address our main research questions: does obesity have a quantifiable effect on cognition and related neural systems, and does the presence of a mood disorder further exacerbate this effect? The cognitive domains found to be most at risk in Chapter 2 (executive functioning and memory) are the focus of our prospective cohort study in Chapter 3. A comprehensive set of questionnaires, structured interviews, neuropsychological test measures and imaging techniques were developed or chosen in great detail in order to extensively characterize our study population. Chapter 4 and Chapter 5 present the first set of original results from our study. In Chapter 4, we examine the neuropsychological differences seen in obese patients, with and without MDD when compared to normal BMI subjects. In line with the literature surveyed in Chapter 2, we identified group differences and performance patterns on measures of executive function, attention and memory. In Chapter 5, we present evidence of differing neural activation patterns during memory processing between normal BMI and obese individuals, and also between obese individuals with MDD and without MDD. The neural imaging results in Chapter 5 provide convergent evidence for the neuropsychological data presented in Chapter 4.

Taken together, the results presented in this thesis provide a broad overview of the association of obesity and cognitive impairment, and how this may be of special significance in mood disorder patient populations. The extensive characterization of study population allows us to investigate whether these differences may be partially due to the heavy presence of common medical comorbidities or obesity itself. This study will add to growing literature that obesity may be responsible for cognitive impairment seen in otherwise healthy individuals. The results of this study provide information not yet available on whether individuals with both obesity and MDD may have significantly higher levels of cognitive impairment compared with psychiatrically healthy obese individuals. Preliminary data indicates that obese individuals with MDD perform more poorly on and show distinct neural activation patterns during measures of cognition. These findings may impact future psychiatric medication guidelines and patient treatment strategies.

# CHAPTER 2:

# The effect of obesity on cognition: a systematic review

**The effect of obesity on cognition: a systematic review**

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This chapter seeks to review and summarize the studies completed to date examining the effect of obesity on cognition. The findings of this study provide a background to better understand the magnitude of these associated deficits, and also what cognitive skills are most likely to be impaired.

This paper is prepared for submission to *Obesity Reviews*

**Introduction**

Obesity, now recognized as a disease by the American Medical Association, has become one of the leading causes of disability worldwide (Ferrari, 2013). During the years 2010 – 2030, the rise in obesity is expected to result in 6-8.5 million new diagnoses of Type II Diabetes (TDII) and 5.6-7.3 million new cases of cardiovascular disease (CVD) (Wang et al., 2011). In addition to obesity's association with increased rates of CVD risk factors, obesity is now thought to confer risk for neurodegenerative disorders such as Alzheimer's (Barnes et al., 2009; Bendlin et al., 2012; Biessels & Kappelle, 2005). Moreover, there is now growing evidence that obesity is linked to reduced cognitive function across the lifespan. This finding is especially prominent in the areas of memory and executive functioning (higher-order processes, such as decision making and goal setting) (Alosco et al., 2013; Alosco et al., 2014; Bruce, Martin, & Savage, 2011).

Unfortunately, until the recent decade, many studies describing an effect of obesity on cognition were conducted as secondary analyses in patients with other medical co-morbidities of interest, which may have obscured the primary effect of obesity itself (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). Known associations with particular co-morbidities (notably, TDII and hypertension) and cognitive dysfunction have been well-established and may contribute to the cognitive impairment attributed to obesity in these studies (Anstey, Sargent-Cox, Garde, Cherbuin, & Butterworth, 2014; Brismar et al., 2007; Bruehl et al., 2007; Carlsson, 2010). Interest in determining the primary effect of obesity itself has grown exponentially within recent years. Van den Berg et al. (2009) reported only 6 studies in their systematic review of the association

between obesity and cognition (van den Berg et al., 2009). A more recent review by (Smith, Hay, Campbell, & Trollor, 2011) was able to identify a total of 15 studies investigating the relation between obesity and cognition in adulthood (age 18 – 65). Studies on obesity and cognition have continued to be published at an increasing rate in recent years.

It is the primary aim of this study to summarize all research to-date on the relation between obesity and cognition in an adult population through systematic review procedures. Study results are summarized and contrasted with respect to study population characteristics, cognitive domains investigated and design methodology. In addition, a brief overview of the mechanisms that may underlie the relation between obesity and cognition is discussed.

## Methods

### Study Search

The methodology of this review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009). MEDLINE, PsycINFO and EMBASE databases were searched using the OVID search engine to identify all studies investigating the effects of obesity on cognitive functioning; additional search of the CINAHL database was performed. The most recent literature search was performed April 13, 2015. Subject words were adjusted and matched to structured terms for individual databases to ensure inclusion of all relevant articles. A

medical librarian was consulted during design of the search strategy. Search terms and strategy was individualized for each database. The final search terms obesity, body mass, overweight, body mass index, waist-hip ratio, waist circumference, abdominal fat were searched in conjunction with cognit*, cognitive ability, cognitive assessment, neuropsych*, neuropsychological test, executive function, learning, perception, memory. Search results in each database were limited to studies published in English and in humans. Please see Appendix 1 for further search strategy details.

Study Selection

The initial search was performed by MR and replicated by MN and yielded 20,642 results after applied limits; 5,646 articles were removed as duplicates. Screening for study inclusion was completed in 3 levels. Titles and abstracts were first screened to determine whether the study publication seemed relevant to the study of obesity and cognition. As expected, the initial search returned many publications outside of the scope of our review; 14,146 studies were excluded at this level. Studies were then grouped by study sample age; studies within the age 18 – 65 range were included. Since the primary aim of this review is to investigate the effect of obesity itself on cognition, studies that focused on the comorbid conditions of dementia, psychiatric disorders, cardiovascular disease, diabetes and specific dieting regimens as primary independent variables of interest were not included. Studies with subjects primarily 65 and over (or a mean age of 60.0 or above) were excluded in our analysis for two primary reasons. Firstly, it is widely known that cognitive abilities are markedly diminished by the aging process and are more likely to be

affected by neurodegenerative processes. (Akinyemi, Mukaetova-Ladinska, Attems, Ihara, & Kalaria, 2013). Secondly, decreases in body mass index (BMI) during late-life adulthood are more often due to illness and frailty and may not be intentional (Atti et al., 2010; Atti et al., 2008). As such, comparisons of lean versus obese in late-life populations are not directly comparable to lean versus obese comparisons in early or middle-aged adulthood. Age and onset of cardiovascular risk factors are thought to modulate severity of resultant neuroendocrine dysfunction (Alkerwi, 2014; Anstey et al., 2014). As such, studies focused on children and adolescent subject groups were also excluded as these groups are unlikely to show the same effects of prolonged obesity in adults and are undergoing rapid neurodevelopmental processes. In addition, many of the cognitive measures standardized for adult populations cannot be directly applied to youth populations, nor are obesity cutoff criteria the same as those used in adults.

Lastly, a full text screen was completed for study inclusion criteria. Inclusion criteria was as follows:

1) The study (obese) group characteristics were defined (including how obesity was defined, number of sample, and mean age/age range).
2) The obese study group was compared to a defined control group or against normative data
3) Results presented were from an original study not already reported elsewhere that reported test scores of obese and control groups
4) Cognition was assessed using standardized and validated neuropsychological measures. Measures that only gave one final

composite measures on cognition, or are used as cognitive screens for neurodegenerative disorders (such as the Mini-Mental State Examination) were excluded

Subject group characteristics (age and comorbid medical conditions) for healthy control and obese patient groups in each study were recorded. Studies only reporting on overweight groups (BMI 25.0 – 29.9) were not included.

Full text articles were independently judged to meet inclusion criteria by MR and MN or HJ; in the case of disagreement at first or second level screening, the article was passed to the next level. In the case of disagreement at third (full text review) level, a consensus between the 3 raters was reached. Of the 14,996 articles initially yielded, 32 studies were found to meet review inclusion criteria. Screening processes and results are summarized in Figure 2.1. A listing and summary of each study is found in Table 2.1.

## Results

### Description of Studies

Of the studies reviewed, the vast majority employed a cross-sectional design; the remaining studies had a prospective cohort design (Cournot et al., 2006; Sabia et al., 2009; Gunstad et al., 2010; Wolf et al, 2007). Four studies did not feature a control group, but compared performance to normative task data (Boeka et al, 2008; Chelune et al., 1986; Cournot et al., 2006; Lokken et al., 2010). The sample size in the included studies ranged from 26 – 2233 subjects. With regards to BMI, a number of studies also included

both overweight and obese subjects in the same study group (Bove et al., 2013; Danner et al., 2004; Davis et al., 2004; Fagundo et al., 2012; Gunstad et al., 2007; Nilsson & Nilsson, 2009; Roberts et al., 2007). Previous reviews completed in similar areas have suggested that a minimum of 25 subjects in each experimental group would be required to detect a large effect size (Cohen's d = 0.8) with 80% power at the 0.05 significance level (Van den Eynde et al., 2011). However, the effect of obesity on cognition is likely to be similar in magnitude to the effect of other related cardiovascular and neuroendocrine disturbances (such as Type II Diabetes or hypertension), which are considered to exert a small effect on overall cognition (Cohen's d = 0.3) (van den Berg, 2009). In order to detect a small effect size (Cohen's d = 0.3) with 80% power at the 0.05 significance level, a minimum of 175 subjects in each experimental group would be required. Excluding the 4 studies that only used normative data as a comparison, only 8 out of 28 included studies here met this sample size requirement.

Cognitive Performance Results

Cognition broadly refers to the processing, integration, storage and retrieval of information (Sternberg, 1984). Cognition is commonly broken down into the domains of perception, attention, memory, and executive function, and each one of these can be broken down into further sub-domains. For the purposes of this review, cognitive performance measures were grouped into the following domains: general intelligence/ability, executive function, memory, attention and processing speed.

Additionally, a listing of individual test measure outcomes and the cognitive ability they purport to measure can be found in Table 2.2

The majority of studies reported an association between higher BMI (or obesity measure, such as waist circumference) and poor performance on at least one cognitive measure. Only three studies (Garcia-Garcia et al., 2013; Gonzales et al., 2010; Ward et al., 2005) found no association between obesity and cognition in their cross-sectional study of 34 subjects (N Obese = 18) and 108 subjects (N Obese = 21) respectively.

*General Intelligence/Ability.* This score was often calculated with the intention of being utilized as a covariate (if found to differ across groups) in analysis of other measures of cognition. When reported, no differences were found across studies reporting Full-Scale Intelligence Quotient (FSIQ) through use of the Wechsler Adult Intelligence Scale (WAIS). Two studies found a small negative correlation between full-scale intelligence measures and obesity (Dore et al. [2008] and Sorensen et al. [1986]).

*Executive Function.* This cognitive domain holds the most robust findings for an association between obesity and cognition. Twenty-nine of the studies included reported on at least one measure of executive function. Of these, a negative association with at least one test of executive function was reported across 22 of these studies. Executive function encompasses a wide array of subdomains (or cognitive abilities), including response inhibition/impulsivity, set shifting, decision-making (including risk assessment), and verbal and categorical fluency (Sternberg, 1984). Although there is some overlap in the subdomains assessed by individual executive function test measures, we will review executive function results within the context of these separate domains.

With regards to response inhibition/impulsivity, the Stroop Task (Interference and Color-Word Score) was used in a large number of studies included (Bove et al., 2013; Cserjesi et al., 2009; Fagundo et al., 2012; Garcia-Garcia et al., 2013; Gunstad et al., 2007; Pooja et al., 2014; Volkow et al., 2008). Findings regarding Stroop performance were inconsistent, with approximately half of the studies finding a significant negative association between obesity and performance while the others reported no significant association. A negative association between the Go/No-Go Task and obesity, and the Hayling Sentence Completion Task and obesity was found by the two studies who employed these measures as a measure of response inhibition/impulsivity (Cserjesi et al., 2009 and Galioto et al., 2014 respectively). Overall, there is notable variability in performance on measures of response inhibition by obese individuals as compared to normal weight controls.

The Trail Making Test B (TMT B) was the most commonly administered test tapping set-shifting ability. Of the twelve studies that used the TMT B task, only 4 reported a negative association between obesity and performance (Ariza et al., 2012; Chelune et al., 1986; Cserjesi et al., 2009; Wolf et al., 2007). The second most commonly employed task assessing set-shifting ability was the Wisconsin Card Sorting Task (WCST). Here, findings were once again mixed with four studies (Ariza et al., 2012; Boeka et al., 2008; Fagundo et al., 2012; Lokken et al., 2010) reporting a negative association between performance and obesity while three studies found no significant association (Garcia-Garcia et al., 2013; Roberts et al., 2007; Volkow et al., 2008). Similar

to the overall results reported in the area of response inhibition, findings regarding the association between obesity and set-shifting are inconsistent.

Three studies that assessed verbal fluency using the Controlled Oral Word Association Task [COWAT] were identified: Gunstad et al. (2010) reported a negative association between obesity and performance, Gonzalez et al. (2010) found no significant association, and Boeka et al. (2008) reported a positive association. Additionally, Bove et al. (2013) found no association between performance on the verbal fluency measure of the Delis-Kaplan Executive Function System (D-KEFS) and obesity. Generally, there is insufficient evidence to suggest that obesity is associated with impairment on tests of verbal fluency.

Lastly, there appears to be strong evidence for a negative association between obesity and decision-making (notably with regards to risk-assessment). All six studies using the Iowa Gambling Task found a negative association between performance on this task and obese individuals (Brogan et al., 2010; Danner et al., 2012; Davis et al., 2004; Davis et al., 2010; Fagundo et al., 2012; Pignatti et al, 2006). Overall, studies found that obese individuals performed worse than normal weight controls. Interestingly, one study also found that when obese individuals' performance was compared to individuals with Binge Eating Disorder or Anorexia Nervosa, there were no group differences in performance (Brogan et al., 2010).

*Processing Speed.* The TMT A (tapping processing speed ability) was commonly used across measures, with scores being reported in 11 studies. Of these studies, only 2 (Chelune et al., 1986; Cserjsei et al., 2009) reported a negative association with obesity.

However, in Gunstad et al.'s 2010 study, increased waist circumference and BMI were associated with *better* performance on the TMT A as age increased. The remaining measures reported no significant association (Ariza et al., 2012; Boeka et al., 2008; Bove et al., 2013; Ferhenbaum et al., 2009; Gonzalez et al., 2010; Roberts et al., 2007; Ward et al., 2005; Wolf et al., 2007). Overall, there is little evidence to suggest that there is a significant association between obesity and processing speed.

*Attention.* Seven studies used the Digit Span Test to assess short-term auditory memory (or working memory): 4 studies found a negative association between obesity and test performance (Dahl et al., 2013; Gunstad et al., 2007; Gunstad et al., 2010; Volkow et al., 2008) while the remaining 3 studies found no association (Boeka et al., 2008; Gonzalez et al., 2010; Lokken et al., 2010). Only 3 studies used a measure to assess sustained attention and all three studies reported a negative association between obesity and test performance: Gunstad et al (2007) using the Choice Reaction Test, Cserjsei et al. (2009) using the D2 Endurance Test, and Galioto et al. (2014) using the Go/No-Go Test. Thus, evidence suggests that it may be sustained attention (rather than selective attention or working memory) that is negatively impaired by obesity. However, given that only 3 studies included a measure of sustained attention, further investigation is needed before an association can be firmly established.

*Memory.* The association between obesity and memory was extremely hard to characterize or draw conclusions about due the conflicting results seen when looking at results across sub-domains of memory. Further, there was a lack of consistency and overlap in subdomains being assessed across studies (for example, verbal versus

visuospatial, immediate versus delayed, recall versus recognition). Impairment in at least one of the test outcomes of memory was reported in 7 of the 11 studies that included a measure of memory, but results were not consistent across which subdomain was found to be affected when comparing across studies. One observation that should be noted is that of the 7 studies reporting a significant impairment on a measure of memory in obese individuals, this impairment was most consistently found on a measure of visual-spatial memory (as opposed to verbal memory) (Boeka et al, 2008; Lokken et al., 2010; Pooja et al., 2014; Roberts et al., 2007; Wolf et al., 2007). Two studies (Bove et al., 2013; Gunstad et al., 2010) reported a negative association between obesity and performance on the California Verbal Learning Test – II. However, while Gunstad et al. (2010) found this with regards to the index "Prospective Learning", Bove et al. (2013) found test performance on individual Trials 1 through 5 to be impaired. Overall, while there is some evidence to suggest that visual-spatial memory performance may be associated with obesity, there is insufficient evidence to support a relation between verbal memory performance and obesity.

**Discussion**

The primary aim of this review was to gain a more comprehensive understanding in the association between obesity (independent of comorbid CVD risk factors) and cognitive functioning. Methodological study differences and the lack of reporting null results makes this a challenging task. Several domains of cognition were compared separately in our review, with a different pattern of results seen across domains.

Our review found conflicting evidence for the notion of executive function impairment in obese populations (Boeka et al., 2008; Brogan et al., 2010; Chelune et al., 1986; Cserjesi et al., 2009; Dahl et al., 2013; Danner et al., 2012; Davis et al., 2004; Davis et al., 2010; Fagundo et al., 2012; Fergenbaum et al., 2009; Gunstad et al., 2010; Lokken et al., 2010; Pignatti et al., 2006; Pooja et al., 2014; Sorensen et al., 1982; Stanek et al., 2012; Weller et al., 2008; Wolf et al., 2007); we also found that performance on individual executive function measures was inconsistent across studies. Deficits were most often found in executive functioning tasks of greater complexity, such as the Iowa Gambling Task (which assessed decision making and risk assessment ability) (Brogan et al., 2010; Chelune et al., 1986; Danner et al., 2012; Davis et al., 2004; Davis et al., 2010; Fagundo et al., 2012; Pignatti et al., 2006). It may be that the cognitive impairment caused by obesity is small in magnitude, and using tasks of greater difficulty bestow greater sensitivity and likelihood of reaching significant results. Similarly, many of the studies reviewed across all cognitive domains had a sample size below the estimated sample required to detect a difference. Alternatively, significant associations found between obesity and cognition in small sample size studies should also be reported with caution. Further, several studies did not report data statistics on test measures administered, including effect size or raw summary data (when an effect did reach significance).

The relation between processing speed and obesity remains unclear. This was the only domain where a *positive* association with obesity and cognitive performance was reported (Gunstad et al, 2010). However, in this study, TMT A performance was

positively associated as age increased. It may be that processing speed is differentially affected by weight status at different points in the lifespan. The conflicting results in this particular domain warrant further investigation.

With respect to measures of attention and memory, mixed findings were seen when comparing test measures across studies, with the greatest evidence found for sustained attention impairment and visual-spatial memory impairment in obese individuals. There was insufficient evidence for a significant relation between verbal memory and obesity, or selective attention and obesity. Overall, the findings in this area are not as robust as those seen in the area of decision-making.

The directionality of the relation between obesity and cognition is unclear from the studies reviewed here. Only a handful of studies employed a prospective cohort design necessary to begin answer this question (Cournot et al., 2006; Sabia et al., 2009; Gunstad et al., 2010; Wolf et al, 2007). Taken together, three of these studies found that increased BMI at mid-life was associated with poorer performance on a variety of cognitive domains (namely, executive function, memory and visuomotor skills) later in life (Cournot et al., 2006; Sabia et al., 2009; Wolf et al, 2007). The remaining prospective study followed a longitudinal bariatric sample population (Gunstad et al., 2010). There are several reasons that surgery may result in cognitive functioning improvement, including remission of T2D, hypertension and obstructive sleep apnea. Moreover, the positive health outcomes seen after bariatric surgery may be linked to neurobiological changes associated with the surgery itself. In animal models, De Freitas Sonada et al. (2011) found that rats with reduced gastric capacity exhibited a significant increase in

parvalbumin interneuron expression in the hippocampal CA1 and CA3 regions, linking changes in the hippocampal regions for the first time directly to gastric restriction surgery. Better comprehensive longitudinal studies of bariatric surgery patients, incorporating structural and functional neural imaging to neuropsychological performances measures are needed in human populations to better understand mechanisms of improved cognitive function following surgical intervention.

It has been proposed that cognitive impairment, specifically in the area of executive function, may impart risk for obesity (in those genetically susceptible to weight gain) (Davis et al., 2010). Self-regulation, goal setting and the ability to delay gratification are all important executive function skills that are involved in maintaining a healthy diet and a moderate level of physical activity (Annagur, 2011; Annesi & Whitaker, 2010). Data on nutritional intake and binge eating behaviour would have aided greatly in the summarization of the studies in this review. Unfortunately, the majority of studies failed to include diet measures or place binge eating disorder (BED) or behviour as study exclusion criteria. Alternatively, Attention-Deficit Hyperactivity Disorder (ADHD), a disorder characterized by high levels of impulsivity has been shown to be highly comorbid with overweight and obesity in childhood and adolescent populations, indicating a potential overlapping genetic susceptibility involving impulse control for both disorders (Bazar, Yun, Lee, Daniel, & Doux, 2005; Choudhry et al., 2013; Graziano et al., 2012). We recommend that future prospective cohort studies include measures of binge eating behaviour and overall nutritional intake patterns (diet analysis) in order to be

able to directly understand the relation of impulsive eating behaviour to both obesity and cognitive impairment.

