

**NEUROPSYCHOLOGICAL
FUNCTIONING
AND
GHRELIN SECRETION
IN WOMEN WITH BINGE EATING**

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ABSTRACT

Aims:

Binge eating disorders have a substantial impact on the lives of those affected, both psychologically and physically. The trend towards using a transdiagnostic model to understand binge eating disorders highlights the importance of understanding specific characteristics associated with binge eating rather than relying on diagnostic groupings to inform treatment. The aims of the current study were to examine neuropsychological functioning and ghrelin secretion patterns in women with binge eating to contribute to understanding factors that may be involved in the development and maintenance of binge eating.

Method:

Participants were 112 women with transdiagnostic binge eating using DSM-IV- criteria, who were recruited for the Binge Eating Psychotherapy Study (BEP), and 50 healthy control women. All participants completed the CANTABeclipse neuropsychological battery, the National Adult Reading Test-Revised and the Trail Making Test. A biological assessment of the neurohormone ghrelin, (total ghrelin and C-ghrelin), insulin and glucose after an overnight fast and then following an oral glucose challenge test was completed on 51 of the women with binge eating disorders and 46 of the healthy control women.

Results:

Key findings were:

- No significant impairments were found in neuropsychological functioning in the domains of pre-morbid intelligence, attention, visuo-spatial perception and

memory, and set-shifting in women with binge eating compared with women who do not binge eat.

- Women with binge eating disorder performed more poorly on a test of verbal recall compared to women with bulimia nervosa and women who do not binge eat.
- Neuropsychological functioning was not associated with higher rates of eating disorder severity, depression, anxiety or impulsivity in women with binge eating.
- Total ghrelin secretion is blunted in women with binge eating compared with women who do not binge eat.
- Some aspects of eating disorder pathology including frequency of binges, frequency of vomiting, extent of exercise, perfectionism and drive for thinness were associated with total ghrelin levels.
- Ghrelin levels were not associated with neuropsychological functioning in women with binge eating.

Conclusion:

Results of the current study suggest that neuropsychological functioning is not significantly impaired in women with binge eating, and if relative impairments are present they are unlikely to have a major impact on overall functioning. However, it is possible that the specific neuropsychological tests used may have been of insufficient difficulty to demonstrate differences in this population.

Significant differences in ghrelin secretion were found in women with binge eating suggesting that this may be a useful area to study further in order to understand binge eating. Further research in this area is warranted, with a particular focus on exploring factors which may contribute to the variation in ghrelin secretion among binge eating individuals.

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LIST OF ABBREVIATIONS

AGN	Affective Go/No-go
AN	Anorexia nervosa
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BDI	Beck Depression Inventory
BEDO	Binge eating disorder with obesity
BED	Binge eating disorder
BEP	Binge Eating Psychotherapy Study
BCLC	Big Circle/Little Circle
BIS	Barratt Impulsivity Scale
BMI	Body Mass Index
BN	Bulimia nervosa
ED	Eating disorder
CANTAB	Cambridge Neuropsychological Test Automated Battery
CG	C-ghrelin
CPT	Continuous Performance Test
CVLT	California Verbal Learning Test
DMS	Delayed Matching to Sample
DSM	Diagnostic and Statistical Manual of Psychiatric Disorders
GAF	Global Assessment of Functioning
GDT	Game of Dice Task
IED	Intra-Extra Dimensional Set-Shift
HADS A	Hospital Anxiety and Depression Scale Anxiety;
HADS D	Hospital Anxiety and Depression Scale Depression
HC	Healthy controls
HCO	Healthy controls with obesity
IGT	Iowa Gambling Test
IQ	Intelligence Quotient
MADRS	Montgomery–Åsberg Depression Rating Scale
ms	millisecond
MWT-B	German National Adult Reading Test

NART	National Adult Reading Test
NEO	NEO Personality Inventory
NS	Not significant
RAVLT	Rey Auditory-Verbal Learning Test
ROCFT	Rey Osterrieth Complex Figure Test
RVP	Rapid Visual Information Processing
SCID-I	Structured Clinical Interview I for DSM-IV – Patient Version
sd	standard deviation
se	standard error
sec	second
SOC	Stockings of Cambridge
SRM	Spatial Recognition Memory
SWM	Spatial Working Memory
TG	Total ghrelin
TMT	Trail Making Test
VRM	Verbal Recognition Memory
WAIS	Wechsler Adult Intelligence Scales
WTAR	Wechsler Test of Adult Reading

PART A

1. INTRODUCTION

1.1 Thesis Structure

This thesis is in four parts. Part A describes the role of the author in the current study, describes the characteristics of binge eating and ghrelin secretion in order to present the rationale for the study and state the research questions to be addressed in this thesis. Part B reviews existing research on neuropsychological functioning in binge eating, describes the methodology used to investigate this and reports the results from neuropsychological testing in the current study. Part C reviews existing research on ghrelin, describes the methodology and reports the results regarding ghrelin from the current study. Part D brings these two topics together and explores the relationship between neuropsychological function and ghrelin in women with binge eating.

1.2 Role of the author

My role as the author of this thesis and as a therapist in the Binge Eating Psychotherapy Study is described below. As a treating clinician on the research trial, I was involved of all aspects of delivering the three protocol therapies under investigation, as well as conducting research diagnostic and neuropsychological assessments.)

As one of four therapists working on this study I carried out initial clinical interviews with potential participants to establish eligibility for the study. Once eligibility was established I was involved in the consenting process, and administered the formal assessments including the SCID-I, SCID-II and EDE-2 interviews. I administered a number of the

neuropsychological assessments. As a team member, I was involved in consensus discussions on diagnostic issues and global assessment of functioning ratings.

I devised the research questions investigated in this thesis, carried out the literature reviews, selected the variables to be used to examine these questions, and was responsible for data cleaning and all statistical analysis and interpretation.

1.3 Overview of Binge Eating

A binge is widely considered to be the ingestion of a large amount of food over a discrete time period with an accompanying sense of loss of control over the eating (Wolfe et al., 2009). Bingeing tends to be preceded by negative emotion and is often followed by a sense of shame and guilt. Regular bingeing is the primary symptom of bulimia nervosa and binge eating disorder (American Psychiatric Association, 2013).

Bingeing was recorded in early writings about female saints in the 14th to 18th centuries (Russell, 1997a) in the context of food restriction followed by over eating. Diagnostic criteria for Bulimia nervosa were not published until 1979 (Russell, 1979b), although there were descriptions of patients being admitted to hospital in the 1930's with over-eating, vomiting and weight concerns whom today would likely be diagnosed with bulimia nervosa. Binge Eating Disorder was not formally recognised as a separate disorder until DSM-5 (see section 1.4 for further discussion of diagnostic issues).

The leading theoretical model of binge eating is the Cognitive Behavioural Theory as described in Fairburn, Cooper & Shafran, (2003). This model proposes that eating disorders are both developed and maintained by a dysfunctional belief system which is biased towards negative evaluation of the self with respect to eating habits, weight and shape. Bingeing is seen as a consequence of strict dieting and other weight controlling

behaviours. Risk factors for developing bulimia include genetic factors and early developmental experiences with ongoing research into the interactions between genes and environmental factors (see Striegel-Moore, 2007 for a discussion on the research regarding risk factors in eating disorders).

The lifetime prevalence of bingeing disorders in the general population has been estimated as being between two and three percent (van Hoeken, Seidell, & Hoek, 2003). The World Health Organisation Mental Health survey of 24 000 people across 14 upper to high income countries, including New Zealand, found a lifetime prevalence of 1.0% for bulimia nervosa and 1.9% binge eating disorder (Kessler et al., 2013) with the rates for New Zealand alone as 1.3% for bulimia nervosa and 1.9% for binge eating disorder. Women were 3.6 times more likely to have a bingeing disorder than men. The median age of onset for bingeing disorders was found to be late teens to early 20s (Kessler et al., 2013).

The impact of a bingeing disorder on an individual can be significant across psychological and physical domains. Bingeing disorders have a high rate of psychiatric comorbidities compared to the general population. Rates of lifetime prevalence of over 70% for any Axis-I disorder have been reported for both bulimia nervosa (O'Brien & Vincent, 2003) and binge eating disorder (Grilo, White, & Masheb, 2009; Kessler et al., 2013). In a review of comorbidities in eating disorders, Pearlstein, (2002) reported depression rates in bulimia nervosa were two to three times that in the general population. Other frequently occurring comorbidities in bingeing disorders include anxiety and substance use disorders (Kessler et al., 2013; Grilo et al., 2009).

Significant health problems in individuals with regular binge eating include musculoskeletal problems, chronic pain, diabetes and hypertension (Mitchell, Specker, & de Zwaan, 1991; Reichborn-Kjennerud et al., 2004). Some of these health problems,

particularly diabetes and musculoskeletal problems are likely to be related to, or exacerbated by high body weight. In bulimia nervosa there may be additional physical complications related to regular purging including gastrointestinal complications, degradation of dental enamel, gum disease, enlarged salivary glands, and damage to the oesophagus (Mehler, 2011).

Mortality rates have been reported as nearly twice that of non-eating disordered individuals (Crow et al., 2009). In one of the largest studies to date, Crow et al., (2009) found that mortality from all causes was very similar between bulimia nervosa (3.9%) and “other eating disorders” (5.2%) which is a catch-all category and includes binge eating disorder. These rates were very similar to that in anorexia nervosa (4%) which is usually considered to have higher mortality rates compared with the general population and other psychiatric populations (Sullivan, 1995). Standardised mortality rates due to suicide were 6.5 times greater in bulimia nervosa and 3.9 times greater in “other eating disorders” than the general population and comparable to that found in anorexia nervosa (Crow et al., 2009).

Although the lifetime prevalence of bingeing disorders in the general population is fairly low, the impact on the lives of those affected, both psychologically and physically is significant and therefore this is an important area for further research.

1.4 The Issue of Diagnostic Classification and a Transdiagnostic Approach

Binge eating disorders are most frequently diagnosed using criteria defined in various editions of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM), although ICD codes are also sometimes used (World Health Organisation, 1992). All editions of the DSM have required the presence of regular bingeing in the diagnostic criteria for bulimia

nervosa; however, the frequency and duration of bingeing has varied among editions. Despite these variations, there seems to have been little change in prevalence of bulimia nervosa across various DSM editions (van Hoeken et al., 2003), although a recent study using criteria from the latest edition, DSM-5, suggests that prevalence rates may be higher using this edition, due to the reduction in required frequency of bingeing from twice weekly to weekly in bulimia nervosa (Stice, Marti, & Rohde, 2013). Up until DSM-5, binge eating disorder was not recognised as a separate disorder and instead was captured under the catch-all category of Eating Disorder Not Otherwise Specified (EDNOS); however, DSM-IV contained diagnostic criteria for binge eating disorder under a category for further research. In DSM-5, binge eating disorder has become a separate disorder, with the required duration of bingeing has reducing from six to three months.

Regardless of which criteria are used for diagnostic purposes there appears to be movement of individuals between different eating disorder categories over time. There is significant diagnostic cross over between bulimia nervosa and binge eating disorder (Stice et al., 2013) and it is not uncommon for individuals with anorexia nervosa to move to bulimia nervosa or EDNOS (Agras et al., 2000; Sullivan et al., 1998). This apparent fluidity of movement between diagnostic criteria has led to the development of a transdiagnostic approach to eating disorders. Fairburn, Cooper & Shafran (2003) suggest that eating disorders including anorexia, bulimia nervosa and those previously captured under EDNOS (including binge eating disorder) share distinct clinical features that are maintained by the common underlying psychopathological processes regardless of diagnostic label, and that these features are distinct from other psychiatric diagnoses. This has led to the development of a transdiagnostic treatment approach where treatment is tailored to the individual depending on which clinical features of an eating disorder are

present rather than which DSM diagnostic category the individual is placed in by diagnostic criteria (Fairburn et al., 2015).

Following on from this approach, the greater understanding of the factors that influence the development and/or maintenance of eating disorders the greater the opportunity to tailor treatment to suit individuals with bingeing disorders. Neuropsychological functioning and neuroendocrine factors including the hormone ghrelin are two areas of research which are contributing to understanding bingeing disorders and could potentially inform treatment approaches.

1.5 Neuropsychological Function in Binge Eating

Neuropsychological impairments in eating disorders were first reported over 40 years ago but it was not until the 1980s that research studies looking into this area began to be published. Since then there have been a small, yet steady number of publications investigating the neuropsychological aspects of eating disorders. Initially the focus of this research was on anorexia nervosa and the impact of starvation on neuropsychological function, following on from the findings from the Minnesota Starvation Study (Keys et al., 1950). Over time there has been an increasing focus on neuropsychological function in bulimia nervosa and more recently binge eating disorder.

Changes in neuropsychological function in bulimia nervosa have been reported in some studies but not others; however, methodological issues and small sample sizes have compromised some studies (Lena, Fiocco, & Leyenaar, 2004; Tchanturia et al., 2005). Problems with set-shifting and central coherence have been the most commonly reported areas of impairment in bulimia nervosa (Alvarez-Moya et al., 2009; Degortes et al., 2015; Roberts et al., 2010; Tchanturia et al., 2012). Fewer studies have investigated neurological

functioning in binge eating disorder. Those studies that found differences have reported changes mainly in decision-making ability and inhibitory control (Aloi, et al., 2015; Danner et al., 2012; Kelly et al., 2013). At present it remains unclear as to whether specific neuropsychological changes are characteristic of binge eating and whether there are differences between bulimia nervosa and binge eating disorder.

There are many factors known to impact on neuropsychological functioning including depression and anxiety, both of which are common in patients with binge eating (O'Brien & Vincent, 2003). Although there have been a number of studies reporting levels of depression in binge eating, few have directly investigated the association between depression and neuropsychological functioning. The effect of anxiety on neuropsychological functioning in binge eating is also unclear as even fewer studies have investigated this relationship. More research is needed to understand the impact of depression and anxiety on neuropsychological functioning in binge eating.

1.6 Ghrelin in Binge Eating

Recently there has been interest in the neuroendocrine influences on eating psychopathology (Gottero et al., 2004). Ghrelin, a neuropeptide discovered in 1999, has been of particular interest to eating disorder researchers because of the role of ghrelin in appetite and energy balance. Ghrelin levels are increased by fasting and energy restriction and are decreased by food ingestion and over-eating. This pattern has been found in individuals with eating disorders and obesity. Studies have consistently found elevated ghrelin levels in individuals with anorexia nervosa (Monteleone et al., 2005; Soriano-Guillen et al., 2004; Tanaka et al., 2003; Otto et al., 2004); however, the pattern of ghrelin secretion is less clear in bulimia nervosa and binge eating disorder. Interest has

been expressed in the potential manipulation of ghrelin levels to treat individuals with eating disorders.

Ghrelin is involved with multiple systems in the body including cardiovascular and reproductive, and could potentially play a role in neuropsychological function as there are ghrelin receptors in many areas of the brain including the hippocampus (Müller et al., 2015). The first study to explore the association between ghrelin and neuropsychological function was published by Diano et al. (2006). Levels of circulating ghrelin were manipulated in rats and mice. Animals with increased ghrelin levels performed better on tests of learning and memory performance, whereas, animals without ghrelin receptors performed poorly on these tests. The authors proposed that ghrelin acted on areas of the brain, including the hypothalamus, by increasing synapse density resulting in improved function despite being in a starved state. It was suggested that increased ghrelin levels may be an evolutionary advantage in times of food shortages. The effect of ghrelin on cognitive functioning in humans has not been extensively studied to date. Results of such studies may have implications for the use of ghrelin in future treatment of not just eating disorders but also obesity and dementia (Dickson et al., 2011). However, questions remain about the impact of ghrelin levels on neuropsychological functioning. If cognitive function is negatively affected by low ghrelin levels, as in experimental conditions in rodents, this has implications for the treatments that may attempt to reduce circulating ghrelin levels to treat problems such as binge eating or obesity in humans.

1.7 Current Treatment for Binge Eating

Cognitive Behavioural Therapy (CBT) is the treatment of choice for bulimia nervosa and binge eating disorder (Hay et al., 2014; National Institute for Health and Clinical Excellence, 2004). A transdiagnostic Enhanced CBT approach (CBT-E) has been

developed for use across the eating disorders and found to be effective in treating binge eating (Fairburn et al., 2015). CBT-E incorporates the core foci and techniques used in standard CBT but emphasises an individualised formulation looking at associated difficulties seen in those with eating disorders. It incorporates optional modules addressing more concerns including clinical perfectionism, low self-esteem and interpersonal relationship difficulties. Other adaptations of CBT for binge eating which have included either a schema focus or appetite focus have also been found to be effective (McIntosh et al., 2016). Other therapies, including Interpersonal Therapy and psychodynamic therapies, have been investigated but a meta-analysis found them not to be different from CBT (Spielmans et al., 2013).

Therapies incorporating cognitive rehabilitation have been developed to help those with eating disorders improve cognitive flexibility have also been explored as a treatment to help improve emotion regulation and social function in anorexia (Tchanturia et al., 2015), and bingeing disorders (Fagundo et al., 2013; Roberts, Tchanturia, & Treasure, 2013).

The use of medication to treat binge eating has been an area of investigation over the past 30 years (for a review see McElroy et al., 2012). Studies investigating antidepressant medication in bulimia nervosa have demonstrated a decrease in the frequency of binge eating and purging in bulimia nervosa (Bacaltchuk & Hay, 2003; Goldstein et al., 1999; Guerdjikova et al., 2012); however, few participants experienced remission and there is a high rate of relapse (Agras, 1997). There is some evidence that a combination of medication and psychotherapy (CBT) could be beneficial for some (Agras, 1997). Other areas of interest for potential development in medication include those designed to affect appetite and hunger (Dickson et al., 2011).

In summary, two to three percent of the population is likely to have a bingeing disorder at some point during their lifetime. The burden of a bingeing disorder can have a significant negative impact on psychological and physical health which is reflected in mortality rates similar to that of anorexia nervosa. A transdiagnostic approach to understanding and treating bingeing disorders has been proposed. A better understanding of neuropsychological function and neurohormone systems involved in appetite and energy regulation such as ghrelin, could make contributions to better understanding binge eating.

1.8 Study Rationale

The broad aim of the current study is to contribute to the existing understanding of the neuropsychological functioning and ghrelin secretion in women with binge eating and investigate the relationship between neuropsychological function and ghrelin secretion in this population.

The data on neuropsychological functioning and ghrelin secretion in women with binge eating presented in the current study has been gathered as part of a large randomised controlled clinical trial, the Binge Eating Psychotherapy Study (McIntosh et al., 2016). The Binge Eating Psychotherapy Study was carried out in the Clinical Research Unit, Department of Psychological Medicine, University of Otago, Christchurch, in collaboration with the Canterbury District Health Board. This randomised controlled clinical trial compared three cognitive-based therapies for treating women with transdiagnostic binge eating and examined a broad selection of factors which could inform future treatment developments for binge eating.