A number of neuroendocrine factors have also been proposed as casual mechanisms for the cognitive impairment seen in obese populations. Adipose tissue, traditionally viewed as an energy storage reservoir, is now recognized as a secretory endocrine organ (Kershaw & Flier, 2004). Adipose tissue expresses and secretes endocrine hormones such as leptin and adiponectin, hormones both known to have an effect on memory processing (Daulatzai, 2013; Harvey, 2007; Holden et al., 2009; Kanoski et al., 2011; Zelisko, Kerwin, & Kotchen, 2010). Moreover, obesity is considered to be a low-grade chronic inflammation state (Bruce-Keller, Keller, & Morrison, 2009; DiStefano, Curtis, & Geddes, 2007; Fung, Vizcaychipi, Lloyd, Wan, & Ma, 2012). Elevated levels of pro-inflammatory markers, such as C-reactive protein and tumor necrosis factor, have been linked to cognitive impairment and late-life neurodegenerative disorders (Anan et al., 2011; Arnoldussen, Kiliaan, & Gustafson, 2014; Bruunsgaard et al., 1999; Komulainen et al., 2007). In addition, Volkow et al. (2008) demonstrated that increased BMI was linked to reduced blood flow to certain neural regions important for cognitive control (executive function) while also over-activating neural circuitry important in reward and motivation behaviour (Volkow, Wang, Fowler, & Telang, 2008; Volkow et al., 2009).

Although this review provided a comprehensive review of association between obesity cognition, there are several limitations that need to be noted. This review only examined the link between obesity and cognition in an adult population (age 18 – 65).

The conclusions drawn from this review may not be generalizable to other age groups. Moreover, although it was the aim of this review to investigate the primary effect of obesity on cognition rather than associated comordities, these comorbidities are likely to still moderate or mediate the relation between cognition and obesity. Further work exploring the impact of additional moderating factors, such as psychiatric disorders, sex, and socioeconomic factors on cognition in obese populations is needed. Lastly, as is the case with all systematic reviews, our review was limited by the statistics and data reported by authors of the included studies.

In conclusion, there is inconsistent evidence in the studies reviewed indicating whether obesity is negatively associated with cognitive functioning in adults (ages 18 – 65). Additionally, the directional causality of this association has not yet been determined. There is a strong need for future prospective cohort studies with comprehensive characterization of obese populations (for example, accounting for eating and diet behaviour). As well, these studies would be strengthened by the inclusion of methodologies (such as neuroimaging) that would provide further forms of evidence supporting cognitive outcomes on neuropsychological measures.

**Appendix 1**

Search Strategy (Arranged by Database):

EMBASE:

[obesity (*explode*) OR body mass] AND [cognition OR cognition assessment OR neuropsychology OR neuropsychological test OR executive function OR cognit*]
Applied Limits: "English" AND "Humans"

MEDLINE

[obesity OR obesity, abdominal OR obesity, morbid OR overweight OR body mass index OR waist-hip ratio OR waist circumference OR abdominal fat] AND [cognition OR cognit* OR executive function OR learning OR perception OR neuropsychology OR neuropsychological tests]
Applied Limits: "English" AND "Humans"

PsychInfo

[Obesity OR overweight OR body mass index] AND [cognition OR cognitive ability OR cognitive assessment OR cognit* OR learning (*explode*) OR memory (*explode*) OR attention (*explode*) OR neuropsychology OR neuropsychological assessment (*explode*)]
Applied Limits: "English" AND "Humans"

CINAHL

[obesity OR morbid obesity OR body mass index OR abdominal fat] AND [cognition OR cognit* OR learning OR memory OR neuropsychology OR neuropsychological tests]
Applied Limits: "English" AND "Humans" AND "exclude MedLine records"

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Table 2.1 Summary information of included Studies

Acronyms: BED: Binge Eating Disorder; BMI: Body Mass Index; COWAT: Controlled Oral Word Association Test; CVLT: California Verbal Learning Test; D-KEFS: Delis-Kaplan Executive Function System; DST-Forward/Backward: Digit Span Test; DSST: Digit Symbol Subsitution Task; ESL: English as a second language; HSCT A/B/AB: Hayling Sentence Completion Task A/B/AB; M: Mean; MetS: metabolic syndrome OB: obesity; OW: overweight; NW: Normal Weight; RAVLT: Rey Auditory Visual Learning Test; RCF: Rey Complex Figure Test; TCF: Taylor Complex Figure; TMT A/B: Trails Making Test A/B; WAIS: Wechsler Adult Intelligence Scale; WC: Waist Circumference; WHR: Waist-to-Hip Ratio; WCST: Wisconsin Card Sorting Test; WTAR: Wechsler Test of Adult Reading;

| **First Author (Year)** | **Sample size (or number assigned to each of specific treatment)** | **Study population demographics (mean age or range [years])** | **Obesity Measure** | **Covariates controlled for/Exclusion Criteria** | **Control Group (diagnosis, criteria)** | **Cognitive Test Measure(s)** | **Results** | **Measures found to be significantly affected arranged by domain** |
|---|---|---|---|---|---|---|---|---|
| Ariza (2012) | N = 42 per group (84 total) | M (OB) = 31.8, M (NW) = 29.7 | BMI ≥ 30 | OB group was further split based on DRD2/ANKK1-TaqIA A1-allele status<br><br>Exclusion: neurological/psychiatric disorder, substance/alcohol use, obesity related disorder history (i.e. thyroid disorder), diabetes, hypertension, BMI in OW range, cognitive impairment | BMI < 25 kg/$m^2$ | Letters and Numbers subtest (WAIS), Symbol Digit Modalities Test, TMT, WCST | Significant group effect of obesity not seen; OB group with DRD2/ANNK1-TaqA1 allele associated with poorer outcomes on executive function measures | Allele effect ($p < 0.05$) seen on Executive Function: TMT B and WCST perseverative errors |

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|---|---|---|---|---|---|---|---|---|
| Boeka (2008) | N = 68 bariatric surgery patients (54 after taking out patients who met exclusion criteria) | Age 20 - 57 | Seeking bariatric surgery (BMI ≥ 40, or 35-39.9 with secondary medical conditions) | Age and education matched normative data<br><br>Exclusion: history of learning problems, head injuries, CVA/TIA, seizures, or substance abuse | Normative data, Bonferroni correction (0.006); | TMT A/B, WCST, COWAT, CVLT, Reading Ability (WRAT) WAIS (Similarities, Block Design, Digit Span, Digit symbol), Rey Complex Figure | Only reported findings on executive function tasks – OB performed worse on these measures compared with normative data generally (with exception of COWAT) | Executive Function measures: WCST perseverative errors, performed better on COWAT; Memory measures: RCF (Copy, 3 minute delay, and 30 minute delay, overall errors) |
| Bove (2013) | N = 49<br>OB=37<br>NW=12 | Age 20 - 45<br>M(OB)=35.5<br>M(NW)=31.6 | BMI ≥ 25 | ESL, color-blindness, smoking, pregnant/breastfeeding, hypothalamic/pituitary disorders, diabetes, chronic illnesses, estrogen/glucocorticoid use, statins/anti-hypertensives, moderate/major depression score on Beck Depression Inventory | 18 < BMI < 25 | WTAR, TMT A/B<br>CVLT, Stroop ,TCF, D-KEFS (verbal fluency) | Only CVLT-II had significant negative association with visceral adipose tissue; no significant associations between all other tests and any body composition component | Memory: CVLT-II (Trials 1-5) |
| Brogan (2010) | N = 77<br>AN=22<br>BN=17<br>OB=18<br>HC=20 | Age 18 - 73<br>M(AN)= 29.1,<br>M(BN)= 29.9<br>M(OB)= 52.1<br>M(HC)= 27.8 | Obesity undefined; OB Mean BMI: 36.2 | No history of psychiatric/neurological disorder | NW mean BMI: 21.6 | IGT | Impairment on IGT seen on all three 3 eating disorder groups relative to healthy controls | Executive Function: IGT |

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|---|---|---|---|---|---|---|---|---|
| Chelune (1986) | N = 44 OB adults | Mean age: 33 | > 100% or 100lbs excess ideal weight | N/A | N/A (normative data) | WAIS, TMT A/B, Category test | TMT A: 24% of OB fell in the impaired range, TMT B: OB 21% impaired, Category test: OB50% impaired | Attention: TMT A; Executive Function: TMT B, "Category Test (measure of concept formation and problem solving) |
| Cournot (2006) | N =2,233 OB=291 444 - 445 per quintile | Aged 32, 42, 52, 62 (age classes used) | 291 subjects were OB, but divided by quintile; Q5 = 27.5 – 45.0 | Covariates: Age, sex, education, diabetes, systole BP & perceived health score | No control group | Word list learning (immediate and delayed recall), WAIS (DSST), Selective Attention Test | Poor cognitive performance on all tests; higher BMI at baseline also associated with higher cognitive decline; no association between change in BMI & cognitive function | Highest quintile associated with lower scores on: Attention: Selective Attention Test; Memory: "Word List Learning" (adaptation of the RCF); Processing Speed: Digit Symbol Test |
| Cserjesi (2009) | N = 60<br><br>(OB: 30, NW: 30) | M (OB): 48.8<br><br>M (NW): 49.3 | Obesity diagnosis seeking bariatric surgery | Matched for age, education, and social status (current profession) | BMI Mean = 22.8 | D2 Attention Endurance test, TMT A/B, Hayling A, B, BA | Obesity performed worse on all three measure, but no difference in Hayling test 'number of errors' found between groups | Attention: TMT A, D2 Attention Endurance Test; Executive Function: TMT B, Hayling A/B/AB |
| Dahl (2013) | N = 657 total (26 OB, 407 normal weight) | OB age: 41.5, normal: 39.7 assessed at age 40 & 61 | BMI ≥ 30 | Excluded if had MetS or neuropsychological comorbidity | Normal weight BMI 20-25 | Swedish Adaptations. DST, Thurstone picture memory test, Block Design, Card rotations, Figure logic test of inductive reasoning | Poorer performance in OB versus normal weight later in life across domains | Attention: DST-F/B; Executive Function: Card Rotations, Figure Logic test of inductive reasoning; Memory: Thurstone Picture Memory Test |

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|---|---|---|---|---|---|---|---|---|
| Danner (2012) | N = 75<br>BED=20<br>OB no BED=21<br>NW=34 | M(BED) = 38.1<br>M(OB) = 44.6<br>M(NW) = 36.1 | BMI ≥25 | Exclusion: no Binge eating in NW; excessive alcohol/drug use | BMI 19 -25 | IGT | BED & OB group performed poorly on the IGT (did not improve choice behaviour over time) | Executive Function: IGT |
| Davis (2004) | OW/OB=15<br>NW=26 | M= 28.5 yrs | BMI ≥ 25 | Emotional over-eating | NW | IGT | OB/OW performed poorly on Iowa gambling task | Executive Function: IGT |
| Davis (2010) | OB+BED= 65<br>OB=73<br>NW=71 | Age 25 - 45.<br>100% women<br><br>M(OB+BED)=34.3<br>M(OB)=35.2<br>M(NW)=31.8 | M BMI (OB)=38.6 | Covariates: age, education level<br><br>Excluded if: had serious medical condition, pregnant, not fluent in English, no psychiatric diagnosis/treatment | M BMI(NW)= 21.7 | IGT, Delay Discounting | Lower IGT scores for OB and OB+BED, but not significant; no significant differences between groups on delay discounting task | Executive Function: IGT |
| Dore (2008) | N = 918 | Age 23-98 (M = 62), 59% women | WC & WHR | Excluded stroke, dementia, active dialysis treatment, chronic alcohol abuse, & lack of English fluency. Covariates: age, education, gender, smoking, cholesterol, prevalent CVD, systolic BP, depression, glucose & physical activity | Regression analysis performed by weight group | Global composite, Hopkins verbal learning test, VM: WMS-II, WAIS (core subtests) | WC inversely related to "scanning and tracking, abstract reasoning and global composite" | Global composite score (all tests included); Individual measure results not reported, composite scores of “Visual-spatial Organiation”, “Scanning and Tracking” and “Working Memory” found to be significantly affected |
| Etou (1989) | OB=13<br>NW=13 | Age 21 - 49<br>M(OB)=34.2<br>M(NW)=33.8 | M(BMI OB) = 39.2 | Matched on intelligence, age, height & education | M(BMI NW)=20.7 | Psychomotor: tap test, transfer coordination test, transverse speed test, time cognition | Impaired manual coordination in tapping, dexterity and responsiveness; speed of OB subjects longer | Processing Speed: tap test, transfer coordination test, transverse speed test, time cognition |

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|---|---|---|---|---|---|---|---|---|
| Etou (1989) | OB=13 NW=13 | Age 21 - 49 M(OB)=34.2 M(NW)=33.8 | M(BMI OB) = 39.2 | Matched on intelligence, age, height & education | M(BMI NW)=20.7 | Psychomotor: tap test, transfer coordination test, transverse speed test, time cognition | Impaired manual coordination in tapping, dexterity and responsiveness; speed of OB subjects longer when self-cued versus externally cued | Processing Speed: tap test, transfer coordination test, transverse speed test, time cognition |
| Fagundo (2012) | N=224 AN=35 OB=52 NW=137 | Age 18 - 60 M(NW)=24.8 M(OB)=40.5 | BMI ≥ 25 | History of chronic medical illness or neurological condition that might affect cognitive function; head trauma with loss of consciousness >2 min, earning disability /mental retardation, use of psycho-active medication or drugs, being male, age under 18 or over 60 | NW | WCST, Stroop, IGT | OB had more errors on WCST and significantly fewer correct responses; OB Significantly reduced performance on Stroop; OB Significantly poorer performance on IGT | Executive Function: WCST (preserverative errors, total correct responses, total errors, perseverative errors); Stroop (interference), IGT |
| Fergenbaum (2009) | N = 207 (for CDT), 190 for TMT | Age 19 - 65 (median = 39) | BMI ≥ 30 $kg/m^2$ | Age, sex, hypertension, CVD, diabetes, insulin resistance, smoking | BMI 18.5 - 24.9 | Clock Drawing Test, TMT A, TMT B | No significant effect of BMI on Clock Drawing Test; OB had significantly worse performance on TMT | Executive Function/Processing Speed: investigators chose to create a composite score of TMT A and B performance |
| Galioto (2014) | 62 (32 NW, 30 OB) | Mean age = 21.1 | BMI ≥ 30 | Neurologic disorder, head injury, alcohol or drug abuse, learning disorder, impaired sensory function | BMI < 25 | Go/No-Go, Running Memory Continuous Performance Test | Greater reaction time on Go/No-Go task (OB) | Executive Function: Go/No Go |

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|---|---|---|---|---|---|---|---|---|
| Gonzalez (2010) | N = 32<br><br>NW=9<br>OW=11<br>OB=12 | M(NW)= 51.8<br>M(OW) = 52.0<br>M(OB)= 48.5 | BMI ≥ 30 | Exclusion of medical or neurological disorders | BMI 18.5 - 24.9 | COWAT, TMT A/B, DST, WASI (Vocabulary, Matrices), RCF, CVLT-II | OB group was associated with significantly less task-related activation in right parietal cortex but no direct association between cognitive performance and BMI | N/A |
| Gunstad (2007) | 408 adults<br>NW=178<br>OB=140<br>*Only included 'young' adults for analysis | Age 20 - 50<br>M(NW)=31.56<br>M(OB)=32.40 | BMI ≥ 25 | Psychiatric substance use disorders, family history of ADHD, schizophrenia, BD or genetic disorder = exclusion; covariates: estimated intelligence, education, sex & self-reported measures of anxiety, depression and stress | BMI 18.5 - 24.9 | Digit Span Forward, Choice reaction time | Small negative correlation between Digit Span Forward and BMI (-0.17); small positive correlation between BMI and choice reaction time (0.14) | Attention: DS-F |
| Gunstad (2010) | 1703 individuals | Age 19 - 93; Mean = 55.5 | BMI, WC, WHR entered as regressors | Exclusion: stroke, dementia, myocardial infarction, atrial fibrillation. Covariates: age, sex, education, hypertension, glucose, diabetes, anti-lipid medication | Compared within weight groups in mixed effects regression analysis | WAIS (Digit Span), TMT A, TMT B, Memory (verbal learning test), Benton retention test, Prospective memory test, COWAT/Category fluency, Boston Naming test, Card rotations test | High BMI, WC, & WHR associated with poorer memory, language, global cognitive function; WC & BMI associated with faster time on the TMT A as age increased; memory declined over time as function of increasing weight | Attention: BMI *positively* associated with TMT A over time, DS-F; Executive Function: COWAT (Letter, Category); Memory: CVLT "Prospective Memory/Total" |

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|---|---|---|---|---|---|---|---|---|
| Lokken (2010) | 169 morbidly OB | Mean age = 42 yrs | M (BMI) =49.2 | Included if qualified for bariatric surgery process | Normative data | WRAT, WAIS (Similarities, Block Design, Digit Symbol, Digit Span), WCST, Rey Complex Figure | OB significantly lower on WCST & Rey Complex Figure | Executive Function: WCST (total errors, perseverative errors); Visuomotor: RCF (Copy) |
| Nilsson (2009) | 936<br>NW=347<br>OB=589<br><br>(Only included younger population here) | Age 35 - 55<br><br>Women:<br>M(NW)=46.9<br>M(OB)=49.4<br><br>Men:<br>M(NW)=47.1<br>M(OB)=49.1 | BMI ≥ 25 | Excluded if diagnosis of diabetes or MetS | BMI < 25 | Free recall, Cued recall, Face recognition, Vocabulary test, COWAT, Block Design test | No significant difference between groups on episodic memory tasks (free recall, cued recall); no significant differences between groups on semantic memory tasks (face recognition, vocabulary test, word fluency); significant advantage on visuospatial task (block design) for NW group | Visuomotor/ Executive Function: Block Design (WAIS) |
| Pignatti (2006) | OB=20<br>NW=20 | M (OB)=43.4<br>M(NW)=46.6 | BMI ≥ 30 | Exclude if psychiatric diagnosis or IQ below average | NW | Computerized IGT | OB worse performance on IGT than NW | Executive Function: IGT |
| Pooja (2014) | N = 230 | | OB ≥ 30 | Exclude if unstable medical condition or severe medical history present | Broken into 5 groups based on BMI; group 2 and 3 included in analysis (18.5 – 22.9 and 23 – 24.9) | Reaction Time, DSST, Stroop Color test, Paired Association test (WMS-II), Visual Reproduction test, Ascending Digit task | Obese group significantly poorer on almost all measures except working memory (Ascending Digit Task) | Attention: Stroop; Executive Function: Stroop; Memory: Visual Reproduction Test, Paired Associates; Processing Speed: DSST; exact indices not given for individual measures |

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|---|---|---|---|---|---|---|---|---|
| Roberts (2007) | OW=10<br>NW=50 | Age 18 – 55<br><br>M(OW)=27.7M (NW)=23.1 | BMI 25.7 - 30.1 | N/A | BMI 18.5-24.9 | WCST, TMT A/B, Brixton Task, CatBat Task, Haptic Illusion Task, Rey Complex Figure | OW and NW groups did not differ significantly on WSCT, TMT, Brixton, CatBat, or Haptic Illusion tasks; OW group was less accurate on Rey complex task | Memory: RCF |
| Sabia (2009) | N=5641 | Mean age at cognitive testing=60.8<br><br>At baseline, mean ages were: OB: 44.9 NW:43.3 | BMI ≥ 30 | Covariates: age, sex, education, smoking, weekly alcohol consumption, fruit & vegetable consumption, moderate physical activity per week, MIA, angina, stroke, diabetes, cholesterol, BP | BMI 18.5-24.9 | Short-term verbal memory (AH4-1 for reasoning), COWAT | OB associated with lower memory scores, stronger association when individuals older (44/61 yrs) than at 25; increased BMI predicted lower performance | Individual outcome measures not reported or well described, instead reported on Memory and Executive Function composite scores (both negatively associated in later life with obesity) |
| Sorensen (1982) | OB=1,806<br>NW=2,710 | Men, age 18 -21 | BMI ≥ 31 | Covariates: time and place of testing | BMI 18.5-24.9 | Danish intelligence test (BPP-54). Subtests: Letter-Number, Matrices, Verbal Relations, Number Series, and Figure Analysis | OB men had significantly lower scores than NW men on all test scores, including tests of executive function | General Intelligence: Danish Intelligence Test (BPP-54); further detailed information not provided |
| Stanek (2013) | N=732 | Mean age = 46.69<br><br>Age 18 - 88 | "Morbidly obese" | Exclusion: brain injury, medical/neurological illness history, psychiatric disorder | BMI 19 – 24.9 | Digit Span, Choice Reaction Time, TMT Adaptation | Main regression effect for BMI on motor, and attention/processing speed | Individual outcome measures not reported or well described, instead reported on composite scores – effect seen on |