1.9 Research Questions

The specific aims are:

1. To describe the pattern of neuropsychological function in women with bulimia nervosa and binge eating disorder and compare with those of women without binge eating.
2. To investigate the effects of depression and anxiety on neuropsychological performance in women with binge eating.
3. To describe patterns of ghrelin secretion and associated biological factors (insulin and glucose) in women with binge eating and compare with women who do not binge eat.
4. To investigate the relationship between neuropsychological function and ghrelin secretion in women with binge eating.

Hypotheses:

1. Women with binge eating will have poorer neuropsychological performance compared to women who do not binge.
2. Depression and anxiety will be associated with poorer neuropsychological performance in women with binge eating.
3. The severity of eating disorder symptoms will be associated with poorer neuropsychological test performance in women with binge eating.

4. Ghrelin levels will be altered in women with binge eating compared to women who do not binge.
5. Higher ghrelin levels will have a positive association on some aspects of neuropsychological functioning, particularly an improvement in memory, whereas lower ghrelin levels will be negatively associated with neuropsychological performance in these areas.

PART B

2. LITERATURE REVIEW: NEUROPSYCHOLOGICAL FUNCTIONING IN WOMEN WITH BINGEING DISORDERS

2.1 Why Examine Neuropsychological Functioning?

Neuropsychological testing is used as a tool to explore brain functioning in a non-direct way. It relies on behavioural expression to inform understanding of internal brain processes (Lezak et al., 2012). Lezak et al., (2012) describe the development of the field of neuropsychology from an interest by early philosophers, physicians and scientists in the connections between bodies and how they behaved in certain situations, through to the development of specialised neuropsychological tests to understand the effects of brain damage caused during world war two and the need to develop rehabilitation programmes for surviving soldiers.

Neuropsychological functioning can be divided into several broad areas of functioning; receptive functions (how well the person perceives information), memory (how perceived information is retained), expressive functions (how can the person express a response to the information perceived), thinking (manipulating the information perceived), and executive functions (combining a number of neuropsychological functions to perform a complex task). Neuropsychological tests have been developed to measure these domains; however, the tests generally require more than one domain to complete tasks making it difficult to design “pure tests”. Neuropsychological testing involves examining these areas of function using specifically designed tests and relies on the assumption that certain

neuropsychological deficits correspond to specific areas of brain damage. More recently, the development of imaging techniques, particularly functional imaging, may supersede neuropsychological testing but at present imaging remains expensive and is not widely used in people with eating disorders other than for research.

Neuropsychological testing has traditionally been a deficit model, that is, results are compared to normative results from non-brain-injured people to look for deficits.

Although initially the focus of neuropsychology was in understanding both normal functioning and how this is affected after brain injury, in recent times this has been taken further again and focus has been on using neuropsychology to better understand the impact of mental illnesses on neuropsychological functioning. Keefe, (1995) describes neuropsychological testing in psychiatric populations as being a method of gathering information about an individual that can help inform prediction of the course of illness (i.e., poor performance implies impaired functioning which is associated with poorer prognosis), can be used as a tool for improving diagnostic classification, and may be helpful in treatment planning. These factors have been part of the rationale behind the exploration of cognitive functioning and the development of cognitive remediation (Davies & Tchanturia, 2005; Tchanturia, Lounes, & Holtum, 2014) in anorexia nervosa and other eating disorders such as bulimia nervosa (Fagundo et al., 2013; Roberts, et al., 2013a).

Lena et al. (2004) discuss a potential role of cognitive impairments in the development of eating disorders and propose several mechanisms by which neuropsychological factors may influence the development and maintenance of eating disorders including impairments in set-shifting, decision-making and inhibitory control. Many women report the onset of eating disorder symptoms in adolescence and even childhood and some studies have found

neuropsychological impairments in adolescents with eating disorders (Lock et al., 2011), whereas other studies have not (Darcy et al., 2012; Lang et al., 2014).

There is some evidence that specific neuropsychological traits which may increase vulnerability to the development of an eating disorder are heritable. For example, a British epidemiological study (Kothari et al., 2013) compared the neuropsychological profile of children at age 8 years born to mothers with eating disorders with that of children born to mothers with no life-time history of eating disorders. They found the children of women with bulimia nervosa, a high risk group for developing later eating disorders, showed poorer performance in tests of visuo-spatial functioning and a trend towards decreased behavioural inhibition.

Alternatively, impairment in neuropsychological functioning may be as a result of the eating disorder, rather than a pre-existing condition. If this is the case, neuropsychological function could be expected to improve after treatment of the eating disorder. For example, Lauer et al. (1999) assessed 12 individuals with anorexia nervosa and 14 with bulimia nervosa who were undergoing standard treatment at an eating disorders clinic. They found cognitive impairments were present in 11 of the individuals and these impairments improved after treatment.

1.2 Association between Brain Structure and Neuropsychological Functioning in Binge Eating

There is some evidence to suggest brain structure is different in individuals with bingeing disorders that may impact on neuropsychological function. Woolley et al. (2007) used MRI to examine the brains of individuals with neurodegenerative disease who exhibited binge eating. They found greater atrophy in the right ventral insula, striatum and

orbitofrontal cortex than the left side. They concluded that “ damage to a right orbito-frontal-insular-striatal circuit is associated with overeating behaviour in humans and supports the hypothesis that these regions integrate internal satiety signals with environmental food cues to produce adaptive eating behaviour” (p1429). However, not all studies report changes in brain structure in individuals with binge eating. Joos et al. (2010) found no differences in grey matter volumes using MRI in 17 women with bulimia nervosa compared to healthy controls.

Patterns in brain activity may also be affected, for example, differences in activity in the fronto-striatal learning system area of the brain using fMRI have been found between individuals with sub-clinical bulimia nervosa and matched controls (Celone et al., 2011). Changes in brain activity have been linked to specific areas of functioning that are implicated in bulimia nervosa. Lock et al. (2011) used fMRI to investigate brains of adolescents with binge/purge behaviours and found increased activation in the right dorsolateral prefrontal cortex which they interpreted as an indicator of inefficient or compensatory activation in this region which is involved in executive control.

2.1 Neuropsychological Functioning in Women with Binge Eating

Researchers investigating neuropsychological functioning in people with bulimia nervosa and binge eating disorder have covered a broad range of neuropsychological domains. In the following review, results from these studies have been organised to broadly reflect the neuropsychological domain assumed to be tested. Areas discussed are premorbid functioning, motor function, attention, inhibition, learning and memory and executive function.

Table 2.1 Comparison of neuropsychological domains comparing binge eating to healthy controls.

Study	Current IQ	Motor Function	Attention	Verbal Memory	Visual Memory	Visuospatial	Working Memory	Inhibitory Control	Planning	Decision-making	Set-shifting	Central Coherence	Verbal Fluency	Executive functions
Bulimia nervosa														
Alvarez-Moya et al. (2009)			O								↓			
Batty et al. (1990)			O	↓				↓					↓	
Boeka & Lokken (2006)										↓				
Brand et al. (2007)	O		O	↓	↓		O		O	↓	O		O	
Bosanac et al. (2007)		↓	↓	↓			O			O				
Brogan et al., 2010)										↓				
Chan et al. (2014)										↓				
Darcy et al. (2015)					↓	↓						↓		
Darcy et al. (2012)	↓	O	O								O		O	
Degortes et al. (2015)				O	O	O		O		↓	↓			
Galimberti et al. (2012)								O			O			
Harrison et al. (2011)												↓		
Kim at al. (2011)	O				O	↓								
Laessle et al. (1990)			↓					O						
Liao et al. (2009)										↓				
Lopez et al. (2009)												↓		
McKay et al. (1986)	O	↓												
Murphy et al. (2004)			O		O	O							O	
Pendleton Jones et al. (1991)	O		↓	O		O								
Roberts et al. (2010)						↓					↓			
Roberts et al. (2013b)					↓	↓						↓		
Tchanturia et al. (2012)											↓			
Tchanturia et al. (2004)	O		↓								↓			
Van den Eynde et al. (2012)			↓					O		O				
Weider et al. (2014)	O		O											
Weider et al. (2015)		↓	O	↓	↓	↓	↓							↓
Weider et al. (2016)					↓	↓						↓		
Wu et al. (2013)								↓		O				
Binge eating disorder														
Aloi et al. (2015)			↓		↓	↓				↓		O		
Danner et al. (2012)										↓				
Davis et al. (2010)										↓				
Kelly et al. (2013)			O								O			
Manasse et al. (2015)			O					↓	↓	↓				
Mole et al. (2015)								O		↓				
Svaldi et al. (2010)										↓				
Wu et al. (2013)								O		O				

O = no difference in performance compared to controls; ↓ = lower performance compared to controls

A summary of studies and the specific aspects of neurocognitive functioning investigated is reported in Table 2.1. A fuller description of these studies is given in Table 2.3. Note that some tests have been used to investigate more than one domain.

2.1.1 Intellectual functioning

It is important to consider intellectual functioning (IQ) when comparing other neuropsychological domains among different groups in order to rule out the possibility that any differences in functioning found are due to differences in IQ rather than the neuropsychological domain itself that is being tested. Ideally a full IQ assessment battery would be carried out but in the interest of time many studies have used shortened forms or reading tests to approximate pre-morbid IQ levels (see summary presented in Table 2.2). Intellectual functioning has been measured in two ways by studies reporting neuropsychological functioning in binge eating. Some studies have used a measure of pre-morbid IQ such as the Nation Adult Reading test (NART) or the Wechsler Test of Adult Reading (WTAR). Others have used tests of current intellectual function such as the Wechsler Adult Intelligence Scales (WAIS). Each of these approaches has limitations with reading tests such as the NART being only an estimation of pre-morbid IQ which relies on verbal functioning remaining intact, whereas current IQ assessments cannot account for changes in IQ functioning due to the effects of the psychological disorder and may underestimate pre-morbid IQ functioning.

Table 2.2 Summary of existing studies reporting measures of premorbid intellectual functioning in women with bingeing disorders

Study	Diagnosis	Mean IQ	Psychometric Test
Premorbid IQ			
Liao et al. (2009)	BN	113.9	NART
	HC	112.6	
Lopez et al. (2009)	AN/BN	113.6	NART
	HC	112.2	
Manasse et al. (2015)	BEDO	111.7	WTAR
	HCO	112.6	
Manasse et al. (2014)	BEDO	116.0	NART
	HCO	115.2	
Tchanturia et al. (2004)	BN	111.3	NART
	HC	111.9	
Van den Eynde et al. (2012)	BN	108.0	NART
	HC	114.2*	
Current IQ			
Murphy et al. (2004)	BN	122.7	WAIS (4 subtests)
	HC	117.1	
Pendleton Jones et al. (1991)	BN	108.9	WAIS-R
	HC	114.6	
Weider et al. (2014)	BN	111.1	WAIS-III
	HC	114.6	
Weider et al. (2016)	BN	111.2	WAIS-III (General Ability Index)
	HC	114.3	

*BN < HC, $p < 0.01$, all other comparisons are not significant

AN = anorexia nervosa; BN = bulimia nervosa; BED = binge eating disorder; BEDO = binge eating disorder with obesity; HC = healthy controls; HCO = healthy controls with obesity; NART = National Adult Reading Test; WAIS = Wechsler Adult Intelligence Scale; WTAR = Wechsler Test of Adult Reading.

The average IQ score of individuals with bulimia nervosa or binge eating disorder, both premorbid estimate and current score, is generally around the top of the average range. No significant difference in IQ scores between individuals with binge eating and those without binge eating were reported by all studies, apart for one study (Van den Eynde et al., 2012) which reported a slightly lower IQ in women with bulimia nervosa compared to healthy controls. There is no obvious reason for this finding as the sample they recruited does not seem to differ in from those in other studies with respect of age, BMI or illness severity. Although there are no studies directly reporting a comparison of IQ between bulimia

nervosa and binge eating disorder there does not appear to be any major differences when comparing results between studies.

2.1.2 Motor functioning

Motor functioning must be considered where tests involve the need to move or manipulate objects to complete the task and in particular where tests are timed. Impairments in motor function can therefore mask ability in other areas of neuropsychological function. Slowing in motor functioning occurs due to ageing, physical problems or can also be caused by higher order processing problems (Lezak et al., 2012). Although there is evidence of motor slowing in anorexia nervosa which is likely to be related to the effects of starvation (Green et al., 1996), few studies have reported motor function in bulimia nervosa or binge eating disorder. One study of women with bulimia nervosa found motor processing was slower in bulimia nervosa on an assessment of motor function using a drawing task (McKay et al., 1986). A recent study of women with bulimia nervosa found evidence of impairment in motor function (fine motor skills and strength of pencil grip) compared with healthy controls but not to the same degree as that found in women with anorexia nervosa (Weider et al., 2015). There have been no studies reporting on motor function in binge eating disorder (see Table 2.1)

Although there may not be strong evidence of impairments in motor function in women with binge eating, it is important to include in test batteries that include other tasks that require motor function to complete in order to exclude this as a confounding variable.

Haptic perception is a distinct concept from motor function although motor function is required to manipulate physical objects. Haptic perception is an area of neuropsychological function that requires the integration of sensorimotor information to understand spatial

characteristics of objects (Southgate, Tchanturia, & Treasure, 2005). More recently haptic tasks, such as the Haptic Illusion Task, have been used to investigate the ability to integrate sensorimotor information in people with eating disorders. There is some evidence of impairment on haptic tasks in bulimia nervosa (Roberts et al., 2010; Tchanturia et al., 2004). To date this research group have been the only ones to investigate this area.

2.1.3 Attention

Attention can be divided into different categories with sustained attention and divided attention being the two most common aspects examined in neuropsychological testing (Lezak et al., 2012). Sustained attention or vigilance is the ability to remain focused on a task without being distracted. Tasks measuring sustained attention typically ask the participant to respond when they perceive a target stimulus and can vary from simple (one target stimulus) to more complex in which the participant must respond only under certain conditions, for example only when the target item is preceded by a specified item. Tests of sustained attention are typically forms of a continuous performance test paradigm.

Divided attention involves completing tasks with more than one focus of attention and often uses different modalities such as visual and auditory concordantly. Lezak et al., (2012) notes that performance of these attention tasks are relatively unaffected by age and are usually easily completed by people with intact attention and as such, even a small number of errors may indicate a impairment in attention. Commonly used tests of divided attention in eating disorders research include Letter Cancellation Tasks and the Symbol-Digits Modalities Test.

Sustained attention in bulimia nervosa has been assessed as unimpaired in most studies (see Table 2.1 and Table 2.3). In one study performance on a continuous performance test

of 38 women with bulimia nervosa of normal weight was no different to 39 healthy controls (Pendleton Jones et al., 1991). Attention has been found to be unaffected even when impairments have been found in other areas of neuropsychological functioning. For example, Weider et al. (2015) used Connor's Continuous Performance Task and found no impairment in sustained attention in a group of 38 women and two men with bulimia nervosa compared with matched healthy controls, while finding neuropsychological impairments in other domains of functioning in the bulimia nervosa group.

However, sustained attention may be reduced in individuals with bulimia nervosa if they have poor nutritional status. A degraded-stimulus continuous performance test was used to compare sustained attention in a group of 30 women with bulimia nervosa (DSM-III-R) with 23 healthy controls (Laessle et al., 1990). Those women with bulimia nervosa had a lower hit rate and reduced sensitivity to the target stimuli. They were also slower to respond to the target which the authors interpreted as participants taking a more cautious approach. Half of the bulimia nervosa group had a history of anorexia nervosa. Signs of starvation were measured by levels of betahydroxybutyric acid (BHBA) in the women with bulimia nervosa. Those with signs of starvation were found to have poorer performance on this task than those without such signs of starvation.

Overall results from studies using continuous performance tests as a measure of attention lend more support to sustained attention being unaffected, at least in women who binge eat but are not underweight or exhibiting signs of starvation.

Divided attention can be assessed using the d2-Letter Cancellation Task (d2-LCT) which is also a measure of processing speed. Participants are required to cross out a target character (the letter d with two dashes either above and/or below) and not mark distractor targets (the letter d with more or fewer than two dashes or the letter p with any number of dashes).

The d2-LCT was also used in a study involving 40 women with bulimia nervosa, 30 women diagnosed with Eating Disorder Not Otherwise Specified-Bulimia Nervosa Type (EDNOS-BN), and 65 healthy controls (Van den Eynde et al., 2012). The EDNOS-BN group performed less well than the bulimia nervosa group, and both eating disorder groups had lower attention than the healthy control group. However, once baseline group differences were accounted for (age, NART scores, depression) only the EDNOS-BN group remained significantly poorer in performance than the bulimia nervosa and healthy control groups. The authors noted that the EDNOS group would have met criteria for bulimia nervosa in DSM-5 due to changes in binge frequency and that EDNOS-BN group did not include women with binge eating disorder as they were specifically excluded from the study in order to reduce heterogeneity of the EDNOS-BN group. It is unclear why the EDNOS-BN group had more neuropsychological impairment than the BN group as their ED symptoms (at least in terms of binge frequency) was by definition less severe than full diagnosis cases.

In contrast, Brand et al. (2007) compared 14 women with bulimia nervosa to 14 matched healthy controls using the d2-LCT and found no difference in performance.

Comprehensive matching to control for demographics and levels of psychopathology was evident; however, the study was underpowered and would have been unable to identify a difference of moderate effect size.

Lauer et al. (1999) used the d2-LCT along with a different divided attention task using both visual and auditory stimuli in 14 women with bulimia nervosa and 12 women with anorexia nervosa. An overall score of attention/vigilance was calculated (but not described in the paper) using outcomes from these two measures which indicated mild to moderate impairments in divided attention in both bulimia nervosa and anorexia nervosa. However,

Lauer et al.'s study did not include a control group or describe how the norms were used to define a normal response were obtained. The bulimia nervosa group in were on average 99.6% ideal body weight which suggests that a reasonable proportion of the sample may have lower body weight than that found in the current study.

The Symbol-Digits Modalities Test (SDMT; Lezak et al., 2012) measures visual attention and tracking ability. Geometric designs are presented to the participant who uses a key to substitute a number for each design. The test is scored by the number of correct substitutions made in a 90 second period. Murphy et al. (2004) compared 16 women with bulimia nervosa and 16 healthy controls using the SDMT and found no difference in visual attention between the groups. Another study compared 23 participants with bulimia nervosa with 28 healthy controls using the SDMT (Ferraro, Wonderlich, & Jolic, 1997). They found that the bulimia nervosa group completed the task faster but made more errors, and had greater variability in responses than the healthy control group.

Overall the results from studies investigating divided attention in bulimia nervosa are mixed. Many have methodological issues (including small sample size, lack of detail regarding diagnostic classification and lack of a control group), which makes comparison difficult. In studies that have controlled for confounding factors it appears that if deficiencies in divided attention are present they are likely to be small.

In the only study of attention in women with binge eating disorder to date, Kelly et al. (2013) compared 50 women with regular binge eating but no compensatory behaviours with 66 healthy control women using the Connor's Continuous Performance Task. They found no difference in attention between the two groups. Women in this study were recruited from college students and relatively low mean age of 19 years and a mean BMI

of 24.5. This sample may not reflect the majority of women in the general population with binge eating disorder.

In summary, nine studies have reported on attention/vigilance in women with binge eating. All studies investigated bulimia nervosa, while the remaining study investigated binge eating disorder. Some studies had small sample sizes and were unlikely to have enough statistical power to detect a moderate effect size. No consistent approach to measuring attention has been taken with at least three different tasks employed. On balance it seems that both sustained and divided attention remains reasonably unaffected in women with binge eating but there is a suggestion that divided attention may be impaired if women are in a state of physical starvation and/or low body weight.

2.1.4 Memory and learning

Memory is the ability to hold information, verbal or visual, over time and use it for some purpose. Word lists such as the Rey Auditory-Verbal Learning Test and the California Verbal Learning Test are commonly used to assess memory and learning verbal information. The Rey Osterrieth Complex Figure Test is a test of recall of visual information and also investigates strategies used by participants to carry out this task. Memory can be tested immediately after presentation of the information (immediate recall), or after a time delay (delayed recall) or can be measured using a recognition condition where participants identify whether or not the information has previously been presented to them.

Research on learning and memory with individuals with bulimia nervosa is mixed, with some studies showing impairment in verbal memory in bulimia nervosa and others reporting no impairment. Beatty et al. (1990) found reduced verbal memory in a free

recall condition in women with bulimia nervosa compared with healthy controls and Brand et al. (2007) reported poorer auditory learning in bulimia nervosa. In contrast, two further studies found no impairment in verbal recall memory, both short and long term delay (Murphy et al., 2004; Pendleton Jones et al., 1991). A more recent study reported lower verbal and visual learning and memory in individuals with bulimia nervosa compared with healthy controls but did not report results of individual tests (Weider et al., 2015).

Visuospatial memory has been found to be no different in women with bulimia nervosa compared with matched controls using the Rey-Osterrieth Complex Figure Test (Degortes et al., 2015; Murphy et al., 2004). However, a large study of 42 adolescents with bulimia nervosa did find some impairment in delayed recall in the Rey-Osterrieth Complex Figure Test compared with healthy controls (Darcy et al., 2012). The bulimia nervosa group also showed impairment in the copy condition suggesting that their ability to process spatial information was not as high as their non-eating disordered peers. Reduced delayed recall scores and impairment in the copy condition have also been reported in adults with bulimia nervosa (Brand et al., 2007; Weider et al., 2016).

Surprisingly, a literature search did not reveal any publications reporting verbal learning and memory in individuals with binge eating disorder. There is some evidence for reduced visuospatial memory in binge eating disorder compared to healthy controls both in the ability to accurately copy the figure but also in recalling information (Aloi et al., 2015).

In summary, although there is some evidence for impairment in verbal and spatial memory, there is not a consistent pattern of learning and memory impairment reported in individuals with binge eating. The limited number of studies investigating each aspect of memory (e.g. verbal or visual, immediate or delayed, recall or recognition) makes it difficult to confidently state whether there are memory impairments in women who binge

eat. Methodological issues including small sample sizes, the range of different tests used, and problems with diagnostic categories in many of these studies is also problematic.

2.1.5 Inhibitory control

The ability to inhibit responses is known as inhibitory control and can be demonstrated in different modalities such as inhibition of motor or verbal responses (Evenden, 1999).

Inhibitory control is necessary to avoid making impulsive decisions and has some overlap with tests of decision making such as the delayed discounting task (see the next section: executive functions). Tests which are commonly used to measure response inhibition include various forms of the Stroop Test; however, this is not considered a pure test of inhibition as it also incorporates cognitive interference and attentional bias (Wu et al., 2013). Go/No-go tasks and Stop Signal tasks are more reliable measures of motor inhibition.

There is little evidence of inhibitory control problems in bulimia nervosa. The Stroop task has not found differences between individuals with bulimia nervosa and healthy controls when using neutral stimuli (Alvarez-Moya et al., 2009; Van den Eynde et al., 2012). No difference in inhibitory control was found using a Go/No-go task in one study (Van den Eynde et al., 2012); however women with bulimia nervosa were found to make more errors of commission (respond in the absence of target stimuli) on a Go/No-go task than healthy controls suggesting that those with bulimia nervosa had an increased tendency to respond in an impulsive manner (Rosval et al., 2006). Studies using the Stop Signal Task have consistently shown no difference in motor inhibition between bulimia nervosa and healthy controls (Claes et al., 2006; Galimberti et al., 2012; Wu et al., 2013).

In contrast with the results from individuals with bulimia nervosa, there appears to be some evidence of inhibitory control impairment in individuals with binge eating disorder. Verbal inhibitory control was measured in women with binge eating disorder using Hayling's Sentence Completion Task (Aloi et al., 2015). Women with binge eating disorder were faster to respond but showed reduced inhibitory control by demonstrating less flexibility in their answers. Another study found reduced motor inhibition in binge eating disorder using the stop signal tasks (Mole et al., 2015). However, two further studies have shown no differences in inhibitory control in individuals with binge eating disorder using the Stroop Test (Manasse et al., 2015) and the Stop Signal Test (Wu et al., 2013).

In summary, inhibitory control in women with bulimia nervosa appears to be intact; however, there is a mixed pattern of results for women with binge eating disorder. The small sample sizes in some studies, the use of different tasks measuring inhibitory control, and the lack of replication by other researchers make it difficult to be confident that there are differences in inhibitory control in women who have binge eating disorder.

2.1.6 Executive Function

Executive function is the term given to a higher level of neuropsychological functioning which requires the combination of more than one basic neuropsychological domain in order to successfully complete a task. Examples of executive function include set-shifting, planning, decision-making and central coherence. These executive functions have been investigated in bulimia nervosa or binge eating disorder and are discussed in the following sections.

2.1.7 Set-shifting

Set-shifting describes an individual's ability to shift attention back and forth between multiple tasks (Miyake et al., 2010). Tests that measure set-shifting include the Trail Making Test Part B, the Wisconsin Card Sorting Test, the Brixton Test and the Cat Bat Task. These tests require the participant to switch between different stimuli and show flexibility in thinking to avoid perseverative errors.

Roberts et al. (2007) in their systematic review of set-shifting in eating disorders note that set-shifting problems are often observed as either cognitive inflexibility where problem-solving approaches become concrete and rigid, or response inflexibility where behaviours are perseverative or stereotyped. Set-shifting has perhaps shown the most promise in identifying an eating disorder endophyte (Holliday et al., 2005). Roberts et al. (2010) reported that poor set shifting was associated with eating disorders and that this characteristic was maintained after recovery from the eating disorder and was also detected in patients' sisters with no eating disorder. They found poor set-shifting was associated with longer duration of illness, and severity of eating disorder rituals but was not associated with BMI. Roberts et al. (2010) concluded that set-shifting is a diagnostic feature of eating disorders, including bulimia nervosa, is not related to nutritional status, and is likely to be a familial trait that is involved with the maintenance of eating disorders.

The Wisconsin Card Sorting Test is often used as a measure of set-shifting. An amalgamation of participants from previously published studies from one research group was reported in Tchanturia et al. (2012) to produce an analysis of 82 participants with bulimia nervosa and 199 healthy controls on this task. Results from this large data set support the presence of poor set-shifting in bulimia nervosa.

In contrast, Galimberti et al. (2012), using the Intra-Extra Dimensional Set-shift Test from the CANTABeclipse battery, found no evidence of set-shifting impairments in 16 women with bulimia nervosa compared with 40 healthy controls. The authors speculate that the Intra-Extra Dimensional Set-shift Test does not measure the same set-shifting component as other studies that report impairments in set-shifting. Of note, this study did not find evidence of set-shifting impairment in women with anorexia nervosa in contrast to other literature. Again this suggests that the Intra-Extra Dimensional Set-shift Test may not be as sensitive to impairment in set-shifting compared with some other measures such as the Wisconsin Card Sorting Test.

Alvarez-Moya et al. (2009) suggest that bulimia nervosa is a disorder of impulse control and therefore should show similar neurocognitive impairment as individuals with pathological gambling. They compared executive functioning in 15 women with bulimia nervosa with 15 women with pathological gambling and 15 healthy controls using the Wisconsin Card Sorting Test. Despite their study being small and underpowered, they found that both groups showed impairment in set-shifting compared with controls, and the bulimia nervosa group exhibited greater distractibility by making more random errors.

Few studies have reported set-shifting in binge eating. Kelly et al. (2013) compared executive functioning in 50 women with objective binge eating episodes and/or subjective binge eating at least weekly over the past month and 66 women with no history of binge eating. After controlling for depression, anxiety, BMI and psychotropic medication they found no difference in cognitive impulsivity or rigidity, or in set-shifting, and overall both groups fell in the normal range. The authors noted that their sample was relatively young (mean age 19 years) compared with many other studies investigating set-shifting in individuals with binge eating disorder. Participants had a low duration of binge eating and

consequently may be early in the development of the disorder. Average BMI was just within the normal range and likely to be lower than other studies including the current study. The authors also speculate that impairment in executive function may be evident only when these functions are taxed, such as when experiencing negative affect or being confronted with food or body related stimuli.

Svaldi et al. (2010) used the Trail Making Test to investigate set-shifting using the proportional score $(B-A/A)$ and found lower scores in a group of binge eating disorder compared with a similar weight control group, with both groups in the normal range for weight.

In summary, the findings from several well controlled studies support an impairment in set-shifting in individuals with bulimia nervosa compared with individuals without binge eating. Difficulties in set-shifting may be, at least be in part, due to an impulsive response style resulting in increased errors compared to controls. However, some studies have not found impairments in set-shifting, possibly due to the choice of test used to explore set-shifting. In binge eating disorder the picture is less clear as there are fewer studies reporting on set-shifting. Those studies that have report either no impairment or small impairment in set-shifting; however there are methodological problems with sample characteristics which may not reflect the age and BMI of many individuals with binge eating.

2.1.8 Planning

Planning tasks examine the ability to identify and organise the steps needed to reach a specific goal. This ability requires a combination of sustained attention, impulse control, memory, and the ability to initiate action to devise and carry out a plan (Lezak et al.,

2012). Commonly used tests of planning ability include tower tasks such as the Tower of London, Tower of Hanoi and Stockings of Cambridge. Tower tasks are thought to be good measures of planning and strategy, and are able to present problems of increasing levels of complexity to challenge high functioning participants.

Planning ability rarely been investigated in individuals with bulimia nervosa and binge eating disorder. One small, underpowered study of 14 women with bulimia nervosa and 14 healthy controls found no difference in planning ability using the Tower of Hanoi (Brand et al., 2007). In another study, a group of 31 high weight women with binge eating disorder were found to be no different in performance on tower tasks than a group of 43 high weight healthy controls (Manasse et al., 2015).

With so few studies available to review, no conclusion can be drawn regarding planning ability in individuals with binge eating at present. As planning ability brings together a number of neuropsychological tasks this would seem to be a useful area for further research of neuropsychological functioning binge eating.

2.1.9 Decision-making

Decision making is the ability to weigh up multiple choices and to be able to evaluate which is the best course of action under given circumstances. The most commonly used decision-making tasks include the Iowa Gambling Task, the Delayed Discounting Task and the Game of Dice.

Decision-making may be impaired in bulimia nervosa. A number of studies have reported on decision-making using the Iowa Gambling Task. Brogan et al. (2010) found impairments in decision-making in 17 women with bulimia nervosa compared with 20 healthy weight controls. However, educational level, intelligence or premorbid IQ

estimates which could impact on decision-making ability, were not reported. Boeka & Lokken, (2006) compared 20 women with bulimia nervosa and 20 healthy controls using the Iowa Gambling Task to measure decision-making and also found poorer performance by the group with bulimia nervosa. Performance on this task was negatively correlated with bulimic symptomatology. Liao et al. (2009) also used the Iowa Gambling Task and reported poorer performance by a group of 26 women with bulimia nervosa compared with a group of 51 healthy controls. Brand et al. (2007) investigated decision-making in 15 women with bulimia nervosa compared to matched controls. They also found poorer decision-making in the bulimia nervosa group.

In binge eating disorder there is evidence of some impairment in decision-making. Danner et al. (2012) found impaired decision-making on the Iowa Gambling Task in 20 women with binge eating disorder, and 21 obese women without binge eating disorder compared with 34 healthy controls of normal weight.

Davis et al. (2010) conducted an interesting study comparing women with binge eating disorder with high weight women without binge eating disorder and healthy weight controls. Decision making was impaired in both the binge eating disorder and high weight groups. Furthermore an association was found between poor decision-making and difficulty in delaying gratification measured on the Delay Discounting Task, which is based on the premise that those that are more impulsive prefer more immediate rewards despite the value of the immediate reward being reduced. The binge eating disorder and obese groups had significantly lower level of education and the authors speculated that this may not be an artefact of recruitment but could reflect the impact of obesity (possibly with neuropsychological factors such as decision-making as a moderator) on educational

achievement. Further evidence of impulsivity in decision making has been reported in high weight women with binge eating disorder (Manasse et al., 2015; Mole et al., 2015).

However, another study which has also considered the association between decision-making and high weight suggests that impairments in decision-making in binge eating are independent of high weight (Svaldi et al., 2010). Decision-making was measured using the Game of Dice Task in 17 women with binge eating disorder and 18 high weight controls without binge eating. No difference was found in BMI between the two groups. The binge eating disorder group made more risky decisions and did not utilise feedback as effectively as the overweight controls, suggesting that may not be due to the effects of high weight.

In summary there appears to be some evidence of impairment in decision-making in individuals with bulimia nervosa and binge eating disorder. Women who binge eat may make decisions based on immediacy of reward and are more impulsive in their decision-making than women who do not binge eat. Some studies suggest that high weight may be associated with poor decision-making, although other studies do not support this. Again small samples sizes mean that many of these studies are underpowered. Unlike some of the other neuropsychological domains there is a consistency in tests chosen to measure decision-making which more easily allows comparison among studies. Decision-making was not directly assessed in the present study.

2.1.10 Central coherence

Weak central coherence is described as a cognitive bias towards processing local detail at the expense of more global information processing (Happé & Booth, 2008). Lopez et al. (2008) suggest that weak central coherence may be a feature of eating disorders, but

concluded that such research is at an early stage and neither supports nor refutes this hypothesis. Weak central coherence may be a trait, rather than a state and may be involved in the development of eating disorder cognitive traits such as fear of mistakes, perfectionism and fear of change (Lopez et al., 2009). The majority of research has investigated central coherence in anorexia nervosa. For a systematic review of central coherence across the eating disorder spectrum see Lang et al., (2014).

Harrison et al. (2011) used the Rey Osterrieth Complex Figure Test and the Group Embedded Figures Task to examine central coherence in 48 women with bulimia nervosa, 50 women with anorexia nervosa and 89 women with no eating disorder. They found that although women with bulimia nervosa displayed superior detailed processing compared to healthy controls and performed at a similar level to those with anorexia nervosa, the bulimia nervosa group did not exhibit the global processing deficit found in the anorexia group. In contrast, Roberts et al. (2013) examined central coherence in individuals with bulimia nervosa and did not find superior attention to detail in bulimia nervosa and concluded that poor global integration was more likely to be problematic.

Aloi et al. (2015) compared 45 women with binge eating disorder, 45 women with anorexia nervosa and 45 healthy controls, using the Rey Osterrieth Complex Figure Test. Women with binge eating disorder did not have a pattern of weak central coherence found in individuals with anorexia nervosa, rather they showed a pattern of disorganisation and lack of attention to detail.

In summary weak central coherence appears to be a trait mainly associated with anorexia nervosa; however, some aspects of it including a superiority in processing detailed information was found in one study on women with BN. Another study suggests no superiority in detailed processing but reported problems with global integration. Only one

study of binge eating has investigated central coherence and findings suggest a lack of attention to detail in binge eating. More research is needed in this area before conclusions can be drawn about central coherence in women with binge eating. Central coherence was not directly assessed as part of the current study, but appears to be an important area to consider for future studies.

Table 2.3 Summary of studies reporting on neuropsychological function in women with bingeing disorders

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Bulimia nervosa							
Alvarez-Moya et al. (2009)	15 BN	33.6	26.3	Stroop Colour/ Word Test	Interference	NS	Set-shifting No impairments detected other than non-perseverative errors suggesting greater distractibility in BN.
	15 HC	35.5	-	WCST	Categories	NS	
					Trials to first category	NS	
					Trials administered	NS	
					% perseverative errors	NS	
					% non-perseverative errors	BN>HC**	
Beatty et al. (1990)	32 BN	21.9	NR	Fluency Test	Letter	NS	Verbal fluency, Memory, Impairment in recall of verbal material, increased rule violations in BN (DSM-III)
	42 HC	24.6			Categories	NS	
					Famous people	BN<HC**	
					Design	NS	
					Rule violations	BN>HC*	
						BN<HC*	
Boeka & Lokken, (2006)	20 BN	19.1	18.3	Brown-Peterson Short-term Memory Test	Free recall trials 1-4	BN<HC*	Decision-making, Intelligence Low BMI, young age
	20 HC	18.9	17.7	WTAR	Delayed recall	NS	
				Iowa Gambling Task	Net score last 50 trials	BN<HC*	
Brand et al. (2007)	14 BN	21.9	21.6	Game of Dice Task	Net score		Decision-making, Attention, Memory, Problem solving, Working memory, Visuospatial, Intelligence Overall performance no different to HC and within normal range on tests with
	14 HC	21.6	21.3	Colour Word Interference Test	Interference	NS	
				Trail Making Test	A	NS	
					B	BN>HC*	
					Correct	NS	
				Nelson's Modified Card Sorting Test	Perseverative errors	NS	
					Non-perseverative errors	NS	
				Tower of Hanoi	3,4 discs	NS	

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Brand et al. (2007) continued from previous page				Digit Span	Forward	NS	exceptions of verbal and visuospatial memory and set-shifting. Decision-making showed poorer decision-making and impaired learning in BN group.
					Reverse	NS	
				Block Span	Forward	NS	
					Reverse	NS	
				COWA	FAS	NS	
					Supermarket	NS	
					Animals	NS	
				d2 Selective Attention Test	Total-errors	NS	
				ROCFT	Errors	NS	
					Delayed recall	BN<HC**	
				Auditory Verbal Learning Test	Trials 1-5	BN<HC*	
					Trial 1	NS	
(Ruiz et al., (2008)	25 BN 36 HC	Range 15-25	NR	WCST	Perseverative errors	BN>HC**	Set-shifting, Visuospatial, Planning. Poorer performance by BN but not all variables reported. Not well controlled for confounding variables
				ROCFT	Recall	BN<HC***	
				Tower of London	Moves	NS	
					Time to complete	BN>HC**	
Bosanac et al. (2007)	13 BN 16 HC	28.3 23.8	23.5 22.3	CDR Battery	Attention	BN<HC	Attention, Verbal memory and Motor function imparted in BN. Small sample size. Composite scores only reported.
					Verbal memory	BN<HC	
					Finger tapping	BN<HC	
					Working memory	NS	
Brogan et al. (2010)	17 BN 18 OB ^{\$} 20 HC	29.9 52.1 27.8	31.9 36.2 21.6	Iowa Gambling Task	Overall net score	BN, OB<HC**	Decision-making. Obese group older, no comparison for IQ or educational level.
					Blocks 1 & 2 net scores	NS	
					Blocks 3 & 4 net scores	BN, OB<HC*	