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|---|---|---|---|---|---|---|---|---|
| Stanek (2013) | N=732 | Mean age = 46.69<br><br>Age 18 - 88 | "Morbidly obese" | Exclusion: brain injury, medical/neurological illness history, psychiatric disorder | BMI 19 – 24.9 | Digit Span, Choice Reaction Time, TMT Adaptation | Main regression effect for BMI on motor, and attention/processing speed | Individual outcome measures not reported or well described, instead reported on composite scores – effect seen on motor, attention/processing speed composites |
| Volkow (2008) | N =21 (18 normal weight, 3 OB) | Age 22 - 45 | BMI ≥ 30 (n = 3); entered as a regressor | Exclusion: left-handededness, neuropsychiatric/significant medical illness, over the counter drugs, pregnancy | BMI entered as a regressor | WCST, Stroop, Symbol Digit Modality, WAIS-R (Digit Span, Matrix Reasoning), WRAT, WASI (Matrices), Pegboard, Finger tapping, CVLT | BMI was negatively correlated with Digit Span, Matrices (WASI) | Attention: DS-F/B Executive Function: Matrices (WASI), DS-B |
| Ward (2005) | N = 208 (21 OB) | Mean Age = 54.2<br><br>Age 40 - 66 | BMI entered in stepwise linear regression analysis | Exclusion: age, BMI, family history of Alzheimer's Disease, APOE genotype, total cholesterol, systolic/diastolic blood pressure, gender, education | BMI entered in stepwise linear regression analysis | RAVLT, TMT A, TMT B | No association found between measures and obesity | N/A |
| Weller (2008) | 55 OB; 57 NW | Age 17 - 23 | BMI ≥ 30 | | BMI: 18.5 – 24.9 | Delay Discounting, Behaviour Inhibition System | Obese women but not men show higher levels of delay discounting | Executive Function (Reward): Delay Discounting |
| Wolf | N=1814 | Age 40-70 | BMI ≥30 | Age and educational | BMI ≥ 30; WHR | Visual | Upper WHR | Executive Function: |

Table 2.2. Description of Cognitive Ability Assessed by Test Measure Outcome

(See Table 2.1 of Test Abbreviations)

| Cognitive Domain | Test Measure | Test Variable |
|---|---|---|
| Executive Function | Block Design (WAIS) | Visual-spatial analysis |
| | COWAT | Letter/Category Fluency (Verbal Fluency) |
| | Go/No-Go | Response Inhibition |
| | HSCT-A | Initiation Speed |
| | HSCT-B | Response Suppression |
| | HSCT-AB | Mental Flexibility |
| | IGT | Total (Decision-Making and Risk Assessment) |
| | Matrix Reasoning (WAIS) | Visual-perceptual abstract reasoning |
| | Stroop | Colour-Word Score (Response Inhibition) |
| | | Interference Score (Response Inhibition) |
| | TMT B | Set-Shiting, Mental Flexibility |
| | WCST | Total Errors, Perservative Responses, |
| | | Perservative Response Errors (Set Shifting) |
| Memory | CVLT | Total Correct Responses (Verbal Learning/Memory) |

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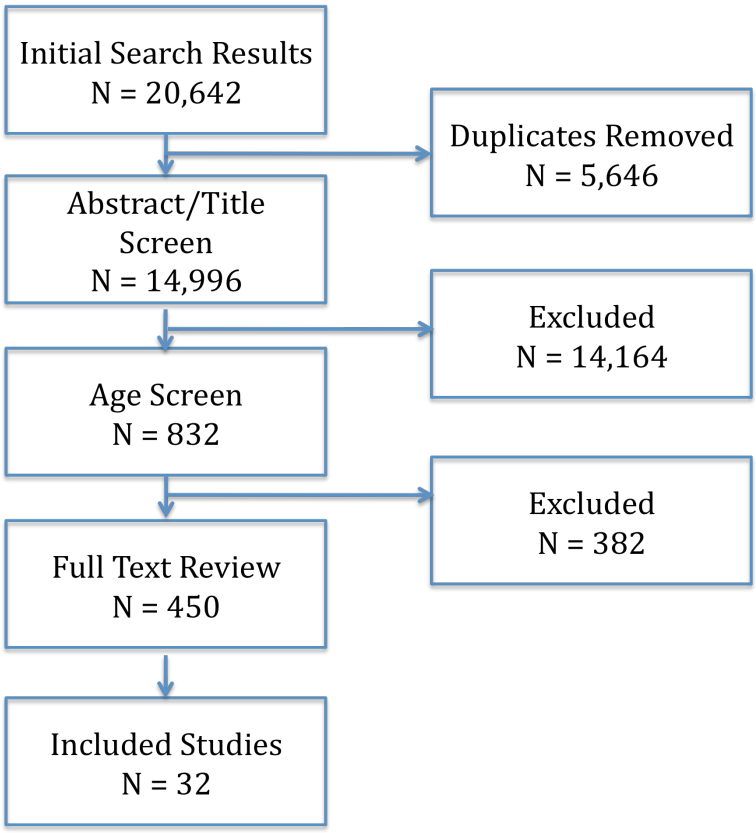
|---|---|---|
| | | Short, and Long, Delay Cued Recall (Verbal Memory) |
| | | Short, and Long, Delay Free Recall (Verbal Memory) |
| | RCF | Copy (Visual-Spatial Constructional Ability) |
| | | 3-Minute Recall Trial (Short-Term Visual Memory) |
| | | 30-Minute Recall Trial (Long-Term Visual Memory) |
| | Thurstone Picture Memory Test | Visual memory |
| | WMS-III | Logical Memory I (LMI) and II (LMII) (Short- and Long-Term Verbal Memory) |
| | | Paired Associates I and II (Short- and Long-Term Verbal Recognition Memory) |
| | | Visual Reproduction (Short- and Long-Term Visual Memory) |
| Processing Speed | DSST (WAIS) | Perceptual-motor speed |
| | Stroop | Colour Score (Perceptual-motor speed) |
| | | Word Score (Perceptual-motor speed) |
| | TMT A | Perceptual-motor speed |
| Intellectual Functioning | WASI/WAIS | Full-Scale Intelligence Quotient |

| | | |
|---|---|---|
| Attention | Choice Reaction Time | Sustained attention |
| | D2 Attention | Attention capacity, concentration ability |
| | DST-F | Working memory (short-term auditory memory) |
| | DST-B | Working memory, mental manipulation |
| | Endurance Test | attention distractibility |
| | Go/No-Go | Sustained Attention |

Figure 2.1. Flowchart describing results of search strategy used in systematic reviews



# CHAPTER 3:

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

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

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The relation between obesity and cognition, and how this relation may be altered in the presence of a mood disorder has not yet been determined. Despite a growing number of cross-sectional observational studies examining the impact of obesity on cognition, further studies assessing the contribution of obesity and many of the associated potential comorbidities that may exert an influence on cognitive function (including mood) are needed. In order to meet this need, we designed a prospective cohort study that would allow us to better quantify the impact of obesity on cognition. Here we present the study design and methodology for our study.

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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.

**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 3.1.

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 [3 8]. 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 3.1

Table 3.1 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 Only) | 8 (fMRI Version) | 18 – 70 | Assesses recognition memory for printed words |
| 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 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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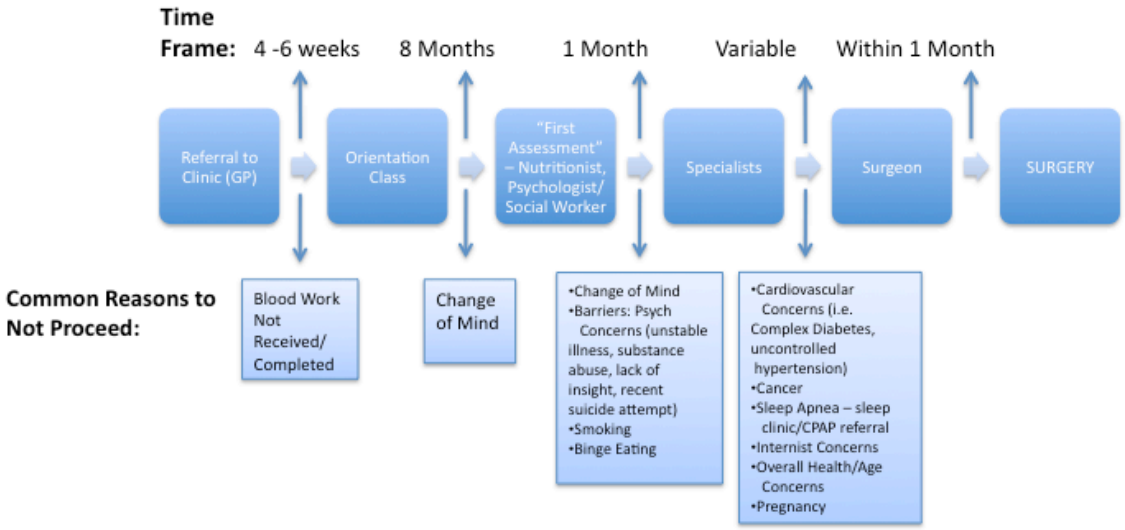
Figure 3.1. Bariatric Surgical Candidacy Timeline at St. Joseph's Healthcare Hamilton



# CHAPTER 4:

# The impact of obesity on neuropsychological functioning in adults with and without major depressive disorder

**The impact of obesity on neuropsychological functioning in adults with and without major depressive disorder**

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In the recent decade, there has been emerging evidence that obesity has a negative impact. The cognitive deficits reported across studies however are not consistent. Further, it is unclear how this impairment may present itself in patients already susceptible to cognitive impairment (such as those with MDD). Here, we study cognitive impairment due to the effect of obesity in study samples both with and without MDD. In our study we find that while there is some evidence that obesity has a subtle impact on cognition in obese individuals, this impact does not reach significance without the additive effect of MDD.

This paper has been prepared for submission to the *International Journal of Obesity*

**Introduction**

Obesity is etiologically associated with cardiovascular disease, in part due to its contribution to risk factors such as dyslipidemia, hypertension and type II diabetes (T2D) (Costa, Santos-Silva, Paul, & Gonzalez Gallego, 2015). As a consequence, public health interest in obesity prevention and treatment has been significant (Janssen, 2013). This effort has started to target specific populations, as there is an inherent increased vulnerability towards weight gain associated with mental illness. Major Depressive Disorder (MDD), predicted to be the biggest cause of disability worldwide by 2020 (Ferrari, 2013), is associated with higher rates of risk factors for cardiovascular disease, such as T2D, smoking dyslipidemia and hypertension than in the general public (Fiedorowicz, He, & Merikangas, 2011). There are also much higher rates of obesity in individuals with MDD, and the National Comorbidity Survey-Replication (NCS-R) reported odds ratios (OR) for obesity of 1.21 for lifetime MDD (Simon et al., 2006). The deleterious effects of obesity on peripheral systems have been well elucidated but its impact on central, brain function remains much less well understood (Alonso-Alonso & Pascual-Leone, 2007). A novel area of investigation suggests that adiposity may impact negatively on cognitive functioning (Alosco, Galioto, et al., 2014; Benito-Leon, Mitchell, Hernandez-Gallego, & Bermejo-Pareja, 2013; Beth Spitznagel et al., 2013). For example, studies of obese adults seeking bariatric surgery have shown significant impairment (relative to healthy controls) on measures of executive functioning in particular (Alosco, Spitznagel, et al., 2014; Boeka & Lokken, 2008). Although executive functioning (higher-order cognitive processing) is the cognitive domain most often affected, performance on

tasks of memory also point towards a potential negative association with obesity (Smith, Hay, Campbell, & Trollor, 2011a).

The potential impact of obesity on mental health could be especially problematic in this population given it has been well established that MDD is associated with impairment in cognitive functioning across multiple cognitive domains, including executive functioning, attention and memory (Rock et al., 2014; Trivedi & Greer, 2014). Impairment on tests involving the conscious recollection of facts or events (semantic and episodic memory respectively) has been reported in patients with a mood disorder (McDermott & Ebmeier, 2009; Rock et al., 2014). Studies also point towards executive function impairment on tasks involving the selection, timing, monitoring and interpretation of behavior, including working memory and selective attention (Harvey et al., 2004; Wagner et al., 2012). Moreover, cognitive deficits in processing speed, attention, executive functioning and memory are present during a first-episode MDD, as well as persisting into euthymia (Bora, Harrison, Yücel, & Pantelis, 2013, 2013; Hasselbalch et al., 2011; Lee et al., 2012).

Despite clear links between obesity and cognition, and cognitive functioning and MDD, the extent to which obesity contributes to cognitive functioning in patients with MDD has never been investigated. Despite the greater prevalence of overweight or obese individuals in the MDD population, our review of recently published meta-analyses and systematic reviews investigating the association between MDD and cognitive impairment found that participant weight was not reported as a demographic characteristic or

potential covariate in any of the reviews identified (Bora , Harrison, Yucel, & Pantelis, 2013; Hasselbalch, Knorr, & Kessing, 2011; Lee, Hermens, Porter, & Redoblado-Hodge, 2012; McDermott & Ebmeier, 2009; McLennan & Mathias, 2010; Rock, Roiser, Riedel, & Blackwell, 2014; Wagner, Doering, Lieb, & Tadic, 2012). Given that impaired cognition is often linked with a failure to return to full functioning, despite a remission in other symptoms, (McIntyre, Liauw, & Taylor, 2011; Oliveira de Lima Queiroz et al., 2013; Trivedi & Greer, 2014) and that obesity is a potentially preventable or modifiable risk factor, there is an urgent need to explore this association.

In this study, we sought to examine the individual impact of obesity and MDD on cognitive function in an adult population (age 18 – 60). Cognitive performance was assessed in obese individuals seeking bariatric surgery, with and without MDD, and compared to a healthy control (non-depressed, normal body mass index [BMI)]) group. Here, we hypothesized that healthy controls would outperform both bariatric (obese) participant groups on measures of cognitive performance, with bariatric controls (free of psychiatric illness) outperforming bariatric participants with MDD. In addition, we examined how potential confounding variables, such as nutritional intake and the presence of medical illnesses commonly co-morbid with obesity might impact these associations.

## Methods

### Participants

This study was conducted as one arm of a large prospective study examining the effect of obesity on cognition in adults with and without a mood disorder study undergoing bariatric surgery in the Bariatric Surgery Program at St. Joseph's Healthcare Hamilton (SJHH). A total of 82 participants have been recruited to date into this study. Here, we report on the pre-surgical neuropsychological and cohort profile data collected for the healthy (normal) BMI control group (HC; n = 20), bariatric (obese) control group free of psychiatric illness (BC; n = 25), and bariatric MDD patient group (MDD; n = 21) for which recruitment is now completed.

At the time of study submission, approximately 3100 charts had been reviewed for potential study eligibility (age 18-60, meeting the physical restrictions of a magnetic resonance imaging (MRI) scanner, and not having yet received surgery). Six-hundred-and-eighty-three patients were contacted regarding study participation and, if interested, given a full telephone screening questionnaire. Full recruitment procedures and a full description of study protocol are outlined in Restivo et al. (submitted, 2015). *Inclusion criteria* for all groups was 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 were required to have a BMI between 18.5 – 24.9 (normal range) (WHO, 2008). *Exclusion Criteria* included 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), 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. 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.

Of those who met criteria and chose to participate, a total of 82 consented and were enrolled, of which 78 completed the neuropsychological testing portion of the study reported here. Two participants chose to no longer pursue surgery and did not complete their scheduled neuropsychological testing study visits as a result and an additional two participants withdrew consent due to scheduling conflicts. Of the 78 who completed neuropsychological testing, two participants were excluded from analysis: one participant for disclosure of exclusionary medical comorbities during a study visit and a FSIQ <70 and the second participant for diagnosis of previous substance use dependency. In order to investigate the representativeness of the bariatric study participants in relation to the wider bariatric surgery patient population, descriptive summary information was obtained

from the Ontario Bariatric Registry (Anvari, Sharma, Yusef, et al., 2015). The Ontario Bariatric Registry (OBR) is an initiative of the Ontario Bariatric Network, established in 2009 by the Ministry of Health and Long Term Care in Ontario . The OBR is a province-wide (multi-site) registry database that collects medical and demographic data on patients who were enrolled in a bariatric surgery program in Ontario as of 2010 (see Appendix 1 for further information regarding the Bariatric Registry Study). OBR data is completely anonymous and de-identified. All patients enrolled in a bariatric surgery program in the province of Ontario are offered enrollment in the Bariatric Registry Study which captures detailed demographic and medical patient data both pre- and post-surgically. Study investigator submitted a summary data request to the OBR which was approved and released in a password encrypted Excel file. A comparison of demographic and clinical characteristics of the study sample with data available from the provincial registry is available in Table 4.1

Independent Variables

BMI groups were defined based on the criteria established by the National Heart Lung, and Blood Institute, Obesity Education Initiative: normal weight (18.5 – 25.0 $kg/m^2$) and obese ($\geq$30 $kg/m^2$) (Pi-Sunyer, 1998). BMI for the bariatric participants ranged from 37.0 (class 2 obesity) to 55.7 (class 3 or morbid obesity), with 83.0% of bariatric participants falling in the class III range (Katzmarzyk & Mason, 2006). Psychiatric status (current and lifetime history) was evaluated via the Structured Clinician Interview for DSM-IV (SCID). Participants with either a current or previous diagnosis of

MDD status were both included in the bariatric MDD participant group. Previous Binge Eating Disorder was not an exclusionary criteria for either bariatric participant group.

Covariates

An extensive list of corollary information was also obtained. Data from administered standardized questionnaires, clinical interviews, and patients chart and medication profiles were collected in order to investigate and control for potential confounders.

*Medical.* Anthropomorphic and medical comorbidity data are shown in Table 4.2. For all three groups we obtained weight, height, BMI, waist and hip circumferences, average systolic and diastolic blood pressures (averaged from a left and right arm independent reading), and a random glucose 'finger prick test' value (taken a minimum 2 hours after having last eaten). In addition, lipid profile values and hemoglobin (Hb)A1c values were obtained for bariatric patient groups. The Berlin Sleep Questionnaire (Chung et al., 2008), which assesses the risk level for current Obstructive Sleep Apnea (OSA) or sleep disordered breathing, was also completed by each participant. Participants were coded as high-risk or low-risk; participants whose previously diagnosed OSA was being currently treated and controlled by a Continuous Positive Airway Pressure (CPAP) ventilator were coded as low-risk. Nutritional intake was assessed via a non-consecutive 3-day dietary record (Food Frequency Questionnaire [FFQ]), with one day being a weekend day (Willett & Leibel, 2002). In addition to obtaining information on overall average daily caloric intake, diet component analysis was also completed by examining,

total daily caloric intake, cholesterol, fibre, sugar, sodium and percent and total intake of proteins, carbohydrates, and fat. Smoking was coded as a dichotomous variable (current versus non-smoker). Participants were asked to provide a complete listing of current medications, vitamins, and herbal supplements (including dosage and indication) during their first study visit; medication history was also confirmed via data extraction of bariatric patients' medical charts and recorded clinic staff encounters. Following previously employed methodology by Sackeim (2001) and Hassel et al. (2008), we generated a composite measure of total (psychotropic) medication load. Individual medication codes reflected dosage and medication class, and were calculated and summed into a composite score for each bariatric MDD participant.

*Demographic.* Age at time of neuropsychological testing, years of education, sex, and ethnicity was collected for each participant (see Table 4.3). The Cognitive Failure Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982) was used to assay participative feelings of cognitive dysfunction, while the Sheehan Disability Scale (SDS) was used to assay participative feelings of impairment across three life domains (Work/School, Social Life, and Family Life/Home Responsibilities) (Sheehan, Harnett-Sheehan, & Raj, 1996).

*Psychiatric.* Mood ratings questionnaires on the day of testing (or within a 2-week period of the a previous study visit) were administered. The Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression-17 (HAMD-17) were used to control for the presence of depressive symptoms, while the Altman Rating Scale for Mania (ARSM) and Young Mania Rating Scale (YMRS) were used to control for mania symptoms.

Additionally, the Childhood Trauma Questionnaire was administered to control for previous trauma exposure. Current and past psychiatric morbidities were captured through the SCID. Additional information regarding MDD illness burden for the bariatric MDD population was collected, including illness age of onset and number of episodes (clinical characteristics listed in Table 4.4).