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Chan et al. (2014)	63 BN 67 HC	26.9 25.5	22.8 20.6	Iowa Gambling Task	Total score	BN<HC*	Decision-making BN more sensitive to gains than losses – reward sensitivity
Claes et al. (2006)	22 BN 83 HC	22.7 20.1	NR	Stop-go Task	Reaction time Accuracy	NS NS	Inhibitory control
Darcy et al. (2015)	42 BN 25 HC	16.9 15.5	NR	ROCFT WAIS (4 subtests)	Accuracy delay Accuracy copy Central coherence index Estimated IQ	BN<HC BN<HC NS BN<HC	Visuospatial, Intelligence Adolescents. BMI not reported – used % median body weight.
Degortes et al. (2015)	89 BN 160 HC	24.9 24.5	21.7 21.6	WCST IGT ROCFT Block Design Memory with interference Stop Signal Task		NS BN<HC** NS NS NS NS	Decision-making, Set-shifting, Visuospatial, Memory, inhibitory control. High proportion with previous AN – associated with poorer performance on WCST & IGT.
Galimberti et al. (2012)	16 BN 40 HC	25.3 26.0	20.4 19.2	CANTAB Battery: Stop Signal Task IED Task	Detection errors on “go” Mean correct reaction time SSRT ^{##} Errors block 6 Errors block 8	NS NS NS NS NS	Set-shifting, motor control No difference in BN compared to HC. All ED participants were on SSRI medication. Low BMIs

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Harrison et al. (2011)	48 BN 89 HC	27.1 28.5	21.0 21.6	Group Embedded Figures Test Fragmented Pictures Task ROCFT	Mean frame Time Coherence index	NS NS BN<HC	Central coherence: No global details problem but suggests more attention on detail rather than global in BN. Included AN participants. Age reported for ED overall and not for BN
Kim et al. (2011)	28 BN 26 HC	23.0 23.5	20.4 21.4	Group Embedded Figures Test ROCFT	Total Copy Recall	NS BN<HC* NS	Visuospatial. impairment on copy, no memory impairment in BN
Laessle et al. (1990)	30 BN ^{\$\$} 23 HC	24.9 25.0	19.6 20.3	CPT	Hit rate False alarm Sensitivity Response criterion	BN<HC* NS BN<HC* BN<HC*	Attention (DSM-III-R)
Lauer et al. (1999)	14 BN 12 AN No HC	21.9 19.7	(% IBW) 99.6 70.1	Letter Cancellation Task Trail Making Test Free Paragraph Recall Test CVLT Raven Standard Progressive Matrices	Number correct % Errors Items/second Items short-term Items long term Correct on 5 th trial Correct	NS NS NS NS NS NS	Attention, Set-shifting, Memory. No difference between AN and BN. Compared to norms some impaired performance in attention tasks but not in other domains. Small sample, no HC, Norms used were not defined.
Liao et al. (2009)	26 BN 51 HC	27.8 29.4	25.3 23.1	NART Iowa Gambling Task	Premorbid IQ Block net scores	NS BN<HC*	Intelligence, Decision-making

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments	
Lopez et al. (2009)	42 recovered AN/BN 42 HC	25.0	20.9	NART	Premorbid IQ	NS	Intelligence, Central coherence, Visuospatial Mixed sample diagnostically. AN/BN performed better on tasks requiring detail focussed processing but performed more poorly on tasks requiring global integration compared to HC	
		26.0	21.9	Embedded figures test	Total time taken	AN/BN<HC***		
					Time out failures	AN/BN<HC**		
				False claims	AN/BN<HC*			
					Unsegmented/segmented block design	Unsegmented		NS
						Segmented		NS
				Benefit from segmentation		NS		
				ROCFT	Order	AN/BN<HC*		
					Style	AN/BN<HC**		
				Sentence Completion Task	Coherence index	AN/BN<HC***		
					Local processing	AN/BN>HC***		
				Homograph Reading Task	Local completions	NS		
		Total score	NS					
McKay et al. (1986)	30 BN 30 HC	20.2	NR	Luria-Nebraska	Motor	BN>HC*	Motor function impaired in BN. Pathognomonic indicates possible right hemisphere dysfunction. DSM-III inpatients	
		21.5		Neuropsychological Battery	Pathognomonic Intelligence	BN>HC*		
					Memory	NS		
					+ 10 others	NS		
						NS		
Murphy et al. (2004)	16 BN 16 HC	22.0	20.1	MWT-B	Verbal intelligence	NS	Intelligence, Memory, Visuospatial, Attention, Set-shifting Small sample Comparing with OCD	
		25.3	22.0	Buschke’s Selective Reminding Test	Immediate recall	NS		
					Delayed recall	NS		
					Recognition	NS		
					Letters	NS		
				Controlled Oral Word AssociationSymbol-Digits Modalities Test	Category naming	NS		
					Alternation	NS		
					Correct substitutions	NS		

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Murphy et al. (2004) continued from previous page				ROCFT	Copy Delayed recall	NS NS	
				Trail Making Test	Part A Part B	NS NS	
Pendleton Jones et al. (1991)	38 BN 39 HC	24.1 24.9	NR	Neuropsychological battery reported in domains rather than individual test results.	Vigilance Focus/executive Verbal Memory Visuospatial	NS BN<HC** NS NS NS	Attention, Memory, Visuospatial Concluded any differences in function were “subtle”. % ideal weight reported
Roberts et al. (2010)	30 BN 88 HC	26.4 28.4	21.7 22.1	Trail Making Test WCST Brixton Task Haptic Illusion	Time B-A Errors Perseverative errors Categories completed Errors Perceptual illusions	BN>HC* NS BN>HC* BN<HC* NS BN>HC*	Set-shifting, Motor perception BN poorer set-shifting overall than HC. Some evidence for impairment set-shifting in unaffected sisters.
Roberts et al. (2013a)	30 BN 88 BN	26.4 28.4	21.7 22.1	GEFT ROCFT	Median Time-out errors Copy Recall Coherence index	NS NS BN<HC** BN<HC** BN<HC**	Visuospatial
Van den Eynde et al. (2012)	84 BN 61 HC	25.0 24.3	21.3 21.9	Go/No-go Task	Commission errors Omission errors	BN>HC NS	Inhibitory control
Tchanturia et al. (2012)	82 BN 199 HC	27.3 27.7	21.3 21.9	WCST	Number of trials Total correct Total response errors Categories completed	BN>HC* NS BN>HC* BN<HC*	Set-shifting BN performed slightly worse than HCs in most tasks

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Tchanturia et al. (2012) continued from previous page					Perseverative responses Perseverative errors Non-perseverative errors Trials to complete 1 st category Conceptual level responses Failure to maintain set Learning to learn	BN>HC* BN>HC* BN>HC* NS BN<HC* BN>HC* BN<HC*	
Tchanturia et al. (2004)	19 BN 35 HC	26.5 24.8	21.8 21.8	Trail Making Test Brixton Test Picture Set Test Verbal Fluency Task Cat Bat Task Haptic Illusion Task	Time Errors Total Pictures FAS Time Errors Illusions	NS NS NS NS NS BN>HC NS BN>HC	Set-shifting, Motor perception
Vall & Wade, (2015)	23 BN 149 HC	23.0 19.3	22.9 22.6	Trail Making Task	B-A	BN>HC**	Set-shifting
Van den Eynde et al. (2012)	40 BN 65 HC	28.3 24.0	25.2 22.2	d2 Brickencamp Letter Cancellation Task Stroop Word/Colour Test Go/No-Go Task Game of Dice Task	Number items processed % Errors (E) Concentration performance Fluctuation rate Interference Commission errors Net score	NS NS NS NS NS NS NS	Decision-making, Attention, inhibitory control, Intelligence ANCOVA for differences in age, NART and depression. No difference in function to HC.

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Weider et al. (2014)	40 BN 40 HC	27.6 27.9	21.7 22.5	WAIS-III	FSIQ VIQ PIQ	NS BN<HC* NS	Intelligence BN lower in verbal but not performance IQ
Weider et al. (2015)	39 BN 40 HC	27.5 27.5	21.8 22.4	Large neuropsychological test battery	Verbal learning & memory Visual learning & memory Visuospatial ability, Working memory, Executive function, Motor function	BN<HC BN<HC BN<HC BN<HC BN<HC BN<HC	Memory, Visuospatial, Working memory, Motor function BN lower performance on all measures than HC. No data reported for individual tests
Weider et al. (2016)	40 BN 40 HC	27.7 27.7	21.6 22.6	ROCFT	Copy Immediate recall Delayed recall	BN<HC BN<HC BN<HC	Visuospatial When controlling for depression differences were no longer significant
Wu et al. (2013)	19 BN 19 HC	27.1 26.6	22.2 22.1	Stop Signal Task Game of Dice Task	Reaction time Accuracy Total score	BN>HC* NS NS	Inhibitory control, Decision-making BIS – no significance ED psychopathology no different
Binge Eating Disorder							
Aloi et al. (2015)	45 BED 45 HC	30.6 25.6	35.2 20.2	Iowa Gambling Task ROCFT Trail Making Test WCST	Total score Accuracy Recall B-A Global score Part A (speed)	BED<HC* BED<HC** BED<HC* BED>HC*** BED>HC*** BED>HC*	Decision-making, Attention, Visuospatial, Set-shifting

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
Aloi et al. (2015) from previous page				Haying Sentence Completion	Part B (flexibility)	BED<HC**	
Danner et al. (2012)	20 BED 21 OB 34 HC	38.0 44.6 36.1	38.7 30.8 22.3	Iowa Gambling Task	Overall net score Blocks 1 - 5 net scores improvement (learning)	BN, OB<HC* HC**; BN, OB NS	Decision-making impairments in BN and OB both in overall score & learning.
Davis et al. (2010)	65 BEDO 73 HCO 71 HC	34.3 31.8 35.2	35.7 38.6 21.7	Iowa Gambling Task Delay Discounting Task	Block net scores Indifference points	BED, OB<HC* BED, OB<HC***	Decision-making HC group sig higher education.
Kelly et al. (2013)	50 subclinical BN 66 HC	19.3 19.0	24.5 23.4	WCST Connor's Continuous Performance Task	Errors Perseverative responses Commission errors	NS NS NS	Set-shifting NS after controlling for depression, anxiety, BMI, IQ and medication use.
Manasse et al. (2015)	31 BEDO 43 HCO	45.1 51.1*	36.8 37.9	Delayed Discounting Task Tower Task Stroop, colour/word Penn Conditional Exclusion Penn Letter N-back Task Balloon Analogue Risk Task	Level of discounting Achievement score Errors, time	BED-O<HCO* BED-O<HCO** NS NS NS NS	Decision-making, Impulse control, Problem solving, Working Memory, Intelligence. BED group includes subthreshold Controlled for age and IQ
Mole et al. (2015)	30 BEDO 30 HCO 30 HC	42.9 44.1 43.6	34.7 32.7 24.1	Delayed Discounting Task Stop Signal Task Information Sampling Task		BED-O=HCO<HC BED>HCO NS	Decision-making, Inhibitory control
Svaldi et al. (2010)	17 BED 18 HCO	42.4 38.3	32.8 30.7	Trail Making Test	Part A Part B Time B-A/A	NS BED>HCO* BED>HCO*	Attention, Set-shifting, Decision-making. BED made riskier decisions

Study	Diagnostic Groups	Age	BMI	Neuropsychological Test	Outcome variable	Results [#]	Domain tested/Comments
				Game of Dice Task	Net score	BED< HCO *	
Wu et al. (2013)	54 BEDO 43 HCO	40.1 39.8	34.0 35.1	Stop Signal Task Game of Dice Task	Reaction time Accuracy Total score	NS NS NS	Inhibitory control, decision-making.

* p<0.05, ** p<0.01, ***p<0.001, NS = not significant

[#] The group in bold had the superior performance

^{##} SSRT is the mean time in ms to suppress motor response

^{\$} Obese sample recruited from an obesity management clinic. No definition of obesity reported.

^{\$\$} DSM-III-R diagnostic criteria used

AN = anorexia nervosa

AN/BN = mixed group of anorexia and bulimia nervosa

BED = binge eating disorder

BEDO = obese binge eating disorder

BN = bulimia nervosa

EDNOS = eating disorder not otherwise specified

HC = healthy controls

HCO = obese healthy controls

IBW = ideal body weight

NR = Not reported

CVLT = California Verbal Learning Test

DSM-III-R = Diagnostic and Statistical Manual, 3rd edition, revised

IED = Intra Dimensional/Extra Dimensional Shift Task

IGT = Iowa Gambling Task

NART = National Adult Reading Test, NS = no significant difference

ROCFT = Rey Osterrieth Complex Figure Test

SSRI = selective serotonin reuptake inhibitor

WCST = Wisconsin Card Sorting Test

2.2 Neuropsychological Functioning in Obesity

Obesity is defined as the excess of body fat (adipose tissue) and is increasing in prevalence worldwide (World Health Organization, 2000) and in New Zealand (Ministry of Health, 2015b). Body Mass Index (BMI) is commonly used as a way of measuring levels of obesity. A BMI of less than 20 is considered to be underweight, 20-25 is considered to be a normal, healthy weight, whereas a BMI of between 25 and 30 is considered overweight and BMI over 30 is classified as obese (World Health Organization, 2000).

There are significant health risks associated with obesity including diabetes, hypertension, other cardiovascular problems, cancer, sleep apnoea and depression (Dixon, 2010; Mokdad et al., 2003). There is also some evidence of reduced neuropsychological functioning in obese individuals. As a proportion of women who binge eat have BMIs in the overweight (BMI between 25 and 29) and obese (BMI 30 and above) ranges, it is important to consider the potential contribution of obesity itself as a factor when examining neuropsychological functioning in this group. Possible mechanisms include genetically influenced factors, the impact of known medical consequences such as hypertension and insulin resistance, and direct effects of obesity through mechanisms such as inflammation.

Recent studies indicate that obesity and neuropsychological functioning could be genetically linked. Specific single nucleotide polymorphisms (SNPs) found in higher levels with increasing obesity have been associated with cognitive decline in adults (Whitmer et al., 2005). Further to this finding, Bressler et al. (2013) found that a specific SNP called FTO, is more prevalent in obese individuals, and has negative effect on cognitive ability, independent of BMI.

The effect of obesity related illnesses such as cardiovascular disease and diabetes on neuropsychological function has also been examined. It has been suggested that lower neuropsychological function in obese individuals has been linked to the impact of these illnesses rather than the effect of obesity. Yesavage et al. (2014) explored these associations among obesity, hypertension, diabetes and sleep breathing disturbance and performance on tests of executive function and auditory verbal memory in four different community samples of men and women aged over 50 (mean ages 61 to 69, total sample $n=369$). They found in this older population that poor executive function and auditory verbal memory were more likely to be due to insulin resistance and “metabolic syndrome”. The authors note that this could have implications for individuals with binge eating as they are more likely to have insulin resistance.

Fitzpatrick, Gilbert, & Serpell, (2013) in their systematic review of obesity and neuropsychological functioning note that none of the studies they identified could be used to examine the direction of any association between obesity and neuropsychological functioning. Theories have been postulated for both directions. Boeka & Lokken, (2006) suggest that the tendency for some individuals who have had weight loss surgery and have difficulty maintaining the weight loss and adjusting to changes following surgery indicates a pre-existing weakness in executive functioning. Others have theorised that obesity causes changes in physiology that are detrimental to neuropsychological functioning as already described (Yesavage et al., 2014).

There have been two comprehensive reviews of obesity and neuropsychological function (Prickett, Brennan, & Stolwyk, 2015; Smith et al., 2011). Few studies have been published in this area but there is some evidence for reduced functioning in tests of intellectual function (IQ), motor speed, visuo-spatial skills, set-shifting and decision-

making. There was no strong evidence of impairments in memory, divided attention or verbal fluency. The majority of studies did not account for potential confounding variables such as depression and other comorbidities.

A few studies have looked at the association between obesity, binge eating and neuropsychological functioning. Inhibitory control was explored using a go/no-go task using food related stimuli in one condition and body related stimuli in the other (Mobbs et al., 2011). Obese participants were no different from healthy weight controls in performance on this task; however, obese participants who also met criteria for binge eating disorder made significantly more errors than the other two groups. This suggests that differences may be due to the presence of binge eating rather than obesity.

Decision-making in obese women was compared with that in women with binge eating disorder and healthy controls using the Iowa Gambling Task (Davis et al., 2010). Both the obese and binge eating disorder groups had poorer performance than the healthy controls but were not different from each other; however when levels of education were controlled no significant difference was found. The same study investigated delayed gratification using the Delayed Discounting Task which assumes that more impulsive participants would select more immediate rewards even when the size of the reward is smaller than if they had waited. Again the authors found that the obese and binge eating disorder groups were more impulsive than the healthy control group but again this after controlling for level of education no significant differences were found. Another study also using the Iowa Gambling Task found that obese women with binge eating disorder had similar impairments in decision-making to obese women without binge eating (Danner et al., 2013). Both groups performed worse on this task than healthy controls of healthy weight.

Manasse et al. (2015) found that obese women with binge eating disorder performed less well on tasks of decision-making and risk taking than obese women without binge eating. However, there was no difference between groups on tasks of problem solving (Tower Task) or working memory (Penn Letter N-back Task, Penn Conditional Exclusion Task) or sustained attention (Stroop Test).

Mole et al. (2015) also found no difference in decision-making between obese women with and without binge eating disorder, yet both groups scored more poorly than non-obese healthy controls. The obese binge eating group had better inhibition control than the obese non-bingeing group. Svaldi et al. (2010) found no difference between the obese binge eating group and the obese control group on motor inhibition control on the Stop Signal Task and decision-making on the Game of Dice Task.

A small study (Roberts et al., 2007) investigating set-shifting and central coherence in obese participants compared with healthy weight controls found evidence of weak central coherence exhibited by a disorganised response style in the obese group but did not find any differences in set-shifting ability. This study was limited by the small sample size (10 in the over-weight group) so was underpowered.

In summary findings on the impact on obesity in binge eating on neuropsychological function are inconsistent. Some studies show impairment, particularly in decision-making, are greater in obese binge eating groups than in obesity without binge eating. Other studies suggest decision-making in obese groups with binge eating is no different from obese controls. Other neuropsychological domains including motor inhibition are also inconsistent with one study showing enhanced performance in obese binge eating group compared with obese controls. The use of different neuropsychological tests to measure the same neuropsychological constructs also presents problems when comparing studies

and may contribute to different findings being reported by different research groups. As with research into binge eating reported in the preceding section, many studies have not taken potential confounders into account and some suffer from being statistically underpowered.

2.3 *Comorbidities: Depression and Anxiety*

2.3.1 Depression

Depression is the most common comorbid psychiatric disorder in bulimia nervosa (O'Brien & Vincent, 2003) and is associated with severity of bulimic symptoms (Spindler & Milos, 2007). The life time prevalence of any mood disorder has been reported at 59% in bulimia nervosa and 46% in binge eating disorder in a World Health Organisation survey of over 24 000 individuals across 14 countries including New Zealand (Kessler et al., 2013).

Depression is known to have a negative impact on neuropsychological functioning. Meta-analyses have found evidence for a negative association between level of depression and processing speed, episodic memory, working memory, inhibitory control, problem solving and planning (Marazziti et al., 2010; McDermott & Ebmeier, 2009), with semantic memory and visuospatial memory being unaffected.

As depression is common in women with binge eating and is known to negatively affect neuropsychological functioning, it is important to investigate this further. A number of studies of neuropsychological functioning in women with binge eating have reported the rate of comorbid depression or have measured the severity of depression using a psychometric tool such as the Beck Depression Index (BDI). Some studies have used depression measures as co-variables in their analyses; however, few have directly investigated the relationship between depression and neuropsychological functioning in

individuals with binge eating. A summary of studies that have examined this association is presented in Table 2.4

Table 2.4 Summary of studies reporting on impact of depression on neuropsychological function in women with binge eating

Study	Groups	Depression measures	Relationship with neuropsychological tests
Beatty et al. (1990)	32 BN 14 MDE 42 HC	BDI BN>HC	Verbal memory: negative association with BMI Verbal fluency: negative association with BMI
Boeka & Lokken, (2006)	20 BN 20 HC	BDI-II BN>HC***	Decision-making (IGT): no association with BDI-II
Chan et al. (2014)	65 BN 67 BED	BDI BN>HC***	Decision-making (IGT): no association with BDI-II
Liao et al. (2009)	26 BN 51 HC	BDI BN>HC***	Decision-making (IGT): no association with BDI-II
Roberts et al. (2010)	30 BN 88 HC	HADS D	Set-shifting composite variable small association with HADS D
Roberts et al. (2013)	30 BN 88 HC	HADS D	Weak central coherence: positive association with HADS D
Weider et al. (2016)	40 BN 40HC	BDI-II BED>HC***	Visual memory (ROCFT): negative association with BDI-II
Aloi et al. (2015)	45 BED 45 HC	BDI BED>HC***	Cognitive flexibility (HSCT): negative association with BDI IGT, ROCFT, WCST, TMT: no association with BDI
Svaldi et al. (2010)	17 BED 18 HC	BDI-II BN>HC***	Decision-making (GDT): no association with BDI-II

* p<0.05, ** p<0.01, ***p<0.001

BED = binge eating disorder; BN = bulimia nervosa; HC = healthy controls; BDI = Beck Depression Inventory; GDT = Game of Dice Task; HADS D = Hospital Anxiety and Depression Scale Depression; HSCT = Hayling Sentence Completion Task; IGT = Iowa Gambling Task; ROCFT = Rey Osterrieth Complex Figure Test; TMT = Trail Making Task; WCST = Wisconsin Card Sorting Test

Levels of depression were found to be slightly higher in women with bulimia nervosa who showed greater set-shifting difficulties than those with lower levels of set-shifting difficulties (Roberts et al., 2010), although effect sizes were small. A similar pattern of increased depression was also found in women with bulimia nervosa who had weaker

central coherence than those with better performance in this area (Roberts et al., 2013). In these studies severity of eating disorder symptoms was more strongly related to neuropsychological difficulties than depression.

Only one study has reported impairment in verbal memory and verbal fluency in 17 individuals with bulimia nervosa and severe depression compared with 15 individuals with bulimia nervosa who had less severe levels of depression (Beatty et al., 1990). No difference between the groups was reported for verbal fluency; however, verbal recall was found to be lower in the severely depressed group.

No association between severity of depression and decision-making ability measured by the Iowa Gambling Task has been found in individuals with bulimia nervosa or binge eating disorder (Boeka & Lokken, 2006; Chan et al., 2014; Liao et al., 2009). This suggests that if impairments in decision-making are present in women with binge eating is not likely to be due to the influence of depression.

In binge eating disorder, (Aloi et al., 2015), found reduced cognitive flexibility to be correlated with depression; however no correlations were found for test of decision-making, visuospatial ability or set-shifting.

Reduced ability to manage negative mood states in individuals with binge eating have been associated with impairments in set-shifting using an experimental paradigm (Dingemans et al., 2015). Women with binge eating disorder (DSM-5 criteria) completed the Trail Making Test (TMT) after to exposure to either a sad film clip (n=36) or a neutral clip of a weather report (n=39). The participants randomised to the negative film clip reported lower mood states on a visual analogue scale and recorded lower ratio scores on the TMT than those that had been randomised to the neutral condition. That is set-shifting was

relatively impaired when individuals are in a negative mood state compared with a positive mood state. This is interesting as it suggests that affective state at the time of testing may influence set-shifting ability in a very immediate way that may not be captured in traditional measures of mood such as diagnostic criteria or psychometric measures of depression.

In summary, few studies have directly investigated the association between depression and neuropsychological functioning in individuals with binge eating and to date there is not sufficient evidence as to whether depression impacts on neuropsychological performance in this group. However, some interesting findings regarding mood states and set-shifting suggest further exploration of this is warranted.

2.3.2 Anxiety

Anxiety is a highly prevalent comorbidity in binge eating. Lifetime prevalence of any anxiety disorder has been reported as high as 65% in bulimia nervosa (Kessler et al., 2013) and 56% in binge eating disorder (Hudson et al., 2007). The prevalence of anxiety disorders in individuals with binge eating is much higher than in general population and can precede development of an eating disorder (Kaye et al., 2004). Attentional Control Theory (Eysenck et al., 2007) suggests that anxiety has a negative impact on goal directed attention resulting in problems with shifting attention and inhibitory control but conversely anxiety may improve function in conditions where compensatory strategies such as enhanced effort are used. Therefore the effect of anxiety could be detrimental in some areas of neuropsychological function but may enhance others. As might be expected, the pattern of neuropsychological impairments have been reported to differ depending on the type of anxiety disorder being tested (Castaneda et al., 2008).

A number of studies investigating neuropsychological function in women with binge eating have reported the prevalence of comorbid anxiety disorders using diagnostic criteria or have measured anxiety with psychometric measures to describe their sample's characteristics. However, very few have directly investigated this relationship in bulimia nervosa and none in binge eating disorder (see Table 2.5).

Consistent with Attentional Control Theory (Eysenck et al., 2007), Roberts et al. (2010) found a small association between anxiety during the past week and poorer performance on set-shifting tasks in women with bulimia nervosa. There was also found to be a small association with anxiety and weak central coherence (Roberts et al., 2013). However, Pendleton Jones et al. (1991) found no significant correlations between anxiety and any of the neuropsychological domains tested as part of a large neuropsychological battery. Specific statistics were not reported in this study, making it difficult to interpret the results.

Table 2.5 Summary of studies reporting on impact of anxiety on neuropsychological function in women with binge eating.

Study	Groups	Anxiety measures	Relationship with neuropsychological tests
Pendleton Jones et al. (1991)	38 BN 40 AN 39 HC	TSCT	Comprehensive test battery: relationship between decreased performance and anxiety. Specific statistics not reported. AN and BN were not differentiated in results.
Roberts et al. (2010)	30 BN 88 HC	HADS A	Set-shifting: small negative association with HADS A
Roberts et al. (2013)	30 BN 88 HC	HADS A	Weak central coherence: positive association with HADS A

NS= no significant difference; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

AN = anorexia nervosa; BED = binge eating disorder; BN = bulimia nervosa; HC = healthy controls; MDE = major depressive episode; BDI = Beck Depression Inventory; GDT = Game of Dice Task; HADS A = Hospital Anxiety and Depression Scale Anxiety; HADS D = Hospital Anxiety and Depression Scale Depression; HSCT = Hayling Sentence Completion Task; IGT = Iowa Gambling Task; ROCFT = Rey Osterrieth Complex Figure Test; TMT = Trail Making Task; TSCT = Tryon Stein & Chu Tension Scale; WCST = Wisconsin Card Sorting Test

In summary the prevalence of comorbid anxiety disorders is very high in individuals with binge eating. Potentially anxiety could reduce or enhance performance on neuropsychological tests depending on the domain being measured. There is some evidence for anxiety to be associated with attention and set-shifting, and possibly central coherence in women with bulimia nervosa; however, there have been no studies reporting on this association in binge eating disorder. More research is needed in this area.

2.4 Impulsivity in Neuropsychological Functioning

A number of studies reviewed in previous sections of this chapter have noted the tendency for individuals to respond impulsively on some neuropsychological tests, particularly on decision-making tasks. An impulsive response on a test does not necessarily indicate a more general impulsive personality but is useful to investigate this characteristic in more detail in individuals with binge eating as a potential mechanism to understand neuropsychological function in this group.

Impulsivity can be defined as “a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others” (Moeller et al., 2001, p 1784) and has found to be present in a range of psychiatric disorders including eating disorders. Impulsivity has been found to be able to differentiate those with binge eating from those without binge eating (Waxman, 2009) and may even play a role in the development of binge eating (Dawe & Loxton, 2004). Impulsivity in binge eating may also extend to increased comorbidity of other impulsive behaviours such as alcohol and substance use in this population (Bulik et al., 2004; Dansky, Brewerton, & Kilpatrick, 2000).

Impulsivity has generally been measured using self-report questionnaires, with the Eysenck Impulsiveness Scale and the Barratt Impulsiveness Scale the most commonly used (Waxman, 2009). The BIS-11 is comprised of three subscales; Non-planning which measures lack of future orientation, Motor which is a measure of impulsive actions, and Cognitive which measures impulsive thinking and lack of patience (Barratt, 1994).

In neuropsychological testing, impulsivity has been examined in two main domains; motor impulsivity and cognitive impulsivity and can further be broken down into the failure to stop a response (inhibitory control) or responding prematurely in anticipation of the target stimuli (Mole et al., 2015).

Studies directly investigating impulsivity in individuals with binge eating have examined tests of set-shifting, impulsivity control, and decision-making and are summarised in Table 2.6. Claes et al., (2006) compared 63 women with bulimia nervosa to 67 healthy controls and reported no association between impulsivity and set-shifting. At present there are insufficient studies to be able to state whether impulsivity in binge eating has an impact on set-shifting ability.

Kemps & Wilsdon, (2010) investigated the role of impulsivity in neuropsychological function in 13 women with bulimia nervosa and 13 healthy control women. They found impairment on tasks of verbal inhibitory control (Stroop Test and Excluded Letter Frequency Test) in the bulimia nervosa group which correlated with scores on the Barratt Impulsivity Scale. The authors concluded that “poor inhibitory control in bulimia nervosa is at least partially attributable to an impulsive disposition” (Kemps & Wilsdon, 2010, p515). Impulsivity in bulimia nervosa has also been associated with increased errors on tests of motor inhibitory control on the Stop Signal Task (Galimberti et al., 2012) and Go/No-go Task (Rosval et al., 2006).

Table 2.6 Summary of papers reporting on impulsivity and neuropsychological function in women with binge eating

Study	Groups	Impulsivity measures		Relationship with neuropsychological tests
Boisseau et al. (2012)	21 ED [#] 21 HC	BIS Cognitive Motor Non-planning	ED>HC*** NS ED>HC*	Inhibitory control: stop signal task no association with BIS subscales
Brand et al. (2007)	14 BN 14 HC	NEO Impulsivity	BN>HC***	No association between impulsivity and neuropsychology measures
Claes et al. (2006)	63 BN 67 HC	BIS total	NS	Set-shifting: TMT, Stroop no association with BIS
Danner et al. (2012)	20 BED 34 HC	BIS	BED>HC	IGT No association with BIS
Galimberti et al. (2012)	16 BN 40 HC	BIS Cognitive Motor Non-planning	BN>HC*** NS NS	Inhibitory control: Stop signal errors associated with BIS Cognitive
Kemps & Wilsdon, (2010)	13 BN 13HC	BIS	BN>HC*	Inhibitory control: Stroop Task, HSCT, Excluded Letter Frequency, Matching Familiar Figures. Controlling for impulsivity removed significance for Stroop and Excluded Letter Fluency differences. Concluded that impulsivity contributes at least in part to poor inhibitory control.
Liao et al. (2009)	26 BN 51 HC	BIS	NS	IGT: no association with BIS.
Rosval et al. (2006)	84 BN 61 HC	BIS	BN>HC*	Go/No-go: BN more commission errors but omission errors no different
Svaldi et al. (2010)	17 BED 18 HC	BIS BAS fun seeking BAS reward responsiveness	NS BED<HC** BED<HC*	GDT: No association with BIS Negative correlation between BAS fun seeking and GDT net score i.e. more fun seeking, more riskier decisions.

NS=no significant difference; * p<0.05, ** p<0.01, ***p<0.00; # sample made up of 12BN and 9 EDNOS; BED=binge eating disorder; BEDO = binge eating disorder with obesity; BN=bulimia nervosa; HC=health controls. BAS = Behaviour Approach Scale; BIS= Barratt Impulsiveness Scale-11; ID/ED = Intra Dimensional/Extra Dimensional Shift Task; NEO = NEO Personality Inventory; TMT=Trail Making Test.

Despite the small number of studies, there seems to be some evidence of impulsivity personality traits to be associated with increased errors in task of inhibitory control in women with bulimia nervosa. In binge eating there is a paucity of studies investigating this area. Svaldi et al. (2010) did not find an association between impulsivity and decision-making in 17 women with binge eating disorder compared to 18 healthy control women; however, this study was underpowered.

It has been suggested that individuals with binge eating may perform poorly on decision-making tasks due to a tendency to choose immediate rewards despite long-term consequences which may be related to “impulsive personality traits” (Danner et al., 2012, p60). However, several studies have not found an association between impulsivity using the Barratt Impulsivity Scale and decision-making using the Iowa Gambling Task. (Danner et al., 2012; Liao et al., 2009; Svaldi et al., 2010). As with set-shifting and inhibitory control, there have not been enough studies directly investigating the links between impulsivity and neuropsychological performance to be able to conclude whether there is an association between these factors in women who binge eat.

2.5 Potential Confounding Factors on Neuropsychological Functioning

A number of factors can affect performance on neuropsychological tests. Some of these factors are fixed and long term influences such as history of head injury or handedness whereas others are not fixed and have a proximal influence, such as recent consumption of psychoactive substances. This section discusses the relevance of factors that could influence neuropsychological test performance.

Handedness is genetically determined and can influence relative strength and weaknesses in neuropsychological testing (Lezak et al., 2012). There is evidence that right-handers tend to score more highly on tests requiring visuospatial ability whereas left-handers may have an advantage in artistic and mathematical tasks (Lezak et al., 2012). Handedness has not been investigated in people with binge eating but a study by Tenconi et al., (2010) found that handedness did not alter neuropsychological functioning in a group of 153 people with anorexia nervosa.

Head injury through accident or illness may impact neuropsychological abilities depending on the area and extent of damage. A few studies of anorexia have reported rates of potential brain injury which were no different from the healthy control groups (Southgate et al., 2006). Most studies of bulimia nervosa and binge eating disorder have not reported histories of brain injury.

As noted earlier, psychiatric co-morbidities, particularly depression and anxiety, are common in bulimia nervosa and binge eating disorder (Pearlstein, 2002) and may impact on neuropsychological function. Physical health may also impact on neuropsychological function. Health conditions may affect auditory and visual perception, influence physical ability to carry out the tasks required, or increase levels of fatigue.

Severity of illness in eating disorders could potentially influence test performance and can be measured a number of different ways. The most common measure of severity in anorexia is BMI; however in the binge eating population the utility of this as a proxy for illness severity is questionable as it may or may not reflect the extent of disordered cognitions and behaviors (such as bingeing and purging frequency). Other common measures of eating disorder illness severity include the duration of illness, a past history of anorexia nervosa, or psychometric measures of symptomatology, such as the Eating

Disorder Inventory (EDI). Measures of overall global functioning are less commonly reported.

Medication status of participants is sometimes not reported despite medication commonly being prescribed to treat individuals with eating disorders. Southgate et al. (2005) noted in their review of neuropsychological function in eating disorders that this was a weakness in the literature in this area. The lack of reporting in this area makes it more difficult to directly compare results of studies.

In New Zealand alcohol use is common in the general population (Ministry of Health, 2015a). The effect of alcohol consumption on neuropsychological functioning is contentious. There is some evidence that moderate levels of consumption are not detrimental to neuropsychological performance and long term may even confer a small positive effect on neuropsychological function in adults. (Britton et al., 2004). Immediate effects of alcohol intoxication include mental and psychomotor slowing and are likely to negatively affect performance on neurological tests particularly verbal working memory (Sullivan et al., 2000), inhibition control (Ray & Bates, 2007) and depth perception (Wegner & Fahle, 1999). Chronic alcohol abuse can lead to Wernicke–Korsakoff syndrome which is characterised by significant decline in cognitive function (Sechi & Serra, 2007).

Caffeine is known to improve psychological function if consumed immediately before testing. Improvements in sustained attention and psychomotor speed, verbal working memory, sustained attention, spatial memory, and reduced mental fatigue have been reported (Haskell et al., 2005; Rees, Allen, & Lader, 1999).

Cannabis is the most commonly used recreational drug after alcohol in New Zealand (Ministry of Health, 2015c). Cannabis use has found to be higher in the bulimia binge-purge subtype compared to bulimia nervosa non-purging and binge eating disorder in this sample (Jordan et al., 2014). Cannabis intoxication has been associated with impairments in recall, decision-making, inhibitory control and reaction times (Gonzalez, 2007).

Studies investigating neuropsychological functioning in binge eating vary widely in the extent to which they have reported and controlled for potentially confounding factors. A summary of confounding factors reported by various studies is shown in Table 2.7. Almost all studies have reported age and BMI; however many have not reported other significant confounders such as substance use, medication use and premorbid IQ estimates.

In summary, it is important to account for a range of factors that could potentially influence neuropsychological test performance. Many studies have not reported these variables which makes direct comparison of studies more difficult.

Table 2.7 Reporting of confounding factors in previous studies investigating neuropsychological functioning in bulimia nervosa and binge eating disorder. X signifies the factor has been reported by the study.