Neuropsychological test battery and procedure

A standardized battery of neuropsychological tests aimed at establishing pre-surgical (baseline) performance on tests of declarative memory, executive functioning and attention was administered. These cognitive domains have been shown to be susceptible to impairment in metabolically dysregulated populations (Elias, 2003; Van den Berg, 2009). The following battery of tests was administered:

*Declarative memory function* battery: California Verbal Learning Test II (CVLT) (standard and alternate forms): this word list learning task provides indices of immediate and delayed memory performance, interference learning, and recognition (Delis, Kramer, Kaplan, & Ober, 1987); Wechsler Memory Scale III - Logical Memory subtest (WMS-III): this contextually-based memory task provides indices of learning slope, immediate and delayed memory performance, retention, and recognition (Wechsler, 1997); Brief Visuospatial Memory Test – Revised (BVMT-R): a nonverbal test of visuospatial memory under explicit encoding conditions (Benedict, 1997)

*Executive functioning and attention battery*: Controlled Oral Word Association Task (COWAT): this task taps phonemic (FAS) and semantic (animals) fluency; Stroop

Colour and Word Test (Golden version): this task taps sensitivity to suppress a habitual response in favor of a less familiar one (Golden, 1978); Wisconsin Card Sorting Task (64-item version) (WCST): this task taps the ability to form and shift concepts based on feedback (Heaton, Chelune, Talley, Kay, & Curtis, 1993); Colour Trails Test (CTT) Part A & B: Whereas Part A assesses processing speed, Part B taps the ability to sequence two stimulus sets while alternating between them (Reitan & Wolfson, 1985); Paced Auditory Serial Attention Test (Victoria Computerized Adaptation) (PASAT): this task assesses capacity and rate of information processing as well as sustained and divided attention (Gronwall, 1977)

Both raw scores and standardized t- and/or z-scores were obtained (normative data was obtained from each test's corresponding administration manual). Performance on the Wechsler Abbreviated Scale of Intelligence was compared across groups in order to investigate whether differences in general intelligence were statistically significant (and needed to be included as a covariate in data analysis). Neuropsychological measures and individual variables tested are grouped by cognitive domain in Table 4.5.

**Statistical Methods**

A double-entry system with independent research personnel was utilized for all cognitive and behavioural data and inconsistencies were checked and resolved by an additional assessor. Any single measure with greater than 30% missing data was excluded from the data set. Exploratory descriptive analysis of dependent variables was completed

in order to whether extreme abnormalities in skew or kurtosis indicated the need for variable transformations.

Exploratory descriptive group analyses were performed to investigate and characterize group means, ranges, and standard deviations. One-way between group Analysis of Variance (ANOVA) tests were performed on all continuous covariates of interest. Chi-square analyses were run to compare group differences on categorical variables. Significant ANOVA test results were then further investigated by means of pairwise comparisons (Tukey-HSD).

Although our primary interest was in the effect of obesity on cognition, additional cardiovascular comorbidities may contribute to cognitive performance in obese (bariatric) participants. As such, proportion of comorbidities (e.g. hypertension, T2D, etc.) was compared between bariatric patient groups to ensure that one group was not heavily loaded with potential confounders. Additionally, comorbidity variables considered potential confounders were further explored in secondary analyses of ANOVA models found to be significant. Pearson product-moment correlation coefficients between cognitive outcomes and medication load composite scores were also calculated.

## Results

### Participants

Participants in the HC, BC and MDD groups did not differ in terms of age, sex distribution, ethnicity or marital status. Although the bariatric groups differed with

respect to years of education compared to healthy controls, they did not perform differently on measures of intelligence (FSIQ). When comparing bariatric controls with bariatric MDD participants, no significant group differences were found with regards to medical comorbidity, including presence of T2D, hypertension, OSA risk, or hyperlipidemia. Healthy control participants did not have any medical comorbidities (e.g. T2D, hypertension, OSA risk, or hyperlipidemia) At the time of testing, only one participant (bariatric control) reported current smoking. Further exploration also indicated that bariatric controls and MDD bariatrics did not differ with regards to weight, BMI, lipid profile levels, blood pressure readings, heart rate, waist and hip circumferences, glucose and HbA1c values. Demographic and medical characteristics of the study sample can be found in Table 4.2 (no medical comorbidities were seen in the HC group). With regards to the bariatric MDD group, there were no significant correlations between psychiatric medication load and cognitive performance.

Additionally, no significant group differences (across the three groups) in developmental trauma exposure were found using the CTQ. Subjective report of disability impairment, due to obesity and health related problems and/or psychiatric health problems was significantly different across groups ($F[2,61]=22.24$, $p < 0.001$). In particular, post-hoc Tukey analysis showed that compared to healthy controls, bariatric controls reported an overall level of mild impairment (Mean [M]=2.65, SD=1.7, $p < 001$), while bariatric MDD participants reported an overall level of moderate impairment (M=4.70, SD=2.74, $p < 001$), on a 10-point scale. Groups also significantly differed on self-reported levels of cognitive impairment on the CFQ ($F[2,62]=12.0$ $p < 0.001$). Pair-

wise contrasts showed that the MDD bariatric group reported significantly higher levels of cognitive impairment when compared to both the bariatric control group ($p < 0.001$) or healthy control group ($p < 0.001$). Group differences on measures of depression, namely the BDI and HAMD, were found ($F[2,62]=17.90$, $p < 0.001$ and $F[2,62]=19.12$, $p < 0.001$ respectively). Post-hoc Tukey analysis indicated that in comparison to healthy and bariatric controls, the MDD bariatric group also exhibited significantly higher levels of depression on both self-report (BDI: $p < 0.001$, $p = 0.03$, respectively) and clinician administered scales (HAMD: $p < 0.001$, $p < 0.001$, respectively), with the overall group means indicating minimal to mild current depression (BDI: M=17.5, SD=10.0; HAMD: M=6.6, SD=4.3). Approximately 34.8% of the MDD bariatric group met DSM-IV criteria for current or partially remitted MDD, while the remaining 65.2% were considered euthymic at the time of testing. Chi-square test analysis showed that Binge Eating Disorder (past or current diagnosis) did not differ between the two bariatric study groups ($p=0.78$). No healthy control patients met DSM-IV criteria for past or current Binge Eating Disorder. Clinical characteristics of each group are summarized in Table 4.3.

Participants did not differ in nutritional intake measures of total daily caloric intake (averaged across 3-days using the FFQ), diet component (diet percentage broken into protein, carbohydrate and fat intake), total fat, cholesterol, total sugar or sodium. Groups did differ in dietary fiber intake ($F[2,61]=3.46$, $p=0.04$), with healthy controls reporting significantly higher levels (M=24.0[9.9] grams) as compared to MDD bariatric participants (M=18.0[5.7]) when examined using post-hoc Tukey analysis.

Neuropsychological Performance

No significant group differences were found in premorbid intellectual functioning (as assessed by FSIQ score on the WASI) and consequently, FSIQ and education were not added as covariates in cognitive performance ANOVA models. All analyses were conducted using both raw and standardized (z-, t- or standard scores) for each measure. Use of standardized and normed values did not alter group effects seen using raw score analysis; thus, all analysis was reported using raw scores or calculated test indices. Given the small size of participants who met the minimum PASAT Trial 1 or Trial 2 threshold for administering Trials 3 and 4, group differences were not explored for Trials 3 and 4.

We observed a consistent pattern across measures of memory, executive functioning, attention and processing speed wherein healthy controls consistently performed better than both bariatric groups across the majority of measures, while bariatric controls tended to outperform bariatric MDD patients (see Table 4.6). Several of these differences reached statistical significance or trended towards significance ($p<0.10$).

*Cognitive Outcome Measures:*

Significant group differences emerged on the interference trial of the Stroop Word-Colour Test ($F[2,63]=3.19$, $p < 0.05$), tapping executive functioning (response inhibition). Post-hoc Tukey analysis showed that this difference was only significant when comparing bariatric MDDs to healthy controls ($p=0.04$). Significant group differences were also observed on the Learning Slope index of the WMS-LM1 subtest ($F[2,63]=4.69$, $p=0.01$), tapping verbal learning. Pair-wise Tukey comparison here

showed that group differences were only significant when comparing bariatric controls with bariatric MDDs (p=0.01) however. Group differences in processing speed also emerged on the Stroop Word (F[2,63]=4.16, p=0.02), with a trend towards significance on the Stroop Colour Raw (F[2,63]=2.96, p=0.06) scores. Specifically, the bariatric MDD group displayed significantly poorer performance compared to healthy controls (post-hoc Tukey-HSD: p=0.02 and p=0.05) on the Stroop Word and Stroop Color subtests respectively.

Additionally, there were trends toward significant group differences on the learning index and total recall score of the BVMT-R (F[2,63]=2.65, =0.08, and F[2,63]=2.66, p=0.08, respectively) tapping visual-spatial learning and memory, the Color Trails 2 test (F=[2,62]=2.81, p=0.07) tapping executive functioning (mental flexibility), and on Trial 2 of the PASAT (F[2,56]=2.94, p=0.06), a measure of sustained attention. No significant group differences emerged on the CVLT and Color Trails 1. A summary of significant and trending group effects (including effect size) can be found in Table 4.7.

Secondary Analyses

Given that the MDD bariatric group consisted of currently depressed, partially remitted, and euthymic patients, exploratory analyses was conducted to see whether BDI or HAMD scores were significant predicators of cognitive performance outcome measures within the MDD group. BDI and HAMD scores within the MDD bariatric group were not significantly correlated with performance on cognitive test measures.

For measures where a significant difference between the bariatric MDD and healthy control groups was identified, analysis was repeated, splitting the bariatric MDD group into two groups based on the comorbidity effect being investigated (namely, hypertension, T2D or OSA). The same process was completed for the bariatric versus healthy control effect model on the WMS-LM1 Learning Slope score. Hypertension status was found to have a significant effect within the bariatric MDD group only on performance on the Stroop Word measure ($F[2,38]=3.37$, $p < 0.05$). Interestingly however, using post-hoc Tukey analysis, this difference in performance was seen between the bariatric non-hypertensive MDD group compared to healthy controls ($p < 0.05$), indicating that the presence of hypertension was not responsible for the differences seen between groups in significant ANOVA models. Similarly, the bariatric MDD patients without T2D performed significantly worse than healthy controls on the Stroop Word task (post-hoc Tukey analysis, $p=0.03$). Finally, no differences in performance between bariatric MDD patients with and without OSA were found on any of measures examined.

**Discussion**

To our knowledge, this is the first study to attempt to examine the potentially deleterious effects of obesity, its comorbidities, and depression on cognitive performance. Here, we found that an effect of obesity on cognition seemed to be significant only when comparing the bariatric MDD patient group to healthy controls. Although bariatric controls often outperformed bariatric MDDs and healthy controls often outperformed bariatric controls (with regards to raw test scores), these differences in cognitive

performance did not generally reach significance. This suggests that MDD and obesity may have an additive effect on cognition that leads to measurable deficits in cognitive performance on neuropsychological measures.

Our work offers further potential support to the growing number of studies linking obesity to poor cognitive performance (Liang, Matheson, Kaye, & Boutelle, 2014; Marques et al., 2014). A current controversy in the area of obesity and its effects on various domains of health is whether there is a subset of the obese population which can be categorized as metabolically healthy (e.g. obese without the detrimental presence of obesity's associated medical comorbidities) (Blüher, 2010; Hamer & Stamatakis, 2012; Sims, 2001). There is ongoing debate on whether many of the deleterious effects often attributed to obesity are not a result of adiposity itself, but rather effects due solely to the common comorbidities associated with obesity (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Smith, Hay, Campbell, & Trollor, 2011b; Wolf et al., 2007). Our study is the only study to date to extensively account for, obtain and include data on nutrition, exhaustive comorbidity history and risk factors, and psychiatric health while investigating cognitive impairment. Given that our sample was recruited from a bariatric surgery program, a certain proportion of common comorbidities were expected in our final sample (which allowed us to perform secondary analyses involving comorbidity presence on cognitive impairment). Results from our study indicate that although obesity may not have a perceptible effect on cognitive performance in otherwise healthy (non-psychiatric) individuals, that this may reach a significant effect in patients already susceptible to cognitive dysfunction (such as those with MDD).

In line with previous studies, the majority of our reported findings of cognitive impairment in the bariatric MDD group were on measures of executive functioning, attention, and processing speed, areas shown to be affected by both obesity and MDD individually (Bora et al., 2013; Cook, O'Dwyer, Steinbeck, Rooney, & O'Connor, 2013; Harvey et al., 2004; Jean & Ajilore, 2014). Further, when comparing performance patterns across groups, MDD (including both past and current diagnosis) seemed to have an additive negative effect on cognition in the presence of obesity, with comparisons between bariatric MDD and healthy controls resulting in significantly different levels of performance on several cognitive tasks (differences were not seen as significant when contrasting bariatric MDD and bariatric controls). This has important ramifications on both clinical practice and theoretical research. Clinically, many psychotropic medications are associated with problematic metabolic side effects, including increased weight gain (Barrett-Connor, 2013; Birt, 2003; Garcia, Logan, & Gonzalez-Heydrich, 2012). A common complaint of MDD patients is cognitive impairment (McDermott & Ebmeier, 200); in line with this, the MDD sample in our study reported high levels of subjective cognitive impairment on the CFQ. Current clinical treatment guidelines do not factor in tolerability when suggesting first and second line options, but knowing metabolic changes can impact cognitive functioning, an outcome used as a measure of remission of psychiatric symptomatology may impact stratification of recommendations, especially given the emphasis on functional recovery (McIntyre, Liauw, & Taylor, 2011). Given an option between several first-line treatment options for MDD, physicians may want to consider a psychotropic medication with a smaller likelihood of significant weight gain,

as well as implementing a weight management or monitoring strategy with medication-treated patients. With regards to cognitive and clinical research, is has been shown that MDD is associated with impairment on tests of memory, attention, executive function and processing speed (Bora et al., 2013; Grassi-Oliveira, Bauer, Pezzi, Teixeira, & Brietzke, 2011; Rock et al., 2014; Trivedi & Greer; Wroolie, Kenna, Singh, & Rasgon, 2015). However, a review of the literature indicates that few studies investigating interactions between MDD and cognitive impairment report on, or account for, the possible confounding effects of obesity in their sample. The hidden contribution of obesity becomes critically important when recognizing the high prevalence rates of obesity in MDD populations when compared to the general population (Simon et al., 2006). In our study, we found that an additive effect of MDD and obesity reached significance on measures of processing speed and executive function (response inhibition and verbal learning). It may be that some of the cognitive impairment traditionally attributed to the presence of a mood disorder may be partly due to the presence of obesity, and/or its related metabolic comorbidities. Due to the absence of a non-bariatric MDD study group, we were unable to draw conclusions regarding the independent effects (and interactions between) MDD and obesity on cognition.

While our study showed that performance on measures of cognition was most often affected when both MDD and obesity were present, reduced cognitive performance may be due to overlapping mechanisms in both disorders (Liu, Carvalho, & McIntyre, 2014). Both MDD and obesity are considered low-grade pro-inflammatory states, resulting in elevation of adipokines such as C-reactive protein. C-reactive protein has

been associated with low cognitive performance in both animal (Perry, Cunningham, & Holmes, 2007) and human models (Anan et al., 2011; Dik et al., 2007; Komulainen et al., 2007). It is also possible that poor performance in executive function is a risk factor for both obesity and MDD, preceding the presence of either disorder.

Although a consistent group performance pattern was seen across almost all measures, results may have failed to achieve significance on certain measures due to our study's modest sample size limitation. As such, our study was unable to conclusively address whether obesity itself may lead to cognitive impairment in otherwise healthy subjects. Due to our modest sample size, we are also unable to exclude a type II error. It should also be noted that our MDD bariatric sample included both currently depressed, partially remitted and euthymic MDD patients. However, BDI and HAMD scores were not found to predict performance on measures of cognitive performance. Moreover, while depression severity has been associated with cognitive performance in areas reported in our study (namely executive function, memory, and processing speed) (McDermott & Ebmeier, 2009), many of these cognitive impairments have been shown to persist during euthymia (Hasselbalch et al., 2011; Rock et al., 2014).

Nevertheless, our study has many strengths. It is the only study in the present literature that attempts to quantitatively investigate and contrast the effect of obesity in a population with and without MDD. Moreover, we are not aware of a study investigating the impact of obesity on cognitive performance reporting and capturing information for the exhaustive list of potential confounders investigated in our study. Using data provided

by the Bariatric Registry Study (Anvari, M., Sharma, A., Yusuf, S. et al., 2015), we can conclude that our sample is representative of individuals seeking bariatric surgery across the entire province of Ontario, and is likely generalizable to individuals with both class II and class III obesity.

Further work is needed to determine the directionality between obesity and cognitive impairment and to further disentangle the interactive effects of mood disorder diagnosis, obesity and cognitive performance. Future addition of a MDD non-bariatric group to our study design would allow us to better characterize the independent associations between MDD, obesity, and cognition, along with their interactions. Prospective studies following participants prior to and following significant weight changes and studies monitoring progress of cognitive symptoms and psychiatric health outcomes, are also needed to help determine whether cognitive impairment is reversible in at-risk populations and we will extend this study to examine if changes are seen in these groups post-bariatric surgery. The work to date indicates that obesity may impact cognitive performance in individuals with preexisting vulnerability, such as those with MDD, and weight management is especially important in this population in order to ensure the best outcomes.

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**Conflict of Interest**

The authors declare no competing interests in the writing of this manuscript. The study sponsors play no role in study design, data collection, data analysis, data interpretation or report writing.

**Appendix 1**

The Bariatric Registry Study is a province wide study that seeks to gather information on provincial bariatric patients from time of referral until 5 years post-surgery. The program first commenced in January, 2010 and as of March 31, 2015, there were 40 788 patients referred to the study. Of those referred, 1883 patients declined consent. In addition, as of March 31, 2015, 21 534 patients were not included in the registry for other reasons, including: transfer to a medical program, death, ineligibility for a bariatric surgery program, lack on interest in continuing to pursue surgery, or patient was placed on hold (for example, due to smoking). More information regarding the program and common barriers is also available in Restivo et al. (submitted, 2015). As of March 31, 2015, 15,082 patients were currently in the registry. Prior to surgery, all individuals referred for bariatric procedures undergo a series of assessments, including a detailed demographic profile and medical review during a first (baseline) assessment. Most program sites obtain study consent at the patient's first assessment (baseline) visit in the clinic, while some choose to consent at the time of orientation (a class attended prior to baseline assessment wherein individuals seeking bariatric surgery are given an overview of the surgical candidacy process and surgical procedure) . Those who dropout of the study are no longer followed by the registry, and thus, may not be entirely similar in terms of medical profile to those who remain in the study and are reported on. Based on the information captured by the registry, the study has estimated that the rate of decline (to consent to study enrollment) is 4.61%. As such, we believe the information

captured by the study provides a fair representation of the average bariatric surgery candidate in Ontario.