Study	Age	BM	Education	Handedness	Caffeine	Alcohol	Cannabis	Anxiety	Depression	Medication	Head injury	Illness severity	Illness duration	Global function	Premorbid IQ
Bulimia nervosa															
Alvarez-Moya et al. (2009)	X		X							X					X
Beatty et al. (1990)	X	X	X					X	X	X					
Boeka & Lokken, (2006)	X	X	X						X		X	X			X
Brand et al. (2007)	X	X	X					X	X				X		
Bosanac et al. (2007)	X	X						X	X	X			X		X
Brogan et al. (2010)	X	X	X												
Ruiz et al. (2008)	X		X												
Chan et al. (2014)	X	X							X						
Claes et al. (2006)	X	X													
Darcy et al. (2015)	X	X							X	X		X	X		X
Darcy et al. (2012)	X	X							X	X	X	X	X		X
Degortes et al. (2015)	X	X	X	X						X					
Galimberti et al. (2012)	X	X	X							X			X		
Harrison et al. (2011)	X	X	X					X	X	X		X	X		X
Kim et al. (2011)	X	X	X					X	X	X		X	X		X
Laessle et al. (1990)	X	X								X		X	X		
Lauer et al. (1999)	X	X	X						X			X	X		
Liao et al. (2009)	X	X	X						X		X		X	X	X
(Lopez et al. (2009)	X	X	X					X	X		X				X
McKay et al. (1986)	X		X							X					
Murphy et al. (2004)	X	X							X	X	X	X			X
Pendleton Jones et al. (1991)	X	X	X	X				X	X	X					
Roberts et al. (2010)	X	X	X					X	X		X	X	X		
Roberts et al. (2013)	X	X	X			X		X	X			X	X		
Rozenstein et al. (2011)	X	X	X						X			X			
Tchanturia et al. (2012)	X	X											X		
Tchanturia et al. (2004)	X	X													
Van den Eynde et al. (2012)	X	X						X	X	X		X	X		X
Weider et al. (2014)	X	X	X						X	X	X		X		
Weider et al. (2015)	X	X	X	X					X	X	X	X	X		X

Study	Age	BM	Education	Handedness	Caffeine	Alcohol	Cannabis	Anxiety	Depression	Medication	Head injury	Illness severity	Illness duration	Global function	Premorbid IQ
Weider et al. (2016)	X	X	X						X	X	X	X	X		X
Wu et al. (2013)	X	X	X												
Binge eating disorder															
Aloi et al. (2015)	X	X	X						X		X	X			
Danner et al. (2012)	X	X													
Davis et al. (2010)	X	X	X						X						
Kelly et al. (2013)	X	X	X					X	X	X	X	X			X
Manasse et al. (2015)	X	X							X	X	X	X			X
Mole et al. (2015)	X	X	X			X	X		X		X	X	X		X
Svaldi et al. (2010)	X	X	X						X			X			
Wu et al. (2013)	X	X									X	X			

2.6 Summary

Neuropsychological testing is a non-invasive way to explore brain function. The information gathered from such testing can help inform understanding of the processes involved in the development, maintenance factors and treatments for individuals with binge eating. To date there have been a number of studies investigating the neuropsychological functioning in individuals with binge eating. Overall studies often report contradictory findings and methodological issues make direct comparisons difficult. For example, studies use different tests to measure the same neuropsychological concepts, and even when the same test are used, often different variables have been reported. This results in little replication of studies which is important to establish that a finding is able to be replicated by other research groups. Where variables have been calculated there is often no explanation of how they have been calculated. Many studies are underpowered and would be unable to detect even a large effect size. Different approaches in assessing

diagnostic categories also differs with some studies using a standard clinical interview with others using the more robust method of a structured clinical interview such as the SCID-I. Changes in DSM classifications over time also has implications when comparing studies as although changes are not usually large they do affect who is eligible for studies. The use of EDNOS is also problematic as each study has defined their own criteria. Despite these problems with methodology there have been a few larger and well controlled studies, mainly investigating bulimia nervosa with a growing number investigating binge eating disorder.

A review of the literature suggests possible impairment across a range of domains including attention, memory and inhibitory control, and executive function. However, where impairments have been found they tend to be relatively small. On balance, neuropsychological functioning in binge eating is likely to be relatively intact, with some subtle impairment detected on some of the more cognitively demanding tests.

3. METHODS

3.1 *Main Study Design*

Data reported in this thesis were obtained as part of the Binge Eating Psychotherapy Study (McIntosh et al., 2016) which was carried out in the Clinical Research Unit, Department of Psychological Medicine, University of Otago, Christchurch, and the Canterbury District Health Board. The Binge Eating Psychotherapy Study was a randomised controlled clinical trial comparing three cognitive-based therapies for treating women with transdiagnostic binge eating. Inclusion criteria were:

- Women aged 16 years or older
- Regular binge-eating (at least twice weekly for three months if compensatory behaviours are present: at least two days weekly for six months if no compensatory behaviours)
- Body mass index (BMI) >17.5

Exclusion criteria were:

- Current severe major depression
- Current severe psychoactive substance dependence
- Current or past history of bipolar I disorder or schizophrenia
- Developmental learning disorder or cognitive impairment
- Major medical or neurological illness that could interfere with assessment or treatment
- Treatment (psychotherapy and/or medication) for binge eating or other eating disorder in the previous 12 months.
- Current use of psychotropic medication

Data was also collected from a recruited control group of women who had no eating disorder (healthy control group). The control group were recruited through community advertisements placed on notice boards in supermarkets, gyms, universities, buses and other public spaces around Christchurch. Inclusion and exclusion criteria were the same as for the treatment group as described above, other than regular binge eating being an exclusion criterion rather than an inclusion one. Absence of eating disorders symptoms in the control participants was determined using the Eating Disorders Examination (EDE), a structured clinical interview.

Ethical approval was granted by the Upper South A Regional Ethics Committee for the initial BEP study and for the subsequent control group extensions (Ethics reference number: CTB/04/08/139).

3.2 Participants

Participants were recruited by referrals from General Practitioners, The Eating Awareness Team (EAT), The South Island Eating Disorders Service, as well as by self-referral through advertising. Advertising posters were placed at tertiary institutions, on public buses, at supermarkets and gymnasiums in Christchurch. Awareness of the study was also raised by newspaper articles. Participation was voluntary and written informed consent was obtained. One hundred and twelve women consented to participate in the psychotherapy study. Figure 3.1 shows the number of women screened, eligible and completing neuropsychological and biological assessments is shown. Fifty women were separately recruited for the healthy control group.

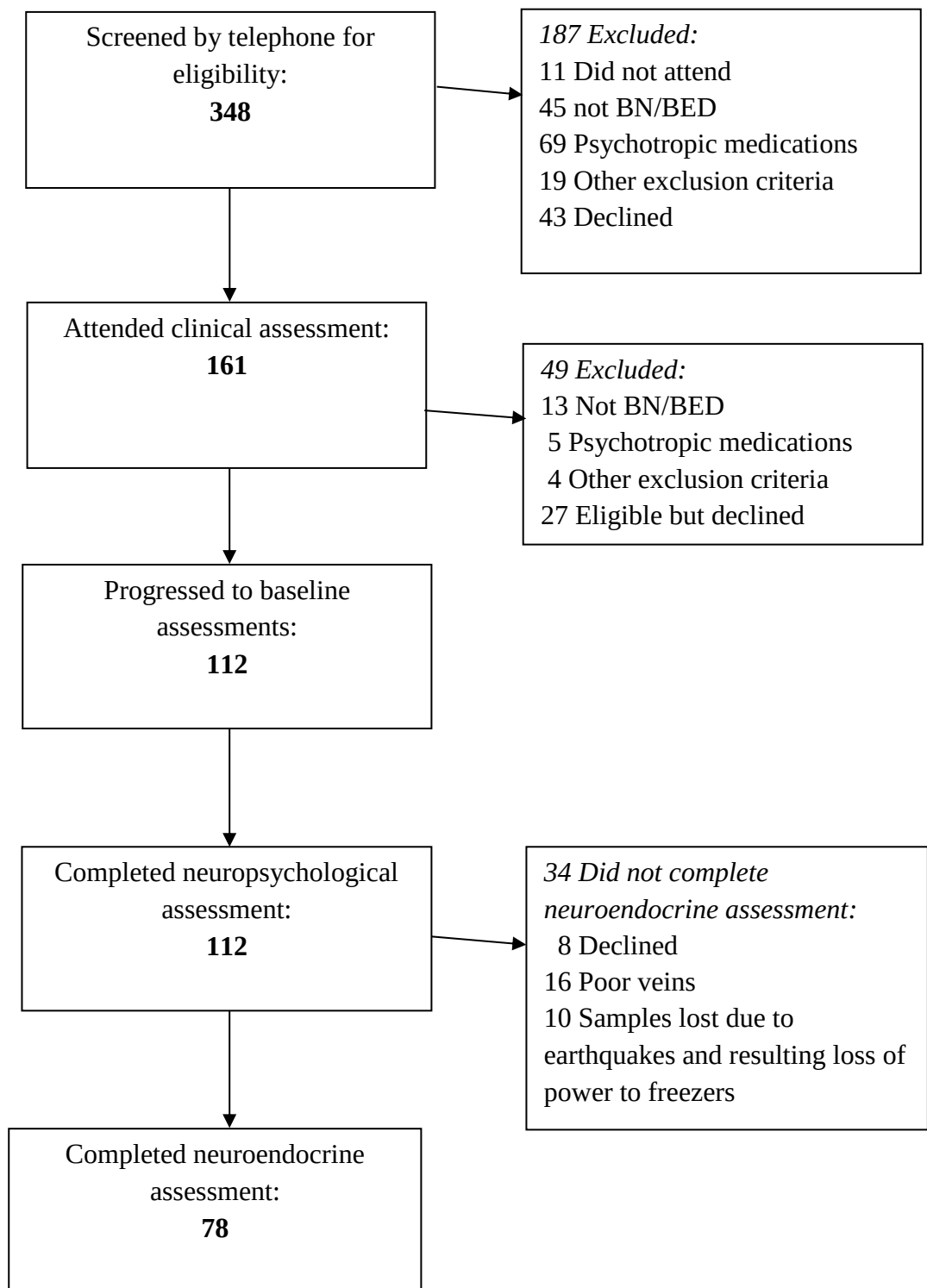


Figure 3.1 Flow chart showing number of participants screened, eligible, and completing neuropsychological and neuroendocrine assessment

The comprehensive baseline assessment of eating disorder psychopathology, neuropsychological functioning and biological measures completed before the initiation of treatment of current binge eating symptoms is reported below.

3.3 Procedure

Potential participants were screened over the telephone by the study coordinator. Those meeting entry criteria were then allocated to a study therapist who contacted the participant to organise the initial assessment (clinical interview to confirm diagnosis and confirm inclusion and exclusion criteria were met). Informed written consent was gained at this point. Patient Information Sheets and Consent Form are reproduced Appendices A and B respectively. Participants were then scheduled for subsequent assessments.

Neuroendocrine assessment was conducted in the morning and neuropsychological assessment in the afternoon. Between these assessments participants were given lunch and had an hour of free time. Most participants completed both assessments on the same day but 25% of participants were unable to commit to this and their neuroendocrine and neuropsychological assessments were conducted on different days. All self-report questionnaires were completed on the day of the neuroendocrine assessment.

3.4 Screening Instruments and Clinical Rating Scales

Structured Clinical Interview I for DSM-IV – Patient Version (SCID-IP, Spitzer, Williams, & Gibbon, 1987) is a clinician rated interview that assesses the presence of current and past Axis I major psychiatric disorders including eating disorders. The SCID is made up of various modules that can be put together for a comprehensive assessment of mental health diagnoses. In the current study the modules selected were: Modules A and D Mood Disorders, Module E Substance Use Disorders, and Module F Anxiety and other

disorders. There has been a wide range of reliability scores reported for this measure. Factors affecting reliability include staff training, subject population and base rates. Zanarini et al., (2000) reported Kappa values for inter-rater reliability of 0.77 (good) and test re-test in 7 days of 0.64 (fair). All staff were fully trained in administering this measure. Reliability data was not available for the SCID-I measures used in the current study, however, these most of the raters used in this study have conducted inter-rater reliability checks for Axis I in an anorexia treatment study and a depression study. The overall kappa for these range from 0.78 to 0.85 which suggests good concordance for these raters (Carter et al., 1999; Jordan et al., 2008). Although the validity of categorical diagnostic systems has been widely debated the SCID-I has been described as the “gold standard” in determining diagnostic accuracy and has been found to be more accurate than standard clinical interviews (Basco et al., 2000; Fennig et al., 1994).

The Global Assessment of Functioning (GAF), Axis V of Diagnostic and Statistical Manual 4th Edition (DSM-IV, American Psychiatric Association, 1994) is a measure of current psychological, social and occupational functioning over the previous week. Scores range from 0 to 100 and are grouped in bands describing levels of functioning. For the current study the clinical aspects of eating disorder symptomatology were specifically considered along with other factors such as levels of anxiety and depression, and social and occupational functioning. Guidelines for rating the GAF, developed for the current study are reported in Appendix C.

The GAF has been criticised for problems with reliability and validity partly due to the minimal guidelines for administrators (Aas, 2011). Despite these difficulties good inter-rater reliability has been reported where administrators have been trained in using this measure; for example Hilsenroth et al., (2000) reported an inter-rater reliability of 0.7

(good).” In the current study those administering the GAF discussed each GAF rating as a group to overcome some of this difficulty.

The Eating Disorder Examination (EDE), is a semi-structured interview designed to assess eating disorder psychopathology over the previous 28 days (Cooper, Cooper, & Fairburn, 1989). It comprises of four subscales; Restraint, Eating Concern, Shape Concern and Weight Concern. Items are scored on a scale from 0 to 6 depending on the prevalence of the behaviour. It is extensively used for diagnosing eating disorders in research settings (Guest, 2000) and is seen as the ‘gold standard’. It has good validity and reliability (for a systematic review see Berg et al., 2012).

The Eating Disorders Inventory-2 (EDI-2) is a 91 item self-report questionnaire measuring behaviours and other psychological constructs related to eating disorders (Garner, 1991). Items are rated on a 7 point scale from 6 (never) to 1 (always). Eight subscales are calculated; Drive for Thinness, Bulimia, Body Dissatisfaction, Ineffectiveness, Perfectionism, Interpersonal Distrust, Interoceptive Awareness, and Maturity Fears. The first three subscales assess eating disorder specific attitudes and behaviours, whereas the following five subscales investigate more general psychological constructs. The EDI has good reliability, particularly in adult clinical samples (Gleaves et al., 2014). This test was administered in pen and paper form as part of a larger booklet of self-report questionnaires. Note that since the initiation of this study the EDI-3 was released in 2004. This updated measure has six composite scores which cannot be directly compared with the EDI-2.

The Barratt Impulsiveness Scale -11 (BIS-11) is a 30 item self-report measure of impulsivity (Barratt, 1994). It is comprised of three subscales; Non-planning which measures lack of future orientation, Motor which is a measure of impulsive actions, and

Cognitive which measures impulsive thinking and lack of patience. The Barratt Impulsiveness Scale -11 has good test-retest reliability and convergent validity (Stanford et al., 2009). This test was administered in pen and paper form as part of a larger booklet of self-report questionnaires.

The Edinburgh Handedness Inventory assesses hand dominance using 10 items including preferred hand for writing, drawing and throwing (Oldfield, 1971). Handedness has been found to influence some aspects of cognitive functioning (Lezak et al., 2012). The Edinburgh Handedness Inventory has good test-re-test reliability (McMeekan & Lishman, 1975; Ransil & Schachter, 1994) and internal consistency (Dragovic, 2004). This test was administered in pen and paper form as part of a larger booklet of self-report questionnaires.

The Neuropsychology Demographic Questionnaire was designed specifically for the current study to obtain information factors that could influence neuropsychological test performance. It includes items on the need for hearing or visual aids, and alcohol, cannabis, caffeine and nicotine use in the 24 hours preceding the assessment. The questionnaire is reproduced in Appendix D. This test was administered in pen and paper form at the beginning of the neuropsychological assessment.

3.5 Demographic Factors

Information was collected on age, ethnicity, marital status and years of education.

3.6 Physical Measurements

Physical measurements were collected as part of the baseline biological assessment carried out by the research nurse. Height was measured to the nearest 0.5cm. Weight and percentage

body fat were measured using the Tanita Body Composition Analyzer Electronic Scale (Model TBF-300). Body Mass Index (BMI), was calculated by the following equation: $BMI = \text{weight (kilograms)} / \text{height squared (metres squared)}$. A BMI of less than 20 is considered to be underweight, 20-25 is considered to be a normal, healthy weight, whereas a BMI of between 25 and 30 is considered overweight and BMI over 30 is classified as obese (World Health Organization, 2000).

3.7 Neuropsychological Assessment

A battery of neuropsychological tests was selected to cover a broad range of neuropsychological functions and each test is described more fully in the following section. Tests included were based on previous research on neuropsychological function in women available at the time of initiation of this project.

Premorbid intellectual functioning was assessed as this is a potential confounding factor in neuropsychological functioning. Motor functioning was important to include as motor skills are required to successfully carry out some of the subsequent tests that were administered. A range of basic neuropsychological skills were tested including attention, verbal and visuo-spatial memory and learning, and inhibitory control. These skills are not only informative in their own right but impairment on these tasks may have implications for interpreting performance on tasks of executive function which require some ability in lower order neuropsychological skills (Lezak et al., 20012). Executive functions examined in the current study were set-shifting and planning. Unfortunately at the time the current study was being developed, neuropsychological domains such as central coherence and haptic perception had not been reported in the eating disorders literature.

3.7.1 National Adult Reading Test

The National Adult Reading Tests is a list of 50 phonetically irregular words developed by Nelson & O'Connell, (1978). It is assumed that correct pronunciation infers familiarity with the word and hence higher intellectual ability. NART scores are correlated with IQ scores in the region of 0.72, and as word pronunciation is somewhat resistant to cognitive decline, NART scores are used as a measure of pre-morbid intellectual ability. Individuals for whom English is not their first language have been shown to be disadvantaged in this test even if they are fluent English speakers (Struben & Tredoux, 1989), reported in (Lezak et al., 2012). NART scores are correlated with education ($r = 0.51$), social class ($r = 0.36$) and age ($r = -0.18$) (Crawford, Moore, & Cameron, 1992).

3.7.2 CANTABeclipse Neuropsychological battery

The majority of tests administered were part of the CANTABeclipse computerised neuropsychological battery developed by Cambridge Cognition Limited (2004) to differentiate between those with and without dementia (Robbins et al., 1994). This comprehensive battery has been widely used both in the general population and with samples of those with mental health diagnoses including schizophrenia (Bartok et al., 2005), mood disorders (Matthews et al., 2008) and anorexia nervosa (Fowler et al., 2006). CANTABeclipse had not been used in an eating disorder population at the time of the current study development. Tests included in this battery were assumed to test the same domains as their non-computerised versions although more recent investigation suggests that this may not always be the case (Lenehan et al., 2016). Despite over 1300 published articles using CANTAB test batteries there is a surprising lack of independent reliability and validity information available (Lenehan et al. 2016). The suitability of this test battery for an eating disorder population will be discussed further in section 5.11.