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Table 4.1. Comparison Demographic Characteristics of Study Sample, St. Joseph's Healthcare Hamilton Bariatric Surgery Program Candidates and Provincial Bariatric Surgery Candidates (as reported by Anvari, M., Sharma, A., Yusuf, S., et al., 2015

| | Study Sample | SJHH | All Ontario Centres |
|---|---|---|---|
| Age (Mean) | 43.7 (10.7) | 46* | 45* |
| Male:Female (%) | 9.1:90.9 | 20.0:80.0 | 19.5:8.0 |
| Type II Diabetes (%) | 29.5 | 33.3 | 32.7 |
| Hypertension (%) | 39.5 | 46.0 | 47.4 |
| Hyperlipidemia (%) | 30.2 | 36.5 | 33.7 |
| BMI (Mean) | 44.2 (3.8) | 49.4 | 48.6 |

*Standard Deviation information was not available form the Bariatric Registry

Table 4.2. Demographic and Medical Characteristics of Study Sample

| | Health Controls (n=20) | Bariatric Controls (n=25) | MDD Bariatrics (n=21) |
|---|---|---|---|
| Age (Mean, SD) | 43.8 (11.0) | 43.9 (10.7) | 43.2 (10.9) |
| Sex (Male:Female) | 2:18 | 2:23 | 2:19 |
| Years of Education$^{++}$ | 16.1 (2.3) | 14.2 (2.1) | 14.2 (2.3) |
| Ethnicity (Caucasian %) | 85 | 95.2 | 85.7 |
| Marital Status | | | |
| Married/Common-Law | 80.0 | 76.0 | 57.1 |
| Divorced/Separated/Widowed | 0.0 | 8.0 | 21.5 |
| Single | 20.0 | 16.0 | 21.5 |
| | | | |
| BMI | 22.4 (2.0) | 44.7 (2.9) | 43.7 (4.8) |
| Weight (kg) | 60.3 (7.1) | 122.0 (10.5) | 116.3 (14.5) |
| Height (cm) | 164.0 (8.3) | 165.2 (4.2) | 163.0 (6.6) |
| Waist Circumference (cm) | 74.6 (5.2) | 123.5 (10.2) | 124.1 (12.0) |
| Hip Circumference (cm) | 97.7 (5.8) | 139.7 (8.0) | 134.4 (11.8) |
| Hypertension* (%) | 0.0 | 43.5 | 35.0 |
| Average Systolic BP** (mmHg) | 119.8 (9.3) | 134.3 (18.0) | 132.5 (10.5) |
| Average Diastolic BP** (mmHg) | 74.6 (16.2) | 77.6 (7.0) | 76.5 (11.2) |
| Average Heart rate** | 73.4 (12.8) | 82.5 (13.0) | 80.1 (10.7) |
| TDII (%)*** | 0.0 | 33.3 | 25.0 |
| Ha1bc | n/a | 0.059 (0.019) | 0.059 (0.005) |
| Random Glucose Test | 5.8 (1.6) | 6.1 (2.4) | 5.2 (0.8) |
| Hyperlipidemia**** | 0.0 | 24.0 | 33.3 |
| Total Cholesterol | n/a | 4.60(0.93) | 4.74 (0.95) |
| HDL | n/a | 1.26 (0.33) | 1.15 (0.27) |
| LDL | n/a | 2.65 (0.67) | 2.95 (0.87) |
| Triglycerides | n/a | 1.53 (0.88) | 1.56 (0.58) |
| OSA Risk (%High Risk) | 0.0 | 50.0 | 81.0 |

$^{++}$Significant Group Effect ($p < 0.05$)
*Borderline hypertension was collapsed into the hypertension group
**Two independent measures, 1 minute apart were obtained
***Borderline, well-controlled, and sub-optimally controlled TDII status were collapsed
****Elevated lipid value status was also included as hyperlipidemia

Table 4.3. Clinical Characteristics of Study Sample

| | Healthy Controls (n=20) | Bariatric Controls (n=25) | MDD Bariatrics (n=21) |
|---|---|---|---|
| HAM-D* | 1.6 (2.9) | 1.5 (1.8) | 6.6 (4.3) |
| BDI* | 1.9 (5.6) | 8.3 (8.6) | 17.5 (10.0) |
| YMRS* | 0.6 (0.9) | 0.5 (0.7) | 2.6 (2.5) |
| ASRM | 1.6 (2.6) | 3.1 (3.0) | 2.7 (2.7) |
| Anxiety Comorbidities (%) | n/a | n/a | 42.9 |
| Binge Eating Disorder (%)* | 0 | 8.3 | 23.8 |
| Age of Onset (MDD) (years) | n/a | n/a | 21.9 (7.8) |
| Number of MDD Episodes | | | 6.0 (4.7) |
| | | | |
| CTQ | | | |
| Total | 33.1 (14.9) | 33.7 (17.7) | 41.1 (27.8) |
| Emotional Abuse | 7.5 (4.7) | 8.3 (4.4) | 11.0 (7.3) |
| Physical Abuse | 6.1 (2.7) | 6.4 (2.6) | 7.2 (5.4) |
| Sexual Abuse | 5.0 (0.0) | 6.1 (3.5) | 6.9 (5.8) |
| Emotional Neglect | 8.8 (5.2) | 10.9 (4.9) | 10.5 (6.7) |
| Physical Neglect | 7.5 (3.1) | 7.3 (2.6) | 7.7 (4.6) |
| | | | |
| SDS (Averaged Across Domains)* | 0.0 (0.8) | 2.7 (2.6) | 4.7 (2.7) |
| CFQ Total* | 22.9 (10.6) | 25.2 (6.4) | 40.5 (18.6) |

*significant group effect ($p < 0.01$)

Table 4.4. Nutritional Intake and Diet Component Analysis of the study sample

| | Healthy Controls (n=20) | Bariatric Controls (n=23) | MDD Bariatrics (n=21) |
|---|---|---|---|
| Average Daily Caloric Intake (Kcal) | 2205.8 (655.0) | 2089.8 (584.2) | 2062.9 (491.2) |
| Protein (Kcal %) | 17.8 (3.8) | 17.3 (2.2) | 16.5 (2.7) |
| Carbohydrate (Kcal %) | 47.0 (8.2) | 45.8 (7.9) | 45.6 (6.8) |
| Fat (Kcal %) | 32.5 (6.5) | 36.6 (6.9) | 36.7 (6.9) |
| Total Fat (g) | 81.8 (28.8) | 84.7 (27.8) | 84.2 (24.0) |
| Cholesterol (mg) | 287.1 (212.8) | 285.8 (130.8) | 307.0 (172.7) |
| Dietary Fibre (g)* | 24.0 (9.9) | 19.3 (7.1) | 18.0 (5.9) |
| Total Sugar (g) | 98.6 (41.3) | 83.5 (42.0) | 81.8 (35.5) |
| Sodium (mg) | 3163.9 (1413.9) | 3420.0 (1376.0) | 3586.5 (1198.3) |

*significant group effect ($p < 0.05$)

Table 4.5 Full List of Cognitive Measures and Variables Investigated

| Cognitive Domain | Test Measure | Test Variable |
|---|---|---|
| Executive Function | BVMT-R | Learning Index |
| | COWAT | Letter Fluency (Total Responses – Phonemic) |
| | | Animal (Category) Fluency (Total Responses) |
| | Stroop | Colour-Word Score |
| | | Interference Score |
| | CTT 2 | Time to Completion (Total Seconds) |
| | WCST | Number of Categories Completed |
| | | Conceptual Level Responses |
| | | Total Errors |
| | | Perservative Responses |
| | | Perservative Response Errors |
| | WMS | LMI Learning Slope |
| Memory | BVMT-R | Total Correct Responses |
| | | Delayed Correct Responses |
| | CVLT | Total Correct Responses |
| | | Short, and Long, Delay Cued Recall |
| | | Short, and Long, Delay Free Recall |
| | WMS-III | Logical Memory I (LMI) – Recall |
| | | Logical Memory II (LMII) – Recall |
| | | LMI 1st Recall Total Score Raw |
| | | LMII Percent Retention |

| | | |
|---|---|---|
| Processing Speed | CTT 1 | Time to Completion (Total Seconds) |
| | Stroop | Colour Score |
| | | Word Score |
| Intellectual Functioning | WASI | FSIQ (2-Subtest) |
| Attention | PASAT | Correct Responses (Trial 1, 2) |

Table 4.6. Neuropsychological Performance Across Groups

| Measure Variable | HC (n=20) Mean (SD) | BC (n=25) Mean (SD) | MDD (n=21) Mean (SD) |
|---|---|---|---|
| BVMT – R Total Score Raw [T] | 29.3 (5.9) | 26.6 (5.1) | 25.3 (5.8) |
| BVMT – R Learning Score Raw [T] | 3.4 (1.9) | 4.3 (1.6) | 4.5 (1.6) |
| BVMT – R Delayed Score Raw | 11.2 (1.7) | 10.4 (1.4) | 10.7 (1.4) |
| COWAT (FAS) Phonemic Raw | 46.5 (11.9) | 40.4 (11.9) | 39.3 (12.1) |
| COWAT (Animals) Score Raw | 24.3 (4.9) | 23.1 (4.6) | 22.0 (6.1) |
| Color Trails 1 Raw (seconds) | 31.9 (9.5) | 33.4 (9.2) | 36.9 (11.1) |
| Color Trails 2 Raw (seconds) [T] | 59.3 (17.0) | 66.4 (16.6) | 74.3 (26.2) |
| CVLT-II Total Raw | 49.7 (7.6) | 48.8 (8.6) | 48.8 (9.2) |
| CVLT-II Short-Delay Free Recall Raw | 10.7 (2.6) | 10.5 (2.6) | 10.0 (2.7) |
| CVLT-II Long-Delay Free Recall Raw | 11.5 (2.6) | 10.7 (2.5) | 10.8 (2.4) |
| CVLT-II Short-Delay Cued Recall | 11.7 (2.5) | 11.4 (2.0) | 11.0 (2.8) |
| CVLT-II Long-Delay Cued Recall | 12.1 (2.4) | 11.3 (2.4) | 11.5 (2.5) |
| PASAT Trial 1 | 39.7 (3.1) | 35.4 (11.9) | 32.2 (14.3) |
| PASAT Trial 2 [T] | 36.1 (12.5) | 29.7 (11.5) | 26.8 (11.9) |
| Stroop Word Raw* | 101.4 (11.3) | 92.3 (11.6) | 89.5 (17.8) |
| Stroop Colour Raw [T] | 75.9 (9.2) | 71.4 (10.1) | 67.8 (12.8) |
| Stroop Word-Colour* | 45.8 (7.2) | 42.0 (8.4) | 39.7 (7.7) |
| Stroop Interference | 3.7 (6.9) | 2.5 (7.9) | 1.2 (7.7) |
| WCST Total Errors Raw | 14.5 (9.1) | 19.8 (11.0) | 18.1 (10.0) |
| WCST Perseverative Errors Raw | 8.1 (5.4) | 11.1 (7.5) | 9.3 (4.6) |
| WCST Perseverative Responses Raw | 8.9 (6.6) | 12.5 (9.4) | 10.5 (5.7) |
| WCST Conceptual Level Responses | 46.0 (13.3) | 38.4 (16.0) | 40.3 (15.6) |
| WCST Categories Completed | 3.8 (1.9) | 2.9 (1.7) | 3.1 (1.6) |
| WMS-III LMI – Recall | 40.1 (8.4) | 39.9 (8.6) | 38.6 (11.5) |
| WMS-III LMII – Recall | 25.3 (7.7) | 24.6 (7.4) | 24.4 (8.0) |
| WMS-III LMI 1st Recall Total Score Raw | 24.0 (5.7) | 23.4 (6.1) | 23.2 (8.0) |
| WMS-III Learning | 5.2 (2.4) | 6.3 (2.1) | 4.0 (3.1) |

| | | | |
|---|---|---|---|
| Slope* | | | |
| WMS-III Percent Retention (%) | 84.2 (12.3) | 81.5 (13.7) | 86.4 (12.2) |
| WASI Full Scale IQ | 112.2 (13.6) | 107.0 (12.7) | 105.3 (12.3) |

*significant group effect ($p<0.05$)
$^{T}$ Trending group effect ($p \leq 0.10$)

Table 4.7. Summary of Significant and Trending Group Effects on Cognitive Test Measures

| Cognitive Domain | Measure (Cognitive Subdomain) | 3-Group (ANOVA) Effect Significant (p) | Group Difference (Tukey) | Post-hoc Tukey Significance Level (p)* | Effect Size (Cohen's D)** |
|---|---|---|---|---|---|
| Attention | PASAT (sustained attention) | 0.06 | MDD > HC | n/a | n/a |
| Executive Function | BVMT-R Learning Index (visual learning) | 0.08 | MDD > HC | n/a | n/a |
| | CTT 2 (mental flexibility) | 0.07 | MDD > HC | n/a | n/a |
| | Stroop Word-Colour Test (response inhibtion) | < 0.05 | MDD > HC | 0.04 | 0.82 |
| | WMS-LMI Learning Slope (verbal learning) | 0.01 | MDD > BC | 0.01 | .41 |
| Memory | BVMT-R Total Recall | 0.08 | MDD > HC | n/a | n/a |
| Processing Speed | Stroop Word (perceptual motor speed) | 0.02 | MDD > HC | 0.02 | 0.80 |
| | Stroop Colour (perceptual motor speed) | 0.06 | MDD > HC | n/a | n/a |

* Post-hoc Tukey analysis was only performed where a significant group effect was found

** Cohen's D was calculated when a difference between 2 groups was confirmed via post-hoc Tukey analysis

# CHAPTER 5:

# Functional magnetic resonance imaging correlates of verbal recognition memory in obese adults with and without major depressive disorder

**Functional Magnetic Resonance Imaging Correlates of Verbal Recognition Memory in Obese Adults with and without Major Depressive Disorder**

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In this chapter, we look at the differences in memory performance (during both encoding and retrieval processes) across three groups: healthy controls, bariatric controls (no psychiatric illness), and bariatric MDD patients. Using fMRI, we found different patterns of activation during both encoding and retrieval processes for each of the three groups. These results again support the idea that obesity and MDD may have an interactive effect on cognition.

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## Introduction

Major Depressive Disorder (MDD) and obesity are now considered two of the leading causes of disability worldwide (Ferrari, 2013; Ng et al., 2013). Indeed, data form the latest 2010 Global Burden of Disease (GBD) study published in 2013 ranked MDD second in terms of global disability burden (Ferrari, 2013). Within the same 2010 GBD report, Ng et al. (2013) reported startling increases from the time of the 1990 GBD report in global rates of obesity and overweight in adults and children (increases of 28% and 47%) (Ng et al., 2013). Obesity itself is associated with increased risk for a variety of medical and psychiatric comorbidities, with Janssen et al. (2013) linking 8-14% of depression cases in Canada to obesity (Janssen, 2013).

Although it is well established that obesity is associated with cardiovascular disease (CVD) risk factors, such as type II diabetes (T2D) and hypertension, obesity's detrimental impact on neural health has also been increasingly recognized in recent years (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). Increased body mass index (BMI) at midlife has been positively correlated with increased dementia risk and cerebral atrophy in late-life adulthood (Driscoll et al., 2012; Garcia-Ptacek, Faxen-Irving, Cermakova, Eriksdotter, & Religa, 2014; Letra, Santana, & Seica, 2014). Although this association was traditionally attributed to the common comorbidities associated with obesity, several recent studies have demonstrated an independent effect of obesity even after adjusting for the presence of CVD risk factors (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Smith, Hay, Campbell, & Trollor, 2011; Wolf et al., 2007). Critically,

the deleterious effects of obesity on cognitive functioning have been demonstrated across a variety of cognitive domains, most reliably in the areas of memory, attention and executive function (Alosco et al., 2013; Boeka & Lokken, 2008). Notably, changes in recollective memory and in executive function are also amongst the most consistently reported deficits in patients with MDD in both depressive and euthymic states, pointing towards a potential association between depression and obesity.

Although functional magnetic resonance imaging (fMRI) has been used extensively in an attempt to identify alterations in the neural circuitry underlying cognitive deficits observed in patients with MDD, to date very few studies have used fMRI to investigate these deficits in a population with obesity. The majority of fMRI work done with respect to obesity has instead been focused on appetite regulation, eating behaviour and reward circuitry (Stanek, Smith, & Gunstad, 2011). A small number of studies have further employed neuropsychological measures and fMRI to investigate non-food-dependent task performance in obese versus lean individuals. For instance, Volkow et al. (2009) reported an effect of increased BMI on regional brain glucose metabolism. Higher BMI was associated with reduced metabolism in the prefrontal cortex and cingulate gyrus, as well as reduced performance on neuropsychological tests of memory (California Verbal Learning Test) and executive function (Stroop Interference and Symbol Digit Modality tests). Interestingly, Gonzales et al. (2014) demonstrated that increased waist circumference predicted alterations in the BOLD response on a fMRI 2-back (executive functioning) task, as well as reduced task performance (associations with cognitive performance on standardized neuropsychological measures not performed

within the MRI and waist circumference did not reach significance). However, no study to date has investigated the impact of obesity on memory using an fMRI task activation paradigm. Previous fMRI investigations of memory and vascular risk factors conducted have been in populations at risk for dementia and Alzheimers (Braskie, Small, & Bookheimer, 2010), and their results tell us little about the impact of obesity on neural processing during itself. Additionally, increased BMI has been associated with unique structural brain changes in patients with other mood disorders (Bond et al., 2011; MDD CIT). Bond et al. (2014) found gray matter and white matter volume reductions in frontal, temporal and subcortical limbic regions in BD patients with increased BMI. These areas (such as the medial temporal cortex) are thought to be important in memory processing, as well as implicated in both BD and MDD pathophysiology (Diener et al., 2012; Konarski et al., 2008).

The goal of the current study was to determine how obesity impacts neural activation patterns during a verbal recognition memory task in an adult sample of individuals both with and without MDD. Impairment on tests involving declarative memory (conscious recollection of facts), including verbal recollection and recognition memory, has been linked to MDD (Lee et al., 2012; Rock, Roiser, Riedel, & Blackwell, 2014). Given the clinical significance and high incidence of obesity in the MDD patient population, we sought to examine whether the differences in neural activation during memory processes in MDD patients could be linked to the hidden effect of obesity. The recognition memory paradigm was based on the standardized neuropsychological measure, the Warrington's Recognition Memory Task (RMT), adapted for use in an MRI.

This paradigm has been shown to activate regions of interest important in memory encoding and retrieval, such as the prefrontal cortex (important in working memory and attention processes) (Matsuo et al., 2006) and the lateral temporal cortex (important in verbal memory encoding) (Ojemann, Schoenfield-McNeill, & Corina, 2009), previously in a Schizophrenic patient population (Hofer, 2003). We hypothesized that both obesity and MDD diagnosis would independently predict alterations in the neural activation during performance of the RMT.

## Methods

### Participants

This study was conducted as one arm of a large prospective study examining the effect of obesity on cognition in adults (with and without a mood disorder) undergoing bariatric surgery in the Bariatric Surgery Program at St. Joseph's Healthcare Hamilton (Restivo et al., submitted). Participants were seen once prior to surgery to complete neuropsychological testing, and on a second study visit to complete a neuroimaging session. Neuropsychological and neuroimaging testing was then repeated one year following surgery. Here, we report on participants in the healthy control group (normal-BMI, non-psychiatric), bariatric controls (obese, non-psychiatric), and bariatric (obese) MDD patient groups who completed pre-surgical (baseline) neuroimaging sessions.

All bariatric participants were enrolled in the Bariatric Surgery program at St. Joseph's Healthcare Hamilton at the time of recruitment. Full recruitment procedures and

study protocol are outlined in Restivo et al. (submitted, 2015). *Inclusion criteria* for all groups was 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 were required to have a BMI between 18.5 – 24.9 (normal range). *Exclusion Criteria* included 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), 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. In addition, presence of a past or current psychiatric condition was an exclusion criteria for both healthy and bariatric control groups, while having been administered electro-convulsive therapy (ECT) within the last 24 months was an exclusion criteria MDD bariatric patients.

A total of 21 healthy controls, 25 bariatric controls, and 23 MDD bariatric patients consented and enrolled in the study; 20, 20, and 23 participants from these groups (respectively) completed both the neuroimaging and neuropsychological testing portion of the study. The remaining six participants were unable to complete the neuroimaging testing due to feelings of claustrophobia and anxiety during the MRI session. Participants

were age-matched across all three groups. Psychiatric status (current and lifetime history) was evaluated via the Structured Clinician Interview for DSM-IV (SCID). Both depressed and euthymic patients were recruited into the MDD bariatric participant group (34.8% of MDD patients were currently depressed or in partial remission at the time of testing). Additional information regarding MDD illness burden, including illness age of onset and number of episodes, was collected.

Demographical, Medical and Psychiatric Characteristics

*Medical.* Extensive demographical, medical health and psychiatric information was collected for all participants in order to investigate and control for potential confounders. Anthropomorphic data collected included: weight, height, BMI, waist and hip circumferences, average systolic and diastolic blood pressures, a random glucose 'finger prick test' value, lipid profile values, and hemoglobin (Hb)A1c values. Presence of Type II Diabetes (T2D), hypertension, and dyslipidemia was determined by data extraction of patients' medical charts. Obstructive Sleep Apnea (OSA) was determined via the Berlin Sleep Questionnaire (Chung et al., 2008); participants were coded as high-risk or low-risk (participants whose OSA was being currently treated and controlled by a Continuous Positive Airway Pressure ventilator were coded as low-risk). Nutritional intake was assessed via a 3-day dietary record (Food Frequency Questionnaire [FFQ]), with one day being from the weekend; both total daily caloric intake and diet component analyses were completed.

*Demographic*. Age at time of neuropsychological testing, years of education, sex, and ethnicity was collected for each participant. The Cognitive Failure Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parkes, 1982) was used to assay participative feelings of cognitive dysfunction and the Sheehan Disability Scale (SDS) was used to assay participative feelings of impairment across three life domains (Work/School, Social Life, and Family Life/Home Responsibilities) (Sheehan, Harnett-Sheehan, & Raj, 1996).

*Psychiatric.* Mood rating questionnaires on the day of neuroimaging (or within a 2-week period of the a previous study visit) were administered. The Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression-17 (HAMD-17) were used to control for the presence of depressive symptoms, while the Altman Rating Scale for Mania (ARSM) and Young Mania Rating Scale (YMRS) were used to control for mania symptoms.

Task Paradigm and fMRI Examination

We used a fixed block design, word-encoding and recognition paradigm. Participants performed a MRI version of Warrington's Recognition Memory Test (Warrington, 1984) (word subtest only), used to assess material-specific memory deficits in adults. Participants underwent a practice session outside the scanner on the day of MRI testing. A list of practice words was generated by choosing 5-emotionally neutral words that were similar in word familiarity and frequency to 5 word items from the RMT word list. During the encoding task, participants were presented with a 50-item target word list (taken from the original task) and asked to indicate whether their association with the

word was “pleasant” or “unpleasant” by pushing their left or right index finger respectively. Target words were considered emotionally neutral (participant choice is arbitrary). Following completion of the encoding task, participant recognition memory for target words was assessed immediately. During the recognition subtask, participants were presented with a pair of word stimuli; the previously seen encoding target word was paired with a similar distracter word (also taken from the original task). Participants were asked (in a forced-choice paradigm) to indicate whether the encoding target word appeared on the left or right side of the screen by pressing buttons on a response pad with their left or right index finger. Words were randomized to appear on each side 50% of the time. Both tasks are visually depicted in Figure 5.1.

For both subtasks, stimuli were presented at a rate of 3 seconds each in 10-item blocks (activation condition) and alternated with 21-seconds of a rest condition. The rest condition task was a standard condition during which students were asked to fixate on a cross centered in the middle of the viewing screen. In order to meet the requirements of working with a bariatric population, a unique rear-projection system was engineered (GH, MR) at the Imaging Research Centre at St. Joseph’s Healthcare Hamilton. Stimuli were rear projected to a reflective non-magnetic surface angled to appear on a rear-projection screen, which was visible to participants via an angled mirror placed above the head coil. Stimuli were presented using E-Prime software transmitted from a researcher-controlled laptop via fiber optics to the rear projector (Tools, 2012). Words were centered on the screen prior to scan commencement for each participants and presented as black

block letters against a white background. Responses were recorded by E-Prime and exported to SPSS for analysis (IBM, 2013).

Image Acquisition

Scanning was performed on a General Electric 3 Tesla whole-body short-bore scanner with 8 parallel receiver channels (Milwaukee, WI) located at the Imaging Research Centre at St. Joseph's Healthcare Hamilton. For each participant, functional images were collected using a T2* interleaved echo-planar imaging sequence: 41 axial slices, flip angle $60^{o}$, TE = 35 ms, TR = 3000 ms, FOV = 24 cm, matrix frequency = 128, phase = 64; slice thickness = 3 mm, no skip. T2 images were co-registered to images acquired from a T1-weighted anatomical scan (3D-SPGR pulse; IRP sequence; matrix frequency =512 x 512, flip angle $9^{0}$; TE = 1.32 ms; TR = 6.228 ms; TI = 900ms; FOV = 24 cm; 1-mm axial slices, no skip).

Image Preprocessing

Preprocessing (slice-time correction, motion correction, spatial normalization and smoothing) was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) in MATLAB 8.3.0 (Inc., 2012). The first 3 volumes of each subtask were removed as dummy volumes. The 81 volume images of each task were realigned to the first image of the time series and warped to Montreal Neurological Institute (MNI)-space as defined by the SPM 12 T1-template. Following motion correction in SPM, participant head motion was examined manually for movement greater than 3 mm in any axis direction. All

participants were within the 3 mm threshold. Following this, ArtRepair (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software) was run on individual participants to further correct head movement differences across consecutive volumes. Volumes following movement greater than 0.5 from the previous movement were considered artifacts and removed (deweighted) from the dataset. Functional data sets were smoothed using a full-width-half-maximum Guassian filter of 5 mm.

A time-series model was constructed based on alternating periods of activation and rest using and modeling the hemodynamic response. A general linear model approach for time series data was used to identify significantly activated voxels. A contrast matrix testing for signification activation was defined as the encoding condition versus the rest condition and as the retrieval condition versus the rest condition. Within-group t-statistics were calculated as standardized z-scores in projection maps. Threshold for significant activation (uncorrected) was $p<0.001$. In order to identify regions common to all three groups, we conducted a conjunction (conjunction null hypothesis) of the 3 participant groups across activation > rest task conditions. Statistical maps for conjunction activation were FDR corrected.

Statistical Analysis

Demographic and performance data were analyzed with SPSS (IBM, 2013). Functional imaging data were analyzed using Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm/). To assess group differences in demographic, clinical, and behavioural performance variables, data were first tested for normality ($p > 0.05$,

shapiro-wilk) and group comparisons were calculated using independent samples t-tests. Percentage of words coded as pleasant or unpleasant during the encoding subtask was compared across groups. Raw correct number of words remembered in the recognition task was calculated per participant, along with correct percentage of responses (adjusted to represent percentage of responses where participant responded). Response time (corrected to exclude null responses) was calculated for each participant and subtask; response time differences were contrasted across groups using one-way between group ANOVAs.

**Results**

Participant Demographics

Our final sample consisted of 63 participants, 60 of whom fully completed both neuropsychological (cognitive) testing and MRI imaging test sessions, and were age-matched in 3 groups of 20 participants each (healthy controls, bariatric controls, and bariatric MDD patients). Two scans involving bariatric controls were not available for analysis and are not presented here. Groups did not vary in sex or ethnicity. Healthy controls differed significantly in total years of education compared to the MDD bariatric group (but not with respect to the bariatric control group). However, no differences in FSIQ were found between these two groups. Medical characteristics (such as BMI and comorbidity diagnosis) and nutritional intake did not differ significantly between bariatric MDD and bariatric control participants (medical characteristics and nutritional intake are summarized for all three participant groups in Table 5.1 and Table 5.3 respectively).

Group differences were seen in subjective ratings of overall disability/impairment (as rated by the SDS measure), and cognitive impairment (as rated by the CFQ), with the MDD bariatric group reporting the highest level of impairment on both measures. Scores on the self-reported BDI indicated an overall level of mild depression in the bariatric MDD group (M=17.2[10.1]); BDI scores differed significantly across groups ($F[2,59]=18.09$, $p<0.001$). In addition, a Tukey-Kramer post-hoc analysis indicated that the bariatric control group had a significantly higher ($p=0.01$) BDI score (M=9.3[9.2]) than healthy controls (M=1.7[4.4]); however, this score still fell below the scale threshold for clinical depression. Approximately one-third of the MDD bariatric group met criteria for current or partially remitted MDD (according to DSM-IV criteria) at the time of testing. As such, BDI and HAMD scores at the time of testing was entered in an exploratory ANOVA analysis as independent variables, with behavioural measure outcomes as dependent variables (see below).

Behavioural Data Analysis

*Encoding.* Differences across groups in reaction time (correcting for null trials) were examined using between-group ANOVAs; no significant differences were found ($F[2,61]=.29$, $p=0.74$). Exploratory analyses were performed in order to evaluate if group membership was associated with differences in the amount of words rated pleasant versus unpleasant; a significant group effect was found ($F[2,61]=3.45$, $p=0.04$). Interestingly, post-hoc analyses using the Tukey-HSD test indicated that the bariatric control (but not bariatric MDD) group showed significant differences ($p=0.03$) in the percentage of

words coded as pleasant (M=58.1% [13.1]) as compared to healthy controls (M=67.9%[11.4]). Percentage of words coded as unpleasant did not significantly correlate with HAMD or BDI scores.

*Recognition.* Once again, after correcting for null trials, no significant differences between groups were seen in reaction time [$F(2,61)=0.88$, $p = 0.41$)]. Separate analyses were performed for accuracy on words previously encoded as pleasant, accuracy on words previously encoded as unpleasant, and overall word recognition accuracy. Raw scores were converted to percentage correct and adjusted to exclude null trials. When including lack of response as incorrect, a significant group difference was seen on memory retrieval performance [$F(2,61)=3.32$, $p=0.04$]. However, when adjusted to exclude null trials, group differences on total word recognition were no longer significant [$F(2,61)=1.41$, $p=0.25$]. No group differences emerged when correct responses coded previously as pleasant versus unpleasant were examined. BDI and HAMD scores were not associated with total correct word recognition trials (regardless of whether null trials were included). Behavioural data on both tasks is summarized in Table 5.3.

fMRI Analysis: Encoding

Whole-brain conjunction analysis was performed using all three participant groups, and creating z-score spatial maps, in order to investigate regions commonly activated across groups. Using FDR correction, the greatest conjunction analysis activation (group and encoding > rest contrasts) occurred in the inferior frontal (IFG) and medial frontal gyri (MFG) (see Figure 5.2). Activation was also seen in the posterior

cingulate, cuneus, thalamus and lingual gyrus. Regions of significant activation amongst the three groups during the encoding > rest contrast are summarized in Table 5.5. Differences in regional activations were further explored via 2-group t-contrasts (BC > HC, and MDD > BC) (results are shown in Table 5.6 and Table 5.7). Although overlapping several regions were activated in both t-contrasts, the BC > HC contrast yielded activation largely centered in the middle and superior temporal gyrus (STG). This pattern differed from what was seen in the MDD > BC contrast, which indicated activation in areas of the precuneus (not seen in the BC > HC contrast) and cingulate gyrus. Activations in the middle temporal gyrus, insula, and lingual gyrus were also seen in both contrasts.

fMRI Analysis: Retrieval

Whole-brain conjunction analysis was once again performed using all three study groups in order to investigate regions commonly activated across groups during the retrieval > rest contrast. After applying FDR correction, the greatest number of regional activations was once again seen in the medial frontal gyrus (Figure 5.3). Additional activations were seen in the IFG, thalamus, precuneus, posterior cingulate, middle temporal gyus, cuneus, and cingulate gyrus (see Table 5.8). BC > HC and MDD > BC contrasts comparing retrieval > rest conditions between groups was also conducted. Although numerous regions of activation were yielded by the BC > HC contrast (listed in Table 5.9), only 2 regions of activation were identified in the MDD > BC contrast (the

MFG [MNI coordinates: -38, 26, 24, T = 4.54, p(unc) <0.001) and SFG [MNI coordinates: -6, 18, 52, T=3.64, p(unc)<0.001).

**Discussion**

The primary finding from our current study was that obesity, and obesity in conjunction with MDD, were associated with uniquely different neural activation patterns compared to healthy participants. Moreover, the presence of common comorbidities, namely hypertension, T2D, hyperlipidemia and OSA, were not significant different across the two bariatric groups and thus were unlikely to be driving the group differences between these two groups. The use of both 3-group conjunction analyses and separate pair t-contrast analyses allowed us to identify areas commonly activated across all three groups, while investigating differences in regional activation as well.

During encoding, all three groups showed strong FDR corrected conjunction activations in areas known to be involved in language processing and working memory (IFG), as well as the posterior cingulate (an area important in emotion and memory), indicating the task succeeded in showing activation of encoding and emotional processing of word stimuli by participants. An fMRI adapted version of the Warrington's RMT has only previously been employed in a study of schizophrenic patients and healthy controls (Hofer et al., 2003). Similar to the areas found activated in the present study, Hofer et al. (2003) found that the task resulted in activations seen in Brodmann areas 6, 9, 18, 22 and 47 during word encoding. However, Hofer et al. (2003) also reported activations seen in Brodmann areas 32 (left anterior cingulate), 39 (left angular gyrus), 44 (prefrontal cortex)

and 45 (left frontal gyrus). Although these specific Brodmann areas were not activated in our various encoding analyses, similar regional activations were seen (including the prefrontal, inferior frontal gyrus and anterior cingulate). Differences in scanning parameters (differences in scanning protocol and Tesla strength were present), paradigm details (both studies created independent adaptations of the neuropsychological standard version of the RMT), and study populations investigated (Hofer et al. investigated healthy controls and schizophrenic patients) may have partially contributed to this.

Differences emerged in patterns of regional activation when comparing the BC > HC and MDD > BC t-contrast activation differences. The BC > HC contrast indicated a pattern of activation focused on regions in the temporal gyrus (MTG and STG), regions known to play an important role in memory formation (Squire & Zola-Morgan, 1991). The increased BOLD response seen in these temporal areas in obese (bariatric) patients compared to healthy BMI individuals during memory encoding may be indicative of neural compensation mechanism needed to maintain task performance relative to healthy controls. This is supported by several studies that have reported that increased BOLD response in temporal regions is employed to ameliorate neural efficiency declines seen as a consequence of aging (Cabeza, Anderson, Locantore, & McIntosh, 2002; Rypma & D'Esposito, 2000).

Interestingly however, a differing pattern of regional activation was seen when contrasting bariatric MDD patients to bariatric controls during encoding. This contrast instead indicated that MDD bariatric participants relied on greater engagement of the

precuneus and cingulate gyrus (both structures include Brodmann Area 31, located in the posterior cingulate cortex). Precuneus connections are widespread and involve higher association cortical and subcortical structures, important in the integration of external and self-generated information and higher-order cognitive functions (Cavanna & Trimble, 2006). Moreover, the precuneus (in conjunction with the cingulate and prefrontal cortices) has long been associated with involvement in episodic memory retrieval tasks, including word retrieval (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Sajonz et al., 2010;). It may be that MDD bariatric patients are engaging further compensatory systems, involving the precuneus and cingulate gyrus, as compared to bariatric controls. Increased size of the posterior dorsal cingulate cortex (which showed increased activation in the MDD > BC contrast) has been negatively correlated with verbal memory capacity (Kozlovskiy, Vartanov, Nikonova, Pyasik, & Velichkovsky, 2012), a finding that may contribute to the diminished performance of MDD patients often seen on verbal memory tasks (Bora, Harrison, Yücel, & Pantelis, 2013; Grassi-Oliveira, Bauer, Pezzi, Teixeira, & Brietzke, 2011). However, our study did not find a behavioural difference on verbal memory task performance. Given that all three study groups performed well on this measure, the expected difference between group performance may have been obscured due to a ceiling effect. Moreover, compensatory engagement of the preuneus and cingulate gyrus may have allowed bariatric MDD patients to achieve the same behavioural results as bariatric control patients, at the expense of increased neural energy.

When investigating retrieval memory processes during our word recognition task, all three groups exhibited engagement of the dorsolateral prefrontal cortex, an area known

to be important in working memory and executive function (Kane & Engle, 2002).This area was also activated in Hofer et al.'s (2003) study using the same RMT task paradigm. When comparing paired group differences (t-contrasts) once again, a large number of regions showed increased activation in bariatric controls as compared to healthy controls. The precuneus and posterior cingulate cortex were once again amongst regions of increased activation. These regions were not previously shown to be activated in Hofer et al.'s (2003) study and may be associated with distinct neural activation patterns in bariatric populations. This difference in activation seen due to obese status is supported by recent study in brain metabolism changes following bariatric surgery by Marques et al. (2014). Investigators found that middle-aged women (with a mean BMI of 50.1 $kg/m^2$ ) exhibited increased cerebral metabolism in the posterior cingulate gyrus when compared to women with a healthy BMI. Similar to our study's lack of behavioural results, no difference in neuropsychological test performance was found however, lending further support that increased metabolic activity in this region could be perhaps indicative of a neural compensatory mechanism.

When looking at differences in activation between the bariatric MDD and bariatric control groups during retrieval, little difference was seen, with only 2 sites of increased activation exhibited (MFG & SFG). These brain regions were also activated in both the 3-group conjunction analysis and BC > HC contrast, indicating MDD patients are not recruiting additional neural structures but rather may require increased (compensatory) activation in memory and language processing regions.

Support for the functional differences we have demonstrated is found in both recent structural and functional MRI investigations of obese populations. Growing research indicates that obesity may be associated with structural brain changes that may contribute to the diminished cognitive performance associated with obesity (Gustafson et al., 2004; Pannacciulli et al., 2006). Taki et al. (2008), found that smaller regional volumes were related to higher BMI in the frontal, temporal, and parietal cortices, cerebellum and midbrain in a study of 1 428 individuals (aged 12 – 81). However, differences were found in males only (not females), indicating that obesity may be differentially affected by gender. Although we recruited both males and females, our study sample was predominantly female (92.1%). In support of our results, a study by Walther et al. (2010) in older females found that increased BMI was associated with decreased volumes of gray matter in frontal and temporal regions, as well as the right cerebellar region. Increased BMI was also associated with increased white matter volume in frontal, temporal and parietal lobes. Interestingly, gray and white matter volumes predicted performance on measures of memory (Logical Memory I, Verbal Paired Associates I, and Face Recognition I tasks) and processing speed (Trails A), despite the absence of significant groups differences in cognitive performance. Moreover, recent research by Opel et al. (2015) also supports the hypothesis that obesity is associated with neural alterations in several of the areas implicated in our functional results. One hundred and forty-four MDD patients and 141 healthy controls underwent a structural MRI (analyzed using voxel-based morphometry). Volume reductions in the medial prefrontal

cortex, orbitofrontal cortex, caudate nucleus and thalamus were associated with increased BMI in both MDD patients and healthy controls.

With regards to fMRI investigations involving bariatric populations, previous studies have largely focused on appetite regulation and reward systems in bariatric populations (Carnell et al., 2012). Studies in this area have supported our finding for potential neural irregularities in the areas of the prefrontal cortex and cingulate cortex in bariatric patients (Carnell et al., 2012; Wang et al., 2011). These cortices are thought to be important during tasks involving cognitive control and attention and have shown regional activation differences (as compared to healthy controls) during tasks involving food stimuli and dietary restraint. In particular, obese (versus normal weight) women exhibited increased activation in the medial prefrontal cortex and cingulate cortex in response to pictures of high-calorie foods versus low-calorie or non-foods (e.g. cars) following an 8 – 9 hour fast in a study by Stoeckel et al. (2008). Moreover, Del Parigi et al. (2007) found that a higher score on the three factor eating questionnaire dietary restraint score in women who had successfully reduced their BMI from a minimum of 35 (obese) to 25 (normal weight) was associated with increased activation in the dorsolateral prefrontal cortext (a region shown to be differentially activated in our bariatric study groups as well). Irregularities in dorsolateral prefrontal cortex activations may underlie issues of both dietary and cognitive restraint, as well as contribute to the control and attention processes relevant in memory encoding and retrieval of selected stimuli.

Taking our results together, we have provided support that the effect of obesity may be associated with different neural patterns of activation during both encoding and retrieval processes. Moreover, the addition of a common psychiatric morbidity in obese populations, MDD, may be associated with additional and distinct neural activation changes during memory processing in obese individuals. These changes may represent a neural compensation mechanism, allowing subtle cognitive impairment to go undetected by traditional neuropsychological measures. Further work is required to investigate the potential mechanisms contributing to these changes. For instance, it is possible that neural differences seen in our study may be partially due to elevated pro-inflammatory states associated with both obesity and MDD (Bai, 2014; Capuron, Su, Miller, et al., 2008). Future MRI studies investigating the association between inflammatory markers associated with both obesity and MDD, such as C-reactive protein, cognitive performance and mood may help address this.

There are limitations to our study to be considered. Although differences in emotional interpretation of encoding words were examined for group differences, we were not able to investigate whether differences in emotional valence processing was associated with different neural activations due to use of a fixed block design, rather than an event related, paradigm. However, when compared, no significant differences in coding of words as pleasant versus unpleasant emerged across groups, suggesting emotional coding was not a significant covariate in predicting activation. Further, all three groups performed quite well on the retrieval memory task. This may have resulted in a ceiling effect, obscuring differences between group performance. The advantage

however, is that we know that differences in task difficulty experienced by the three groups are not driving our results.

Certain limiting aspects of our study design must also be considered when drawing conclusions about the results presented. First, our study is cross-sectional, and as such, cannot speak to the causality between the associations seen between obesity, depression, and neural activation patterns. Moreoever, differences seen in neural activations when examining BC > HC and MDD > BC contrasts did not remain statistically significant once FDR corrected. Results should be interpreted as preliminary and would benefit by replication with a larger sample size. Lastly, the absence of a MDD normal weight group does not allow us to draw conclusions regarding the independent effects of MDD and obesity (along with their potential interactions) on cognition.

Future studies should focus on longitudinal changes in BMI and neural systems. Studies reporting associations between cognitive performance prior to and following a significant weight loss, or weight gain over the life span, would help determine the underlying mechanisms driving the cognitive impairment often seen in obese populations. As well, the metabolic ramifications of certain psychotropic medications and implementation of a weight monitoring system in the treatment of MDD should be considered by healthcare professionals. The cognitive impairment associated with MDD and obesity may be distinct, but additive, leading to overall increased impairment and reduced functional ability in psychiatric populations.

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**Conflict of Interest**

The authors declare no competing interests in the writing of this manuscript. The study sponsors plays no role in study design, data collection, data analysis, data interpretation or report writing.