Individual tests selected from the CANTABeclipse battery used in the current study are described below.

3.7.3 Motor Screening

The purpose of this test is twofold; first to train the participant to use the computer and touch screen, and second to screen for difficulties with vision, movement and comprehension that may affect subsequent tests. The participant is asked to touch a series of crosses that appear in different locations across the screen. Latency to respond (ms) and accuracy are recorded.

3.7.4 Affective Go/No-go

Affective Go/No-go is a test of processing bias for positive and negative stimuli and as a measure of the ability to inhibit erroneous responses. In this test, participants are presented with a series of words which are briefly displayed (300ms) in the centre of the screen. The words are each one of three valences:

- Positive (e.g. joyful, warmth, courage)
- Neutral (e.g. item, pause, element)
- Negative (e.g. mistake, hopeless, burden)

Participants are given a target valence and are required to press the response pad when they see a word matching the target valence. They are instructed to respond as fast as they can whilst trying not to make mistakes. Words are presented at intervals of 900ms in blocks of 18. Within blocks only two valences are presented – positive and negative, positive and neutral, or neutral and negative. A total of 20 blocks of words are presented with the first two blocks being practice blocks which are not scored. Both administrator

and participant are aware of the target valence and distractor valence for each block presented as this is displayed on the screen between blocks.

The main outcome variables fall into three categories: mean correct responses, total commissions (response in absence of target stimuli) and total omissions (absence of response in the presence of target stimuli). These variables are differentiated depending on the valence of the target word and whether there is a shift in valence from the previous condition; shift to a negative valence (SN), shift to a positive valence (SP) or shift to a neutral valence (SO). An Emotional Bias Index (EBI) defined as [latency to shift negative targets] – [latency shift to positive targets] was also calculated (Maalouf et al., 2012).

3.7.5 Big/Little Circle

Big/Little Circle is a training test for the Intra-Extra Dimensional Set Shifting test in which participants are required to follow a simple rule and then reverse the rule. Participants are presented with a pair of circles, one big and one small. They are required to touch the small circle for the first 20 trials and then switch to the big circle for the subsequent 20 trials. The variables reported are % correct response and latency of correct responses (ms).

3.7.6 Intra-Extra Dimensional Set Shift

The Intra-Extra Dimensional Set Shifting test was developed from the Wisconsin Card Sorting Test and is reported to be sensitive to cognitive changes associated with the fronto-striatal areas of the brain (Cambridge Cognition, 2004). It is designed to measure attentional flexibility by requiring the participant to reverse a previously correct rule (intra-dimension) and then to shift attention from a previously correct dimension to a previously irrelevant one (extra-dimension). Feedback teaches participants to select the correct

response by choosing between two block colour shapes and they later learn to shift attention to white line shapes (see Figure 3.2).

After six correct responses the rules are changed and the next stage is reached. There are nine stages which progress in demand from shape discrimination (two pink shapes), compound discrimination (two pink shapes and two white line shapes), intra-dimensional shifts (maintaining responses to the pink shapes) and extra-dimensional shifts (switching from pink shapes to white lines). If six consecutive correct answers are not made the trial terminates after 50 incorrect responses. Performance is assessed by the number of errors, number of trials, and number of stages reached.

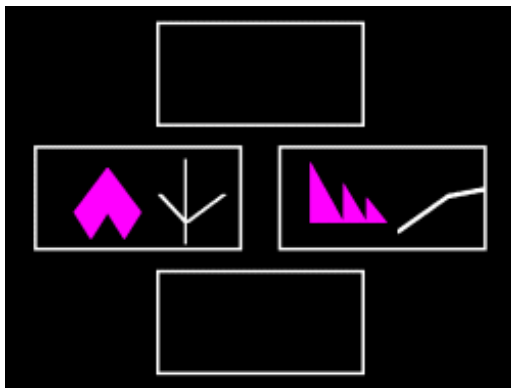


Figure 3.2 An example of an Intra-Extra Dimensional Set Shift screenshot showing pink shapes and white lines

3.7.7 Delayed Matching to Sample

Delayed Matching to Sample is a test of visual memory. Participants are shown a complex figure, made up of four different elements which vary in pattern and colour (Figure 3.3). After a brief delay, participants are required to select the matching figure from a selection of four options. All four options have one quadrant in common with the target figure to avoid a strategy of reliance on remembering one quadrant only. Three practice trials are

presented followed by 20 counterbalanced test trials. Delays vary from simultaneous presentation to zero, four or twelve second delays.

Variables reported for DMS are the percent correct over all delays, mean latency (the mean delay to respond correctly over all delays measured in milliseconds) and two further variables, DMS A and DMS B, which involve analysis of the style of responding. DMS A is a measure of the probability that the participant will make an error following an error. The score ranges between 0 and 1 with high scores indicating a higher likelihood of an error following a previous error, i.e. a measure of an individual's sensitivity to making an error independently of how many errors they make. DMS B measures the strength of the effect of making an error. Scores range from -1 to +1. A negative score indicates many errors regardless, whereas a high positive score indicates the participant is likely to make errors only if they have just made an error in the previous response. DMS B is thought to give an indication of the emotional response to an error (Cambridge Cognition, 2004).

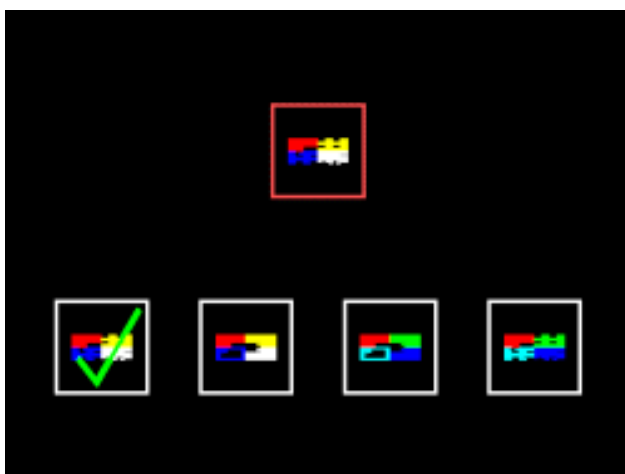


Figure 3.3 Delayed Matching to Sample screenshot showing a simultaneous presentation of the target figure and four potential matches. The green tick indicates a correct response.

3.7.8 Rapid Visual Information Processing

Rapid Visual Information Processing is a test of sustained visual attention, which is thought to be sensitive to the parietal and frontal lobes (Cambridge Cognition, 2004). Digits appear in a white box in the centre of the screen in a pseudo-random order (see Figure 3.4). Participants are required to respond using a press pad when they detect the target sequence of 3 numbers (e.g. 2-4-6, 3-5-7, or 4-6-8). Digits are presented at a rate of 100 per minute and target sequences occur at the rate of 16 every two minutes. Initially participants complete a practice phase of two minutes duration followed by a test phase of three minutes duration. The rate of correct identification, false responses (incorrect identification of a target sequence) and misses are reported.



Figure 3.4 Rapid Visual Information Processing screenshot showing number in the centre box with target sequence to the right.

3.7.9 Stockings of Cambridge

Stockings of Cambridge is a measure of spatial planning and is based on the Tower of London Task (Shallice, 1982). Participants are presented with images of two series of hanging stockings with coloured balls (see Figure 3.6). Participants are asked to move the coloured balls in the lower display so they match the pattern in the upper display. If there is a target ball beneath another ball, the top ball must be moved first. The position of individual balls can be changed by touching the ball to be moved and then touching the position where it is to be moved to. As the test progresses, the number of moves needed to match the upper pattern increases, hence increasing the demand on the participant. If a participant fails to solve the problem in less than double the minimum number of moves then the next problem is presented. Failure on three problems in a row will terminate the test. Performance is measured by the number of problems solved using the minimum number of moves, the mean number of moves for each level of problem (2, 3, 4, and 5 moves), initial thinking time (time taken before the first move is made) and subsequent thinking time (reflecting the speed of movement after the first move).

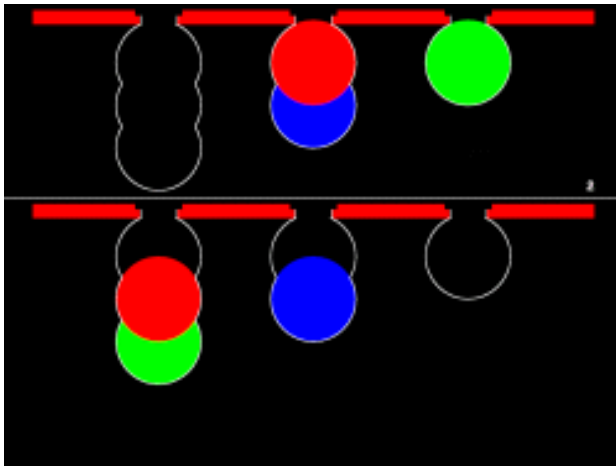


Figure 3.5 Stocking of Cambridge screenshot showing hanging stocking with coloured balls.

3.7.10 Spatial Recognition Memory

Spatial Recognition Memory assesses the ability to recall spatial information. Participants are presented with a white square which appears in five different locations on the screen in sequence. The participants are then given a forced-choice in which they are asked to choose which one of two white squares presented is in a position that they have seen before. Results are reported as the number correct, percent correct, and mean correct latency (ms).

3.7.11 Spatial Working Memory

Spatial Working Memory measures the ability to retain spatial information and to manipulate this information in working memory. Participants must find blue “tokens” hidden under coloured boxes and move them to a column at the side (see Figure 3.6).

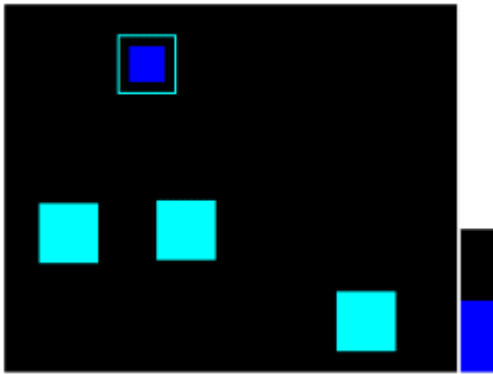


Figure 3.6 Spatial Working Memory Screenshot showing examples of coloured boxes (light blue) under which a token may be hidden. An uncovered token (dark blue) is shown in the opened box at the top of the screen.

As the test progresses the number of boxes increases, thereby increasing the load on working memory. Results are reported as Between Errors (the number of times a participant revisits a box in which a token has previously been found), Within Errors (the number of times a box is revisited during a search that was already found to be empty during the same search), Total Errors (combined Between and Within Errors) and Strategy (how efficient the search strategy was, with a high score representing poor use of strategy and a low score representing effective use of the strategy).

3.7.12 Verbal Recognition Memory

Verbal Recognition Memory tests recall and recognition of verbal information using both immediate and delayed conditions. Participants are shown a list of 12 words, one at a time, on the computer screen. The participants are asked to state as many words from this list as they can recall (immediate recall condition). The test administrator then reads out a list of 24 words, 12 of which were words presented on the screen along with an additional 12 distractor words. The participant is asked to respond whether each word was on the original list (immediate recognition condition). After a delay of 20 minutes participants

are asked to recognise the original words from a list of 24 words containing the 12 original words and 12 new distractor words (delayed recognition condition). This test does not include a learning component as some other verbal recall tests such as the Rey Auditory-Verbal Learning Test and California Verbal Learning Test.

Outcome variables for this test are the number of words recalled in the immediate condition, the number of words recognised in the immediate condition and the number of words recalled in the delayed condition.

3.7.13 Trail Making Test

This pen and paper test was developed as part of the Army Individual Test Battery in 1944 and has been widely used since this time (Bowie & Harvey, 2006). It is a measure of visual attention and tracking ability. There are two parts; A and B. In the A condition the participant must draw lines to connect consecutively numbered circles. Condition B is more complex as it requires participants to alternate between circles with numbers and circles with letters. Instructions are given to connect the circles as quickly as possible without making errors. Each form is scored for the time taken to complete and the number of errors. The time to complete each stage is recorded. In the current study a proportional score was calculated using the equation $(B-A)/A$ which is thought to compensate in part for the effect of basic motor skills and is therefore more sensitive to prefrontal cortex functioning (Stuss et al., 2001) and has been used as a measure of set-shifting.

3.7.14 Order of administration

Tests were administered in the same order to all participants. The order of tests was consistent with requirements for some tests to include delayed testing after specific time intervals (e.g. delayed verbal recall). The order of presentation was as follows:

1. Demographic questionnaire
2. Motor screening (CANTAB)
3. Rapid visual information processing (CANTAB)
4. Verbal recall and recognition memory – immediate (CANTAB)
5. Verbal recognition memory – delayed (CANTAB)
6. Trail making test
7. Affective go/no-go (CANTAB)
8. Big circle/little circle (CANTAB)
9. I/ED set shift (CANTAB)
10. Stockings of Cambridge (CANTAB)
11. Spatial recognition memory (CANTAB)
12. Delayed matching to sample (CANTAB)
13. Spatial working memory (CANTAB)
14. Nation Adult Reading Test

Duration of the neuropsychological test battery was approximately 110 minutes.

3.8 Data Management

Data were entered into the study database. All paper copies of self-report questionnaires, clinical interviews and physical measurements/blood results were stored in a locked filing cabinet in the Department of Psychological Medicine, University of Otago, Christchurch, and were available for data checking.

3.9 Statistical Analysis

Results were analysed using IBM SPSS Version 22. Variables were checked for missing data, and normality of distribution. Where there was a skewed distribution (i.e. those with

a high number of zero responses e.g. vomiting frequency or the number of errors made on some tests) these variables were converted to categorical variables. Where some variables were approaching normality it was decided that the sample size allowed analysis of these variables using parametric techniques. The validity of this was tested by re-analysing variables with non-parametric techniques. For variables that could not be transformed to a normal or near normal distribution non-parametric statistics were used. Descriptive statistics were used to describe the sample characteristics.

Comparisons of neuropsychological performance among the three diagnostic groups (bulimia nervosa, binge eating disorder, and healthy controls) were made using Analysis of Variance (ANOVA) for continuous variables and Chi-square analysis for categorical variables. Results are reported as means and standard errors for continuous variables and number and percentage for categorical variables. Post hoc analysis was carried out using Least Significant Difference (LSD) analysis.

Analysis of neuropsychological performance was repeated using an Analysis of Covariance (ANCOVA) to control for differences among the three groups with respect to age. Z score analysis was used to determine whether the current sample differed from published norms. Correlational analysis was used to investigate associations between neuropsychological performance and variables from the Barratt Impulsivity Scale.

Although there were a large number of analyses carried out it was decided after consideration not to apply a Bonferroni correction for the following reasons:

- The analyses are seen as largely exploratory as there are few studies to date that fully explore neuropsychological function and ghrelin secretion in binge eating

populations. The analyses are intended to generate hypotheses which would need further research.

- Within the groups of variables the analyses are testing a range of correlated outcomes which would mean an application of a Bonferroni correction would be excessively conservative.
- Using a LSD analysis approach provides some adjustment for comparison amongst the different groups (that is comparisons between two groups is only done where a significant difference among all the groups was found). Overall a cautious approach has been used when interpreting significant differences among the groups and use of a Bonferroni correction is unlikely to alter the conclusions of this research.

3.10 Power Calculation

For clinical significance in neuropsychology research a medium effect size is considered necessary and a power of 0.8 is recommended (Bezeau & Graves, 2001). A sample size of at least 135 allows detection of a medium effect size at a level of significance of $p < 0.5$ with statistical power of at least 0.8 (Cohen, 1992). A sample size of 25 would be able to detect a large effect size at a level of power about 0.8 or less depending on the type of analysis. These sample sizes were exceeded in the neuropsychological section of the current study, however, some groups in the ghrelin section contained sample sizes less than 25.

4. RESULTS: NEUROPSYCHOLOGICAL FUNCTIONING

4.1 *Demographic Characteristics by Diagnostic Group*

Demographic characteristics among the three groups (BN, BED and HC) were compared using ANOVA for continuous variables and Chi-square for categorical variables. Results are reported in Table 4.1. Women in the BED group were significantly older and had higher BMIs than those in either the BN or HC groups. There were no differences among the groups for years of education or pre-morbid intelligence (NART scores). There were no differences among the groups for ethnicity. The majority of the sample (85.6%) were New Zealand European/Other Caucasian, with 8.8% Maori, and 5.6% Asian.

Table 4.1 Comparison of demographic characteristics by diagnostic group.

	BN <i>n</i> =58 mean (sd) or <i>n</i> (%)	BED <i>n</i> =54 mean (sd) or <i>n</i> (%)	HC <i>n</i> =48 mean (sd) or <i>n</i> (%)	F or χ^2	p	d	Post Hoc (LSD)
Age (years)	32.2 (11.9)	38.6 (12.6)	30.5 (10.5)	6.93^a	0.001	0.52 0.70	BED>BN BED>HC
BMI	26.4 (6.5)	33.9 (7.2)	26.1 (5.0)	25.79^a	<0.001	1.09 1.26	BED>BN BED>HC
Years of education	15.2 (2.3)	15.5 (3.4)	15.7 (2.9)	0.46 ^a	0.46		
NART	104.0 (7.4)	105.9 (7.8)	104.8 (8.3)	0.75 ^a	0.48		
Ethnicity:				7.89 ^b	0.10		
NZ European	46 (79.3%)	47 (87.0%)	44 (91.7%)				
Maori	5 (8.6%)	6 (11.1%)	3 (6.3%)				
Asian	7 (12.1%)	1 (1.9%)	1 (2.1%)				

^a = ANOVA *df* = (2,156); ^b = Chi square (χ^2); *d* = Cohen's *d*; BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls; NART = National Adult Reading Test.

4.2 Potential Confounding Factors on Neuropsychological Performance

Factors which could potentially impact on neuropsychological functioning were compared among diagnostic groups. Results of ANOVA for continuous variables and Chi-square for categorical variables are reported in Table 4.2.

Usual daily caffeine intake did not differ among the groups but there was a trend towards higher caffeine consumption in the binge eating groups. Overall participants reported reduced consumption of drinks containing caffeine on the day of testing compared with their usual pattern. As 75% of participants were fasting for a biological assessment in the morning, before neuropsychological testing in the afternoon this is not unexpected. The remaining 25% of the sample completed the two assessments on different days and so were able to have their usual caffeine intake on the day of neuropsychological testing. There was a difference among the groups for caffeine intake on the day of testing with both binge eating groups having higher consumption than the control group. To check whether caffeine ingestion may have contributed to neuropsychological performance the total sample was divided into those that had consumed a caffeine drink before testing and those that had not. A 2-tailed t test found no significant differences between the two groups on any of the neuropsychological test variables. This suggests that caffeine did not have a significant impact on neuropsychological functioning.