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Table 5.1. Study Sample Characteristics

| | Healthy Controls (HC) (n=20) | Bariatric Controls (BC) (n=20) | MDD Bariatrics (MDD) (n=23) |
|---|---|---|---|
| Age (Mean, SD) | 43.8 (11.0) | 43.9 (10.7) | 42.6 (11.0) |
| Sex (Male:Female) | 2:18 | 1:19 | 2:21 |
| Years of Education$^{+}$ | 16.1 (2.3) | 14.5 (2.2) | 14.1 (2.3) |
| Ethnicity (Caucasian %) | 85.0 | 93.8 | 78.9 |
| Marital Status | | | |
| Married/Common-Law | 80.0 | 88.0 | 57.9 |
| Divorced/Separated/Widowed | 0.0 | 11.1 | 26.3 |
| Single | 20.0 | 0.0 | 15.8 |
| | | | |
| BMI | 22.4 (2.0) | 44.7 (3.2) | 43.8 (4.7) |
| Weight (kg) | 60.3 (7.1) | 121.5 (11.5) | 116.6 (15.1) |
| Height (cm) | 164.0 (8.3) | 165.2 (4.2) | 163.0 (6.5) |
| Waist Circumference (cm) | 74.6 (5.2) | 121.4 (10.1) | 124.9 (11.8) |
| Hip Circumference (cm) | 97.7 (5.8) | 140.3 (8.4) | 134.4 (11.6) |
| Hypertension* (%) | 0.0 | 40.0 | 39.1 |
| Average Systolic BP** (mmHg) | 119.8 (9.3) | 135.6 (16.1) | 133.6 (12.3) |
| Average Diastolic BP** (mmHg) | 74.6 (16.2) | 78.4 (6.7) | 76.2 (11.7) |
| Average Heart rate** | 73.4 (12.8) | 83.4 (12.3) | 80.3 (10.2) |
| TDII (%)*** | 0.0 | 25.0 | 22.7 |
| Ha1bc | n/a | 0.060 | 0.059 |
| Random Glucose Test | 5.8 (1.6) | 5.9 (2.6) | 5.2 (0.8) |
| Hyperlipidemia**** | 0.0 | 25.0 | 36.4 |
| Total Cholesterol | n/a | 4.55 (0.95) | 4.81 (0.95) |
| HDL | n/a | 1.32 (0.3) | 1.18 (0.30) |
| LDL | n/a | 2.61 (0.69) | 2.96 (0.87) |
| Triglycerides | n/a | 1.39 (0.80) | 1.60 (0.60) |
| OSA Risk (%High Risk) | 0.0 | 45.0 | 69.6 |
| FSIQ (WASI) | 112.2 (13.4) | 107.9(11.7) | 104.8 (12.1) |

*Borderline hypertension was collapsed into the hypertension group
**Two independent measures, 1 minute apart were obtained
***Borderline, well-controlled, and sub-optimally controlled TDII status were collapsed
****Elevated lipid value status was also included as hyperdyslipidemia
$^{+}$Significant group difference ($p < 0.05$)

Table 5.2. Clinical Characteristics of Study Sample

| | HC (n=20) | BC (n=20) | MDD (n=23) |
|---|---|---|---|
| HAM-D*+ | 1.6 (2.9) | 1.6 (1.9) | 6.7 (4.2) |
| BDI*+ | 1.9 (5.6) | 9.3 (9.2) | 17.2 (10.1) |
| YMRS*+ | 0.6 (0.9) | 0.5 (0.7) | 2.5 (2.5) |
| ASRM | 1.6 (2.6) | 4.2 (3.5) | 2.4 (2.5) |
| Anxiety Comorbidities – Past/Present (%) | n/a | n/a | 47.2 |
| Binge Eating Disorder - Past (%) | 0 | 10.0 | 21.8 |
| Age of Onset (MDD) (years) | n/a | n/a | 21.9 (7.8) |
| Number of MDD Episodes | | | 6.0 (4.7) |
| | | | |
| CTQ | | | |
| Total | 33.1 (14.9) | 33.1 (18.3) | 41.1 (27.8) |
| Emotional Abuse | 7.5 (4.7) | 8.3 (4.5) | 11.0 (7.3) |
| Physical Abuse | 6.1 (2.7) | 6.1 (2.4) | 7.2 (5.4) |
| Sexual Abuse | 5.0 (0.0) | 6.3 (3.8) | 6.9 (5.8) |
| Emotional Neglect | 8.8 (5.2) | 11.0 (4.9) | 10.5 (6.7) |
| Physical Neglect | 7.5 (3.1) | 7.2 (2.6) | 7.7 (4.6) |
| | | | |
| SDS (Averaged Across Domains)* + | 0.0 (0.1) | 3.0 (2.8) | 4.8 (2.7) |
| CFQ Total*+ | 22.9 (10.6) | 26.1 (6.5) | 39.1 (19.8) |

*significant group effect ($p < 0.01$)

+significant group effect ($p < 0.05$) between Bariatric Controls and MDD Bariatrics

Table 5.3. Nutritional Intake and Diet Component Analysis of the study sample

| | HC (n=20) | BC (n=20) | MDD Bariatrics (n=21) |
|---|---|---|---|
| Average Daily Caloric Intake (Kcal) | 2205.8 (655.0) | 2040.5 (565.3) | 2005.8 (516.0) |
| Protein (Kcal %) | 17.8 (3.8) | 17.2 (20.9) | 16.2 (2.8) |
| Carbohydrate (Kcal %) | 47.0 (8.2) | 45.8 (7.9) | 46.4 (6.9) |
| Fat (Kcal %) | 32.5 (6.5) | 36.6 (6.9) | |
| Total Fat (g) | 81.8 (28.8) | 83.3 (25.0) | 81.3 (24.9) |
| Total Sugar (g) | 98.6 (41.3) | 77.9 (40.5) | 82.2 (36.4) |

Table 5.4. Behavioural Data for the RMT fMRI task

| | HC (n=20) | BC (n=20) | MDD (n=23) |
|---|---|---|---|
| *Reaction Time* | | | |
| Encoding (ms) | 1316.4 (255.6) | 1275.0 (226.0) | 1264.2 (207.5) |
| Retrieval (ms) | 1398.5 (196.5) | 1506.4 (208.8) | 1415.2 (272.9) |
| | | | |
| *Encoding Task* | | | |
| % Encoded as Pleasant | 67.9 (11.4) | 58.1 (13.1) | 62.5 (10.9) |
| % Encoded as Unpleasant | 31.5 (11.1) | 40.8 (13.1) | 37.2 (10.9) |
| | | | |
| Retrieval Task | | | |
| Total Correct (%)* | 83.5 (5.8) | 76.1 (10.4) | 78.7 (10.6) |
| Total Correct Adjusted (%) | 92.3 (4.5) | 87.8 (11.9) | 88.9 (8.7) |
| Pleasant Words Correct (%) | 82.5 (8.2) | 75.5 (10.5) | 78.0 (11.1) |
| Unpleasant Words Correct (%) | 84.4 (12.4) | 78.7 (17.7) | 80.4 (13.8) |

*Significant group effect (p=0.043)

Table 5.5. Main effect of encoding versus rest condition across groups (conjunction null hypothesis, $p < 0.05$, FDR whole brain corrected)

| | | | MNI Coordinates | | | | | |
|---|---|---|---|---|---|---|---|---|
| Regions | Side | BA | x | y | z | F | Z | $p_{(FDR\ corr.)}$ |
| Inferior Frontal Gyrus | L | 47 | -42 | 18 | -10 | 39.68 | 5.32 | 0.004 |
| Inferior Frontal Gyrus | L | 9 | -50 | 10 | 22 | 39 | 5.28 | 0.005 |
| Medial Frontal Gyrus | L | 6 | -2 | 8 | 50 | 46.44 | 5.66 | 0.002 |
| Medial Frontal Gyrus | L | 6 | -2 | 2 | 60 | 45.18 | 5.6 | 0.002 |
| Medial Frontal Gyrus | L | 6 | -8 | 14 | 54 | 36.34 | 5.13 | 0.006 |
| Lingual Gyrus | R | 18 | 18 | -90 | -12 | 43.17 | 5.5 | 0.003 |
| Posterior Cingulate | R | 31 | 10 | -54 | 30 | 37.02 | 5.17 | 0.006 |
| Posterior Cingulate | R | 23 | 12 | -46 | 28 | 35.32 | 5.07 | 0.007 |
| Cuneus | L | 30 | -10 | -70 | 18 | 33.35 | 4.95 | 0.009 |
| Thalamus (Ventral Lateral Nucleus) | L | | -12 | -8 | 12 | 26.38 | 4.48 | 0.035 |

Table 5.6. Between-Group (BC > HC) Comparisons of the encoding > rest condition ($p<0.001$ uncorrected)

| | | | MNI Coordinates | | | | |
|---|---|---|---|---|---|---|---|
| Regions | Side | BA | x | y | z | T | Z |
| Caudate (Tail) | L | | -14 | -30 | 26 | 4.74 | 4.15 |
| Middle Temporal Gyrus | L | 22 | -56 | -40 | -2 | 4.4 | 3.91 |
| Precentral Gyrus | L | 6 | -44 | 4 | 46 | 4.31 | 3.84 |
| Cuneus | R | 23 | 10 | -74 | 16 | 4.3 | 3.84 |
| Lingual Gyrus | R | 19 | 18 | -68 | 8 | 3.72 | 3.4 |
| Superior Temporal Gyrus | R | 22 | 54 | -8 | -6 | 4.28 | 3.82 |
| Medial Frontal Gyrus | L | 6 | -4 | 12 | 50 | 4.15 | 3.73 |
| Lingual Gyrus | R | 18 | 28 | -58 | 2 | 4.15 | 3.73 |
| Superior Temporal Gyrus | L | 21 | -52 | -24 | -2 | 4.14 | 3.72 |
| Superior Temporal Gyrus | L | | -52 | -16 | -4 | 4.06 | 3.66 |
| Anterior Cingulate | L | 24 | -2 | 26 | 20 | 4.07 | 3.67 |
| Insula | R | 13 | 48 | -20 | -2 | 3.99 | 3.61 |
| Thalamus | L | | -12 | -8 | 16 | 3.98 | 3.6 |
| Anterior Cingulate | R | 33 | 6 | 22 | 12 | 3.94 | 3.57 |
| Caudate (Body) | R | | 12 | 2 | 14 | 3.91 | 3.55 |
| Insula | L | 13 | -34 | -30 | 18 | 3.89 | 3.53 |
| Lingual Gyrus | L | 19 | -20 | -64 | 4 | 3.88 | 3.52 |
| Lentiform Nucleus (Putamen) | L | | -28 | -6 | -6 | 3.79 | 3.45 |
| Medial Frontal Gyrus | R | 6 | 6 | 8 | 60 | 3.75 | 3.43 |
| Caudate (Body) | L | | -22 | 14 | 14 | 3.74 | 3.41 |
| Caudate (Body) | L | | -20 | -8 | 20 | 3.61 | 3.31 |
| Lentiform Nucleus (Putamen) | R | | 32 | 2 | -4 | 3.59 | 3.3 |

Table 5.7. Between-Group (MDD > BC) Comparisons of the encoding > rest condition ($p < 0.001$ uncorrected)

| | | | MNI Coordinates | | | | |
|---|---|---|---|---|---|---|---|
| Regions | Side | BA | x | y | z | T | Z |
| Precentral Gyrus | R | 6 | 40 | -8 | 36 | 4.86 | 4.23 |
| Cingulate Gyrus | L | 31 | 2 | -22 | 40 | 4.72 | 4.14 |
| Precuneus | L | 7 | -2 | -54 | 58 | 4.43 | 3.93 |
| Precuneus | L | 31 | -4 | -66 | 28 | 4.41 | 3.92 |
| Precuneus | L | 31 | -12 | -68 | 30 | 4.08 | 3.67 |
| Cingulate Gyrus | L | 31 | -10 | -34 | 40 | 4.38 | 3.89 |
| Cingulate Gyrus | R | 31 | 10 | -34 | 42 | 4.38 | 3.89 |
| Cingulate Gyrus | R | 31 | 18 | -30 | 38 | 4.11 | 3.7 |
| Medial Frontal Gyrus | L | 8 | -14 | 32 | 44 | 4.33 | 3.86 |
| Lingual Gyrus | R | 18 | 30 | -82 | -4 | 4.18 | 3.75 |
| Cingulate Gyrus | R | 23 | 4 | -22 | 28 | 4.14 | 3.72 |
| Superior Temporal Gyrus | L | 22 | -50 | -24 | -14 | 4.13 | 3.71 |
| Cingulate Gyrus | L | 24 | -16 | 8 | 46 | 4.08 | 3.67 |
| Precuneus | L | 31 | -10 | -48 | 38 | 4.05 | 3.65 |
| Insula | L | 13 | -40 | 0 | 18 | 3.99 | 3.6 |
| Insula | L | 13 | -36 | -4 | 24 | 3.87 | 3.52 |
| Precentral Gyrus | L | 6 | -42 | -8 | 30 | 3.94 | 3.57 |
| Postcentral Gyrus | R | 3 | 34 | -28 | 58 | 3.92 | 3.55 |
| Precuneus | L | 7 | -6 | -44 | 56 | 3.87 | 3.52 |
| Precuneus | L | 7 | -8 | -52 | 62 | 3.85 | 3.5 |

Table 5.8. Main effect of retrieval versus rest condition across groups (conjunction null hypothesis, $p < 0.05$, FDR whole brain corrected).

| | | | MNI Coordinates | | | | | |
|---|---|---|---|---|---|---|---|---|
| Regions | Side | BA | x | y | z | F | Z | $p_{(FDR\ corr.)}$ |
| Medial Frontal Gyrus | R | 6 | 6 | 20 | 42 | 40.3 | 5.36 | 0.006 |
| Inferior Frontal Gyrus | L | 9 | -44 | 12 | 26 | 44.44 | 5.58 | 0.004 |
| Middle Frontal Gyrus | L | 9 | -38 | 18 | 24 | 36.82 | 5.17 | 0.009 |
| Precentral Gyrus | L | 6 | -46 | 2 | 32 | 30.65 | 4.79 | 0.023 |
| Thalamus (Ventral Lateral Nucleus) | L | | -14 | -8 | 12 | 40.65 | 5.38 | 0.006 |
| Thalamus (Mammillary Body) | L | | -12 | -18 | 4 | 33.86 | 4.99 | 0.014 |
| Precuneus | L | 7 | -28 | -66 | 38 | 33.04 | 4.94 | 0.015 |
| Middle Temporal Gyrus | L | 39 | -28 | -58 | 36 | 29.78 | 4.73 | 0.028 |
| Posterior Cingulate | L | 30 | -28 | -74 | 20 | 28.62 | 4.65 | 0.034 |
| Medial Frontal Gyrus | L | 9 | -4 | 56 | 8 | 32.04 | 4.88 | 0.018 |
| Medial Frontal Gyrus | L | 9 | 2 | 60 | 14 | 29.26 | 4.69 | 0.031 |
| Medial Frontal Gyrus | L | 10 | 0 | 56 | 0 | 25.08 | 4.38 | 0.06 |
| Cuneus | R | 18 | 30 | -70 | 22 | 30.66 | 4.79 | 0.023 |
| Precuneus | R | 7 | 30 | -66 | 32 | 25.17 | 4.39 | 0.06 |
| Thalamus (Ventral Anterior Nucleus) | R | | 14 | -4 | 10 | 27.61 | 4.57 | 0.038 |
| Precuneus | L | 31 | -6 | -60 | 24 | 26.78 | 4.51 | 0.044 |
| Posterior Cingulate | R | 23 | 8 | -54 | 24 | 26.59 | 4.5 | 0.045 |
| Cingulate Gyrus | L | 31 | -4 | -38 | 40 | 26.27 | 4.48 | 0.049 |

Table 5.9. Between-Group (BC > HC) Comparisons of the retrieval > rest condition ($p<0.001$ uncorrected)

| | | | MNI Coordinates | | | | |
|---|---|---|---|---|---|---|---|
| Regions | Side | BA | x | y | z | T | Z |
| Superior Parietal Lobule | R | 7 | 34 | -56 | 48 | 5.03 | 4.34 |
| Superior Parietal Lobule | R | 7 | 26 | -62 | 48 | 3.79 | 3.44 |
| Middle Frontal Gyrus | R | 6 | 44 | 8 | 40 | 4.88 | 4.23 |
| Precentral Gyrus | R | 9 | 46 | 14 | 30 | 4.32 | 3.84 |
| Precentral Gyrus | L | 6 | -44 | 2 | 42 | 4.74 | 4.13 |
| Posterior Cingulate | R | 29 | 20 | -48 | 12 | 4.72 | 4.13 |
| Thalamus (Pulvinar) | R | | 28 | -30 | 4 | 4.66 | 4.08 |
| Inferior Parietal Lobule | R | 40 | 38 | -42 | 44 | 4.63 | 4.06 |
| Thalamus (Pulvinar) | R | | 18 | -24 | 16 | 4.24 | 3.79 |
| Superior Parietal Lobule | L | 7 | -24 | -54 | 46 | 4.23 | 3.78 |
| Inferior Parietal Lobule | L | 40 | -36 | -54 | 48 | 3.83 | 3.47 |
| Parahippocampal Gyrus | R | 30 | 16 | -36 | -4 | 4.2 | 3.75 |
| Precuneus | L | 7 | -14 | -64 | 50 | 4.16 | 3.73 |
| Superior Parietal Lobule | L | 7 | -22 | -64 | 52 | 4.03 | 3.63 |
| Thalamus | R | | 8 | -22 | 10 | 4.14 | 3.71 |
| Thalamus | L | | 2 | -28 | 10 | 3.86 | 3.5 |
| Cingulate Gyrus | R | 31 | 20 | -32 | 30 | 4.12 | 3.7 |
| Fusiform Gyrus | R | 37 | 40 | -52 | -12 | 4.02 | 3.62 |
| Precuneus | R | 31 | 16 | -58 | 34 | 4.01 | 3.61 |
| Thalamus (Pulvinar) | L | | -18 | -26 | 18 | 4.01 | 3.61 |
| Superior Temporal Gyrus | R | 41 | 50 | -34 | 8 | 3.86 | 3.5 |
| Thalamus | R | | 24 | -14 | 2 | 3.8 | 3.45 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Thalamus (Medial Dorsal Nucleus) | L | | -8 | -16 | 8 | 3.75 | 3.41 |
| Insula | R | 13 | 44 | -26 | 2 | 3.74 | 3.41 |
| Thalamus | R | | 26 | -14 | 12 | 3.71 | 3.38 |
| Anterior Cingulate | L | 24 | -8 | 36 | 12 | 3.69 | 3.37 |
| Caudate (Body) | R | | 14 | -10 | 20 | 3.63 | 3.32 |
| Thalamus (Pulvinar) | L | | -26 | -26 | 6 | 3.59 | 3.29 |

Table 5.10. Between-Group (MDD > BC) Comparisons of the retrieval > rest condition ($p<0.001$ uncorrected)

| | | | MNI Coordinates | | | | |
|---|---|---|---|---|---|---|---|
| Regions | Side | BA | x | y | z | T | Z |
| Middle Frontal Gyrus | L | 9 | -38 | 26 | 24 | 4.54 | 4.04 |
| Superior Frontal Gyrus | L | 6 | -6 | 18 | 52 | 3.64 | 3.35 |

Figure 5.1a. Visual depiction of RMT Encoding task presentation

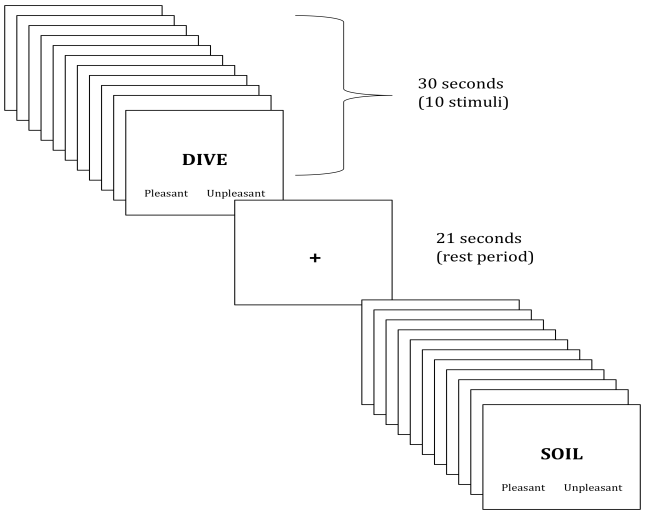



Figure 5.1b. Visual depiction of RMT Recognition task presentation

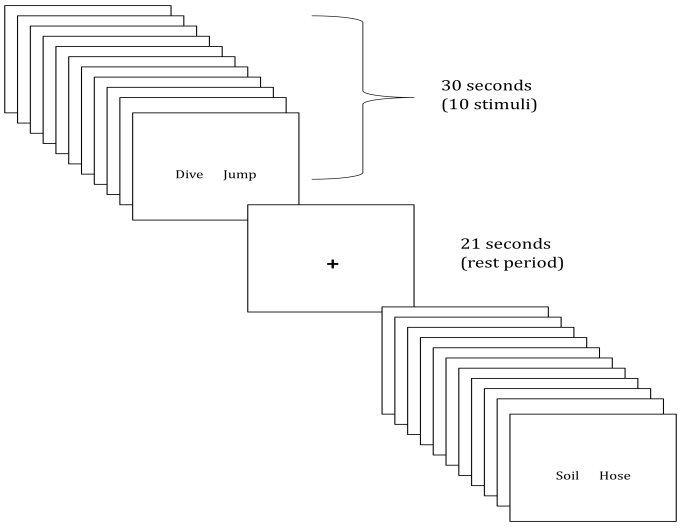


Figure 5.2. Group effect of diagnosis on encoding > rest contrast at the inferior frontal gyrus (MNI coordinates = -50, 10, 22), F = 39, $p_{(FRD\ corr.)} = 0.005$