No differences were found among the three groups for recent consumption of alcohol or medications within the previous 24 hours. The medications reported by participants were paracetamol, ibuprofen, salbutamol (Ventolin) and aspirin and were unlikely to impact on neuropsychological performance. Cannabis use was higher in the bulimia nervosa group

with three participants having used cannabis within 24 hours of testing. One participant had used cannabis with 12 hours of testing (2.5 hours before). This participant's results were retained in the analyses as they were found not to be different from the bulimia nervosa group results.

Table 4.2 The prevalence of potential confounding variables on neuropsychological performance by diagnostic group

	BN <i>n</i> =58 mean (sd) or n(%)	BED <i>n</i> =54 mean (sd) or n(%)	HC <i>n</i> =48 mean (sd) or n(%)	F or χ^2	p	d	Post Hoc (LSD)
Caffeine testing day	0.86 (1.16)	0.94 (1.74)	0.31 (0.47)	3.76^a	0.03	0.62 0.49	BN>HC BED>HC
Caffeine average day	2.79 (2.21)	3.33 (3.43)	2.27 (2.08)	2.02 ^a	0.12		
Alcohol past 24 hours	11 (19.0%)	8 (15.1%)	12 (25.0%)	1.59 ^b	0.45		
Cannabis past 24 hours	3 (5.2%)	0 (0%)	0 (0%)	5.33 ^b	0.07		
Medications past 24 hours	0 (0%)	5 (9.4%)	1 (2%)	7.17^b	0.03		
Right Handedness*	52 (89.7%)	46 (86.8%)	44 (91.7%)	4.18 ^b	0.38		
Visual aids**	21 (36.2%)	30 (56.6%)	16 (33.3%)	6.91^b	0.03		
Hearing impairment [#]	4 (6.9%)	6 (11.3%)	3 (6.3%)	1.06 ^b	0.59		
History of brain injury/neurological ^{##}	11 (19.0%)	6 (11.3%)	5 (10.4%)	2.03 ^b	0.36		
Current medical illness	13 (22.4%)	18 (36.6%)	5 (10.4%)	8.32^b	0.02		

^a = ANOVA, df = (2,156); ^b = Chi square (χ^2); d = Cohen's d;

BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls;

*2 BED participants reported being ambidextrous

**glasses or contact lenses

[#] Hearing impairments were only slight impairment, or only in one ear (self-reported). One participant wore hearing aids.

^{##} History of brain injury/neurological problems was from self-report. Problems reported included loss of consciousness, previous bicycle accident or car accident. Some participants reported seizures but all were of mild seriousness and were not recent events. Neurological illnesses were reported by two participants, one having a history of migraines and the other a previous brain tumour.

No differences were found among the groups for handedness, hearing impairment or history of brain injury or neurological condition. Significantly more of the BED group required glasses or contact lenses compared with the other two groups. All participants requiring visual aids used them during neuropsychological testing. The BED group reported significantly higher levels of current medical illness (see Table 4.3 for a list illnesses reported). Differences in the need for visual aids and increased rate of illness is likely to be due to the higher average age of the BED group.

Table 4.3 Current medical illnesses reported by all participants on the day of neuropsychological testing

Illness reported	Number of participants
Arthritis	1
Asthma	4
Broken arm (non-dominant)	1
Chronic fatigue syndrome	1
Coeliac	1
Diabetes (type 2)	4
Endometriosis	1
Fibromyalgia	1
Hepatitis	1
High cholesterol	2
Hypertension	6
Hyperthyroid	1
Hypothyroidism	4
Irritable bowel	2
Kidney reflux	1
Leukaemia in remission	2
Osteoarthritis	2
Polycystic ovary syndrome	7
Skin cancer	1
Spina bifida	1

4.3 Neuropsychological Test Performance by Diagnostic Group

The results comparing neuropsychological functioning among BN, BED and HC groups are presented below. As there were significant differences among the groups for both age and BMI, these variables were used as co-variables in subsequent analyses. ANCOVA was used for continuous variables and Chi-square analysis was used for categorical variables. All results are reported as mean and standard error for continuous variables and number and percentage for categorical variables. Effect sizes have been calculated for ANOVA and ANCOVA analyses using Cohen's d ($d = \text{Mean1-Mean2} / \text{pooled standard deviation}$).

4.3.1 Motor function

Comparison of motor function among the groups is presented in Table 4.4. No differences were found among the three groups for accuracy of motor response measured by the mean number of errors. However, the BED group had a significantly lower mean latency than the BN and HC groups, indicating that overall the BED group responded more quickly to the presented stimuli.

Table 4.4 Comparison of motor function by diagnostic group

	BN <i>n</i> =58 mean (se)	BED <i>n</i> =54 mean (se)	HC <i>n</i> =48 mean (se)	F[#]	p	d	Post Hoc (LSD)
MOT mean error	9.25 (0.36)	9.25 (0.31)	9.29 (0.39)	0.08	0.97		
MOT mean latency	942 (36.6)	852 (23.3)	1025 (28.8)	4.32	0.002	0.39 0.93	BED>BN BED>HC

[#] = ANCOVA (F), $df = (2,156)$, age and BMI as covariate; d = Cohen's d

BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls; MOT = Motor Screening

4.3.2 Attention

Attention was measured by the Rapid Visual Processing Test and results from this test are reported in Table 4.5. No differences were found among the three groups for measures of accuracy, and latency to respond.

Table 4.5 Comparison of visual attention by diagnostic group

	BN <i>n</i> =58 mean (se)	BED <i>n</i> =54 mean (se)	HC <i>n</i> =48 mean (se)	F[#]	p
RVP total hits	18.60 (0.69)	17.35 (0.60)	18.56 (0.59)	0.42	0.66
RVP total misses	8.38 (0.69)	9.65 (0.60)	8.42 (0.58)	0.44	0.65
RVP mean latency (ms)	408 (12)	428 (11)	423 (10)	0.61	0.51

[#] ANCOVA, *df* = (2,156), age and BMI as covariates; BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls; RVP = Rapid Visual Information Processing.

4.3.3 Memory and learning

Comparisons of performance on verbal and visuospatial memory and learning among the groups are presented in Table 4.6. On a test of verbal memory (Verbal Recognition Memory) the BED group recalled fewer words in the Free Recall condition compared with the BN and HC groups. The BED group gave more false positive responses in the delayed recognition condition compared with the HC group ($\chi^2 = 9.65$, *df*=1, *p*=0.002). No other significant differences were found among the groups on tests of verbal memory.

No significant differences were found among the three groups for accuracy or speed on the Spatial Recognition Memory Task. No significant differences were found among the three groups for accuracy or speed of response on the learning task Delayed Matching to Sample test. No significant differences were found among the groups on the learning strategy scores DMS A' or DMS B''. There were no significant differences among the groups in

accuracy or speed on the Spatial Working Memory test. No significant differences were found on the Spatial Working Memory strategy measure.

Table 4.6 Comparison of verbal and visual memory and learning by diagnostic group

	BN <i>n</i> =58 mean (se)	BED <i>n</i> =54 mean (se)	HC <i>n</i> =48 mean (se)	F[#]	p	d	Post Hoc (LSD)
VRM free recall	8.48 (0.22)	7.65 (0.24)	8.81 (0.21)	3.20	0.04	0.41 0.67	BED<BN BED<HC
VRM recognition	23.22 (0.13)	23.24 (0.134)	23.42 (0.13)	0.40	0.67		
VRM delayed	23.03 (0.15)	23.04 (0.19)	23.44 (0.12)	1.30	0.28		
SRM correct	18.31 (0.21)	18.57 (0.27)	17.83 (0.22)	1.88	0.16		
SRM correct latency (ms)	2269 (73)	2195 (85)	2270 (79)	0.44	0.64		
DMS correct (delay)	4.4 (0.10)	4.4 (0.12)	4.5 (0.09)	0.46	0.63		
DMS correct latency (ms)	4265 (212)	4390 (274)	4145 (270)	0.06	0.94		
DMS A'	0.56 (0.11)	0.50 (0.06)	0.52 (0.19)	0.17	0.85		
DMS B''	-0.79 (0.07)	-0.83 (0.06)	-0.94 (0.04)	2.35	0.10		
SWM between errors (8 boxes)	14.93 (1.50)	16.55 (1.55)	12.98 (1.61)	0.34	0.72		
SWM within errors (8 boxes)	0.83 (0.27)	0.79 (0.22)	1.11 (0.36)	0.83	0.44		
SWM total errors	20.67 (2.06)	24.53 (2.20)	17.98 (2.30)	0.36	0.70		
SWM strategy	31.71 (0.75)	31.91 (0.70)	30.43 (0.87)	0.53	0.59		

ANCOVA, *df* = (2,156), age and BMI as covariates; *d* = Cohen's *d*; BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls; DMS = Delayed Matching to Sample; SRM = Spatial Recognition memory; SWM = Spatial Working Memory; VRM = Verbal Recognition Memory

4.3.4 Executive function

Set shifting was assessed using the Big Circle/ Little Circle test, the Intra-Extra Dimensional Set-Shift test, and the Trail Making Test. The Big Circle/Little Circle Test (BCLC) is a screening test for the Intra-Extra Dimensional Set-shifting Test (IED) and assesses

comprehension, learning and reversal skills which are required before the IED is administered. There were no significant differences in accuracy or latency to respond among the groups on BCLC. All groups scored highly on this test which suggests skill level was at the required level to continue to the IED test. There were no significant differences among the three groups for the number of errors on the IED. However, on average, the BN group completed more stages than the healthy control group. A greater proportion of the BN (82.8%) and BED (77.8%) groups completed all nine stages compared to of the healthy control group (60.4%). There were no significant differences among the groups in the proportion of participants that made at least one error on Part B, the time to complete Part B or the Trail Making Test proportional score.

Table 4.7 Results of tests of set shifting by diagnostic group

	BN <i>n</i> =58 mean (se) or %	BED <i>n</i> =54 mean (se) or %	HC <i>n</i> =48 mean (se) or %	F # or χ^2	p	d	Post Hoc (LSD)
BCLC correct	801	780	855	2.07	0.13		
latency (ms)	(20)	(32)	(26)	(2,158)			
BCLC % correct	100	99.91	99.95	0.50	0.61		
	(0.00)	(0.06)	(0.05)	(2,158)			
IED total errors	23.12	24.87	31.48	2.42	0.09		
adjusted	(2.60)	(2.72)	(3.64)	(2,158)			
IED stages	8.69	8.57	8.25	3.82	0.02	0.50	BN>HC
completed	(0.09)	(0.11)	(0.15)	(2,158)			
IED completed all	48	42	29	7.37^b	0.03		
stages	82.8%	77.8%	60.4%				
TMT B time (s)	57.5	58.7	54.4	0.40	0.67		
	(2.7)	(2.3)	(2.3)				
TMT B errors	15	13	10	0.37 ^b	0.83		
	(25.9%)	(24.1%)	(20.8%)				
TMT proportional	1.27	1.34	1.09	1.63	0.19		
score	(0.09)	(0.09)	(0.08)				

ANCOVA, *df* = (2,156), age and BMI as covariates; ^b = Chi square (χ^2); *d* = Cohen's *d*; BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls; BCLC = Big Circle/Little Circle; IED = Intra-Extra Dimensional Set-Shift; TMT = Trail Making Test.

Inhibitory control and attentional bias to emotional targets was tested in the Affective Go/no-go (AGN) test and results are reported in Table 4.8. No significant differences were found in latency of a correct response among the groups. There were no statistical differences in the number of commission errors or omission errors among the groups.

Table 4.8 Comparison of inhibitory control measured by the Affective Go/No-go Test by diagnostic group

	BN <i>n</i> =58 mean (se)	BED <i>n</i> =54 mean (se)	HC <i>n</i> =48 mean (se)	F[#]	p
AGN SO mean correct latency (ms)	587 (11)	605 (11)	590 (12)	0.46	0.64
AGN SP mean correct latency (ms)	526 (9)	539 (9)	524 (10)	0.24	0.79
AGN SN mean correct latency (ms)	518 (9)	530 (8)	528 (10)	0.44	0.65
AGN SO commissions	4.2 (0.4)	4.6 (0.4)	3.9 (0.4)	1.13	0.34
AGN SP commissions	2.9 (0.4)	4.1 (0.4)	3.2 (0.5)	2.17	0.12
AGN SN commissions	1.9 (0.3)	2.3 (0.3)	2.3 (0.4)	0.67	0.51
AGN SO omissions	4.3 (0.5)	4.1 (0.5)	4.7 (0.6)	0.25	0.78
AGN SP omissions	2.3 (0.3)	2.8 (0.4)	3.1 (0.4)	1.19	0.31
AGN SN omissions	1.5 (0.2)	1.7 (0.3)	1.7 (0.3)	0.19	0.83

ANCOVA, *df* = (2,156), age and BMI as covariates; BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls; AGN SN = Affective Go/No-go Shift Negative; AGN SO = Affective Go/No-go Shift Neutral; AGN SP = Affective Go/No-go Shift Positive.

An Emotional Bias Index (EBI) defined as [latency to shift negative targets] – [latency shift to positive targets] was calculated (Maalouf et al., 2012). There was no statistical difference among the three groups ($F(2,156) = 1.29$, $p = 0.28$) despite the mean Emotional Bias Index being positive for the HC group but negative for both the BN and BED groups (Figure 4.1).

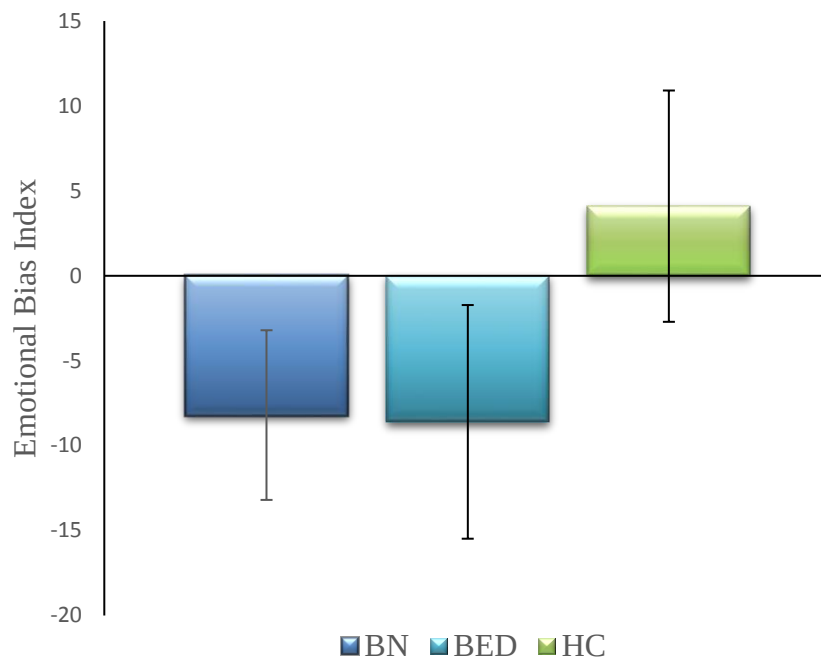


Figure 4.1 Emotional Bias Index by diagnostic group.

Mean and standard error shown. A negative score indicates a bias for negative stimuli whereas a positive score indicates a bias for positive stimuli.

Problem solving was assessed with the Stockings of Cambridge Test (SOC) and results of a comparison among the groups are presented in Table 4.9. No significant differences were found among the groups for the number of problems solved in minimum moves. On 5-move problems there was no significant difference among the groups for the mean number of moves taken to solve the problem. No significant differences were found among the groups for initial thinking time or subsequent thinking time on 5-move problems.

Table 4.9 Comparison of problem solving on the Stockings of Cambridge Test by diagnostic group

	BN <i>n</i> =58 mean (se)	BED <i>n</i> =54 mean (se)	HC <i>n</i> =48 mean (se)	F[#]	p
SOC problems in minimum moves (all problems)	9.48 (0.23)	9.15 (0.22)	9.21 (0.27)	0.61	0.55
SOC mean moves (5-move problem)	6.20 (0.17)	6.46 (0.19)	6.27 (0.19)	0.30	0.74
SOC mean initial thinking time (5-moves problem, ms)	12706 (904)	13360 (1307)	10412 (1452)	2.10	0.13
SOC mean subsequent thinking time (5-moves problem, ms)	1631 (396)	1623 (456)	1033 (283)	0.53	0.59

ANCOVA, *df* = (2,156), age and BMI as covariates; BN = bulimia nervosa; BED = binge eating disorder; HC = healthy controls; SOC = Stockings of Cambridge.

4.3.5 Comparison with CANTAB test norms

Very few significant differences were found between the binge eating groups and the healthy control group. Results were combined and compared to Cambridge CANTAB test norms to assess whether the results found in the current study differed significantly from what had been found previously in other studies using the CANTABeclipse test battery. Norms were obtained directly from CANTAB on request. Norms supplied were for adult females, aged between 16 and 80 years, with IQ range between 100 and 110. Z scores were calculated for all variables with norms available and are reported in Table 4.10.

Table 4.10 Z scores for neuropsychological variables based on CANTAB norms for adult females, IQ range 100-110.

	Current study <i>n=160</i>		CANTAB Norms		Z	%ile
	mean	sd	mean	sd		
MOT mean error	9.26	2.55	18.79	24.61	0.39	65
MOT mean latency (ms)	937	233	1015	279	0.28	61
RVP total hits	18.17	4.64	16.92	3.74	-0.33	63
RVP mean latency	419	81	485	90	0.74	77
BCLC mean correct latency (ms)	810	193	738	121	-0.60	73
BCLC % correct	99.95	0.34	100	0.0	0.00	50
IED total errors adjusted	26.22	21.93	34.31	29.71	0.27	61
IED stages completed	8.52	0.86	8.39	1.11	-0.12	55
IED total trials adjusted	98.41	39.18	96.76	42.59	-0.04	52
SOC problems in min moves	9.29	1.74	8.03	2.22	-0.57	72
SOC mean moves	6.31	1.33	6.4	1.32	0.07	53
SOC mean initial thinking time (ms)	12239	8897	12468	10352	0.02	51
SOC mean subsequent thinking time (ms)	1449	2867	2069	2194	0.28	61
SRM number correct	18.26	1.74	15.8	1.23	-2.00	98
SRM mean correct latency (ms)	2244	577	2314	854	0.08	53
DMS % correct	88.04	10.23	75.39	12.49	-1.01	84
DMS mean correct latency (ms)	3838	1387	3828	1055	-0.01	50
DMS A'	0.53	0.24	0.51	0.2	-0.10	54
DMS B''	-0.85	0.38	-0.41	0.58	0.76	78
SWM between errors	20.57	16.05	39.14	26.43	0.70	76
SWM within errors	1.29	2.44	3.03	5.48	0.32	62
SWM total errors	21.13	16.40	23.26	17.9	0.12	55
SWM strategy	31.39	5.60	34.98	5.11	0.70	76

BCLC = Big Circle/Little Circle; DMS = Delayed Matching to Sample; IED = Intra-Extra Dimensional Set-Shift; NART = National Adult Reading Test; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; VRM = Verbal Recognition Memory

Participants in the current study were more accurate and faster in completing