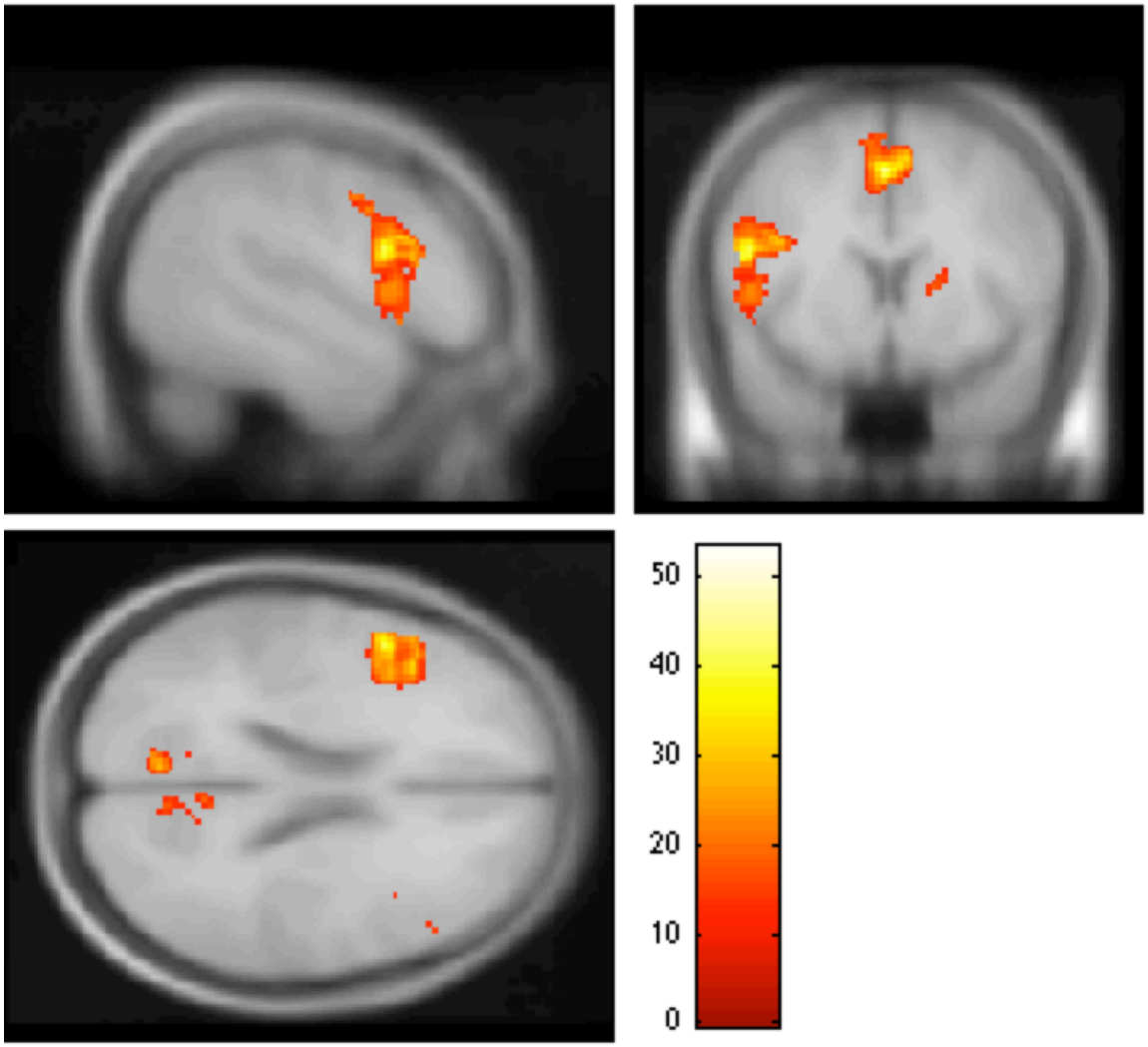


Figure 5.3. Paired group comparison of encoding > rest activation. BC > HC: [-56, -40, -2], T=4.17, p<0.001 uncorrected

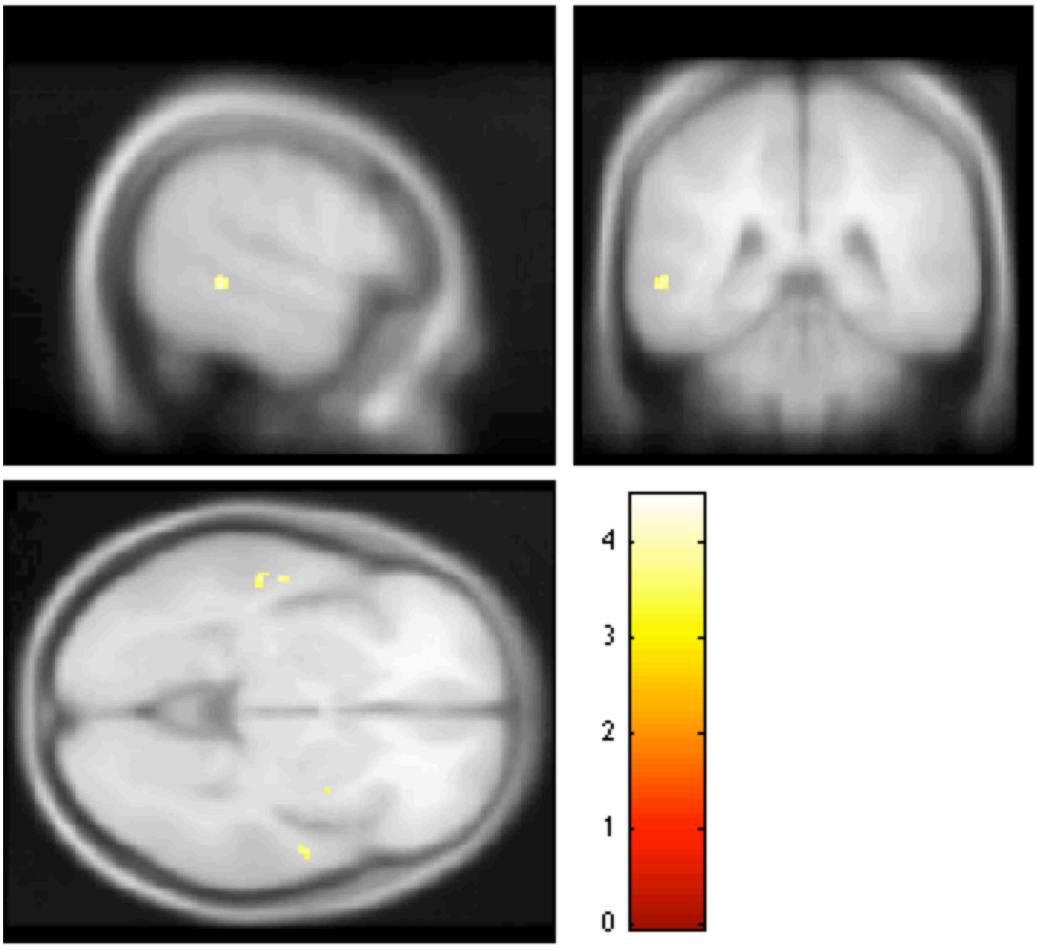


Figure 5.4. Group effect of diagnosis on retrieval > rest contrast at the inferior frontal gyrus (IFG) (MNI coordinates = 39, -28, -58), $p_{(FDR\ corr.)} = 0.005$

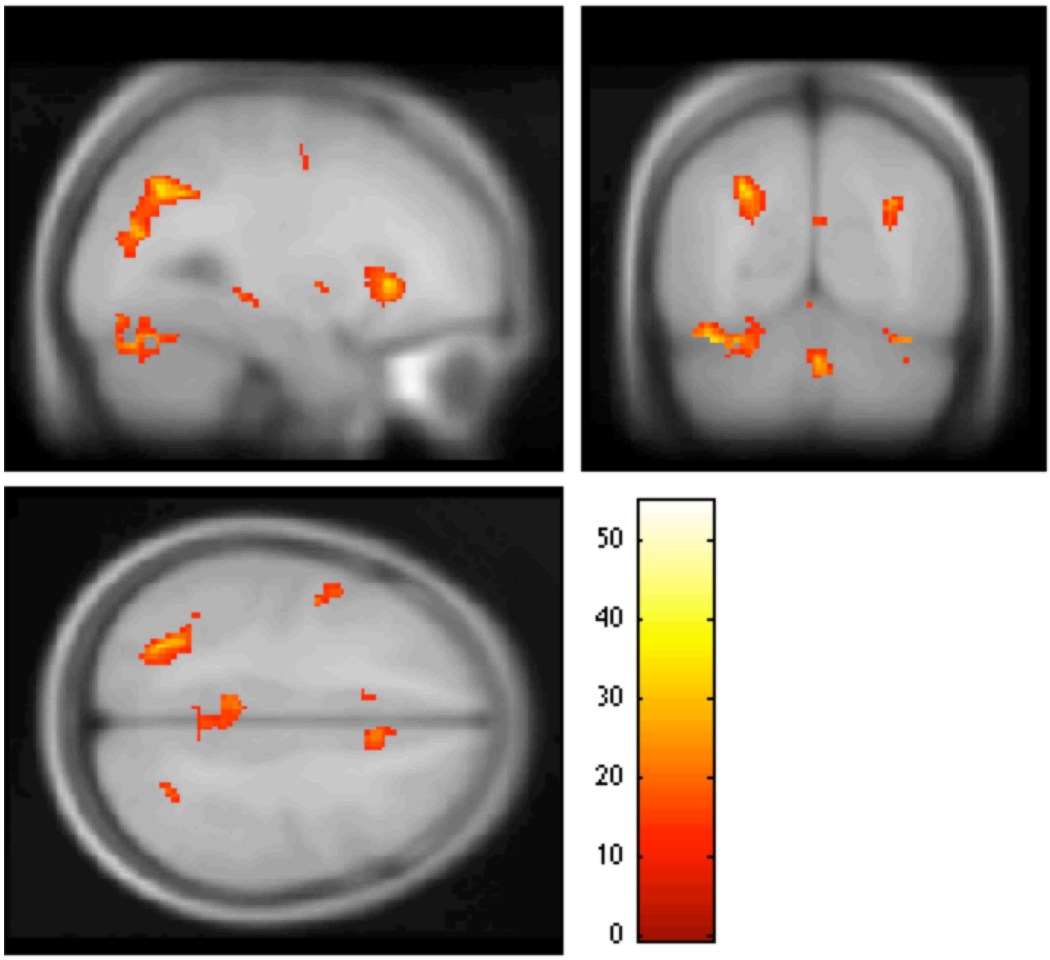
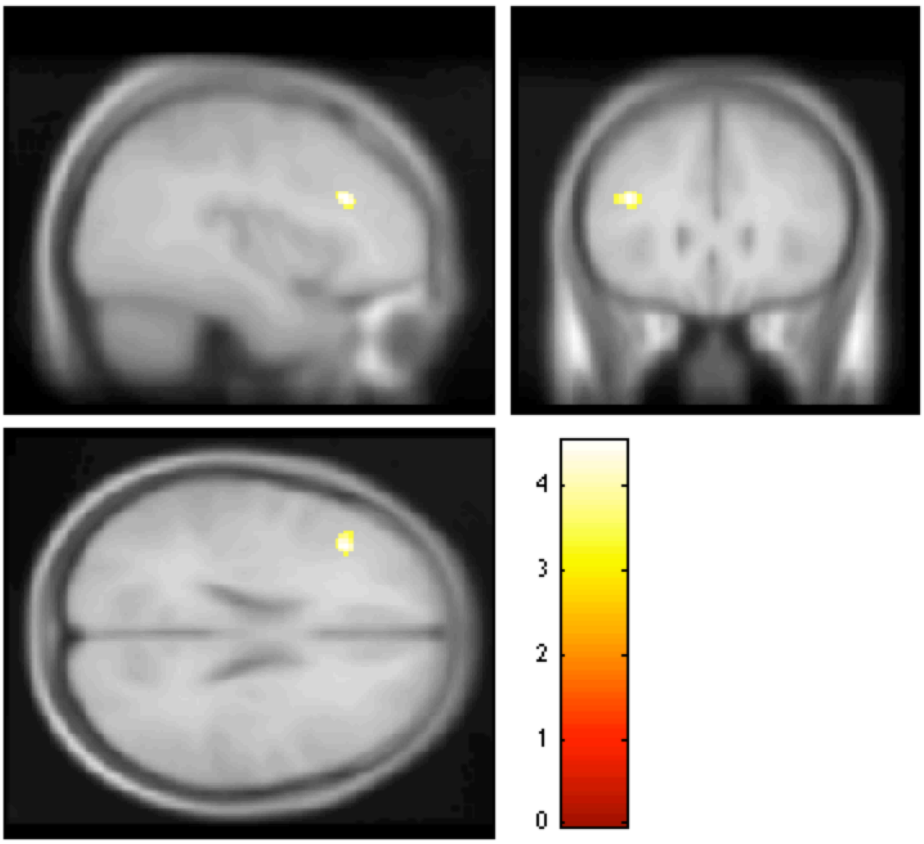


Figure 5.5. Comparison of dorsolateral prefrontal cortex (BA9) activation between MDD & BC groups. Retrieval > rest activation, p <0.001 uncorrected. Increased activation in MDD versus BC group shown.




MDD > BC: [-38, 26, 24 ], T=4.54, p<0.001 uncorrected

# CHAPTER 6:

# GENERAL DISCUSSION

**General Discussion**

The goal of this thesis was to examine the impact of obesity on cognition in adults with and without a mood disorder. Chapter 2 summarizes support from a large number of cross-sectional and prospective cohort studies that have indicated that obesity may have a negative effect on cognition. After a review of the literature on obesity and cognition, a study design and methodology for a novel prospective cohort study that aims to address some of the questions remaining after Chapter 2 is presented. The experimental data presented in Chapters 4 and 5 provide convergent neuropsychological and neural imaging evidence for a subtle association between obesity and cognition, one that becomes more evident with the additive effect of MDD. Although further research is needed to understand the directionality and causal mechanisms that underlie the interactive effects seen between obesity, mood and cognition, our findings presented in this thesis contribute significant and novel evidence that obesity may have an additive effect on cognitive impairment in adults with MDD.

In Chapter 2, we performed an up-to-date systematic review of the literature investigating the association between cognition and obesity. Our review provided evidence suggesting that obesity independently exerted a negative effect on cognition. All but two studies (Garcia-Garcia et al., 2013; Ward, Carlsson, Trivedi, Sager, & Johnson, 2005) reported a negative effect of obesity in at least one test measure of cognition. However, when reviewing the included review studies as a whole, results of test measures that were significantly affected by obesity in one study would not reach significance in a separate study. For instance, obese subjects showed no differences on the Stroop task

when compared to normal weight controls in Duchesne et al. (2010); meanwhile, a negative effect of obesity on Stroop task performance was seen in older obese subjects by Gunstad et al. (2007). The strongest and most consistent cognitive impairment related to obesity was seen in tasks of executive function (Fergenbaum et al., 2009; Gunstad et al., 2010; Volkow et al., 2008). Inadequate sample size and potential confounders uncontrolled for in certain studies may have resulted in this inconsistency. Further, all but 4 of the studies reviewed in Chapter 2 were cross-sectional studies, not allowing for the directionality of the association between obesity and cognition to be inferred. Having identified the gaps and methodological flaws still present in much of the literature reviewed in Chapter 2, we present the study design and methodology of a well-controlled, prospective cohort study in Chapter 3.

In the study design presented in Chapter 3, we were particularly interested in the effect of obesity on cognition in populations with a mood disorder. Individuals suffering from psychiatric illness, notably MDD and BD, account for a large proportion of overall disease burden (Ferrari, 2013; R. S. McIntyre et al., 2013). We designed a prospective cohort study following bariatric surgery patients (bariatric controls, bariatric patients with MDD, and bariatric patients with BD) pre- and post-surgical intervention and comprehensively assessed factors known to be associated with cognitive impairment in mood and/or weight. In Chapter 4 and Chapter 5, we present the first set of original findings from this study.

In Chapter 4, we compared healthy (normal-weight) controls, bariatric controls, and bariatric patients with MDD across cognitive measures assessing attention, memory

and executive functioning. Although we found a consistent pattern in performance (with healthy controls outperforming both bariatric groups, and bariatric controls generally outperforming the bariatric MDD group), many results failed to achieve significance. For measures where significant group differences emerged, post-hoc pairwise comparison tests determined that these group effects were driven by significant differences between healthy controls and bariatric MDD patients. These findings suggest that the presence of MDD and obesity may have an additive effect and that obesity may confer a subtle risk for cognitive impairment in already susceptible populations. A recent meta-analysis by Bora et al. (2013) demonstrated that MDD is associated with a modest negative effect across areas of executive function, attention, processing speed and memory. This effect becomes further pronounced in cases of late-onset, which are associated with particularly poor response inhibition. Inhibitory control was the most pronounced deficit across all MDD cases. Inhibitory control, categorized as a skill of executive function, was also one of the most persistent deficits found in obese individuals in the studies reviewed in Chapter 2. Future studies that compare non-bariatric MDD patients to bariatric MDD patients would better allow us to disentangle the contributory effect of MDD in obese patients.

Lastly, the neural imaging findings presented in Chapter 5 offer further supportive evidence that bariatric MDD patients exhibit neural activation patterns during memory processing that are distinct from bariatric patients without a psychiatric disorder, and from normal-weight individuals. Although commonalities amongst all three study groups were found during both encoding and recognition task activation, bariatric controls and

bariatric MDD patients showed increased activation of unique brain regions. Differences in behavioural task performance did not vary significantly across groups. Understood in the context of group performance differences seen in Chapter 4, it may be that although obesity yields a subtle cognitive change (seen here as differences in neural activation patterning), alone, it does not reach levels of significance where it is readily seen on standardized measures of cognition. Moreover, the additional presence of MDD results in a neural pattern of distinctive regional area activations that may reflect a neural compensation mechanism (ameliorating differences expected on standardized cognitive measures).

Taken together, experimental results from both Chapter 4 and 5 from our study outlined in Chapter 3 indicate that MDD may have an additive on the cognitive impairment caused by obesity. However, without the addition of a non-bariatric MDD study group, we are not currently able to draw firm conclusions regarding the independent effects (and interactions) of both MDD and obesity on cognition. Nevertheless, our findings will have important ramifications on clinical treatment of psychiatric populations. As discussed in Chapter 4, certain classes of psychotropic medication have known metabolic side-effects, including weight gain (Bowden, 2011; Farwell et al., 2004; Nihalani, Schwartz, Siddiqui, & Megna, 2012). The additive effect of obesity on cognitive functioning to the cognitive impairment already associated with MDD patients may be factored into a physician's decision when choosing between several first-line treatment options. Although we only present findings on our bariatric MDD group in Chapters 4 and 5, we can speculate that we would see a similar additive effect of BD and

obesity on cognitive impairment in bariatric BD patients. There is sufficient evidence indicating that during subsyndromal periods, the deficits seen in MDD and BD patients are similar with respect to domain, but differ with regards to severity (with BD patients exhibiting greater cognitive impairment than that seen in MDD patients) (Bora et al., 2013; Roger S McIntyre et al., 2013; Snyder, 2013). Given the high level of weight gain associated with use of anti-psychotic medications in particular, and that cognitive impairment is associated with poor psychosocial and functional outcomes in remitted patients, there is a strong need to consider first-line treatment options and the implementation of a weight monitoring strategy by physicians. To this effect, studies by McIntrye et al. (2013a; 2013b) and Bond et al. (2014) both found obesity in patients with BD was associated with a more severe illness course and poorer outcomes when compared to normal weight BD patients.

**Future Directions**

We are just beginning to understand the interactive effects between mood and obesity on levels of cognitive functioning. The work presented in this thesis provides preliminary evidence that the effects of a mood disorder and obesity are additive with respect to cognitive impairment. We intend to continue to study this population following bariatric surgery, in order to investigate whether improvements in cognition are seen following an expected significant and sustained weight loss. Longitudinal study design would allow us to better understand the directionality of the relation between cognition and obesity, and whether cognitive impairments attributed to obesity can be diminished, or even reversed, following significant weight loss.

Although the pattern of deficits seen in MDD and BD are well-established (Bora et al., 2013; Robinson et al., 2006), our study cannot speak conclusively to the independent effects of MDD or BD on cognitive impairment and how they would compare to our bariatric mood disorder sample. Future studies including a separate normal-weight MDD or BD group may help further disentangle the independent effects of (and interactions with) obesity and mood on cognitive performance. Another area that requires attention is the issue of sex. Our study sample was primarily female and while the bariatric surgery population is predominantly female, males have a higher prevalence rate of obesity in the general population (Wang & Beydoun, 2007). The role of sex-specific effects due to interactions associated with sex steroid hormones on the endocrine system and the resultant impact of obesity, mood state and cognition warrants further investigation.

**Summary Statement**

Mood disorders and obesity are two of the leading causes of disability worldwide, and cognitive impairment is emerging as another shared comorbidity between them. (Ferrari, 2013; Ng et al., 2013). We have provided preliminary evidence that the presence of MDD may have an additive effect with obesity cognition. The subtle cognitive impairment in obesity may become clinically significant in the presence of a mood disorder. Deeper understanding of the exact interactions between these two conditions may change treatment strategies involving these highly comorbid conditions, resulting in improved patient outcomes and decreased public health and economic burden.

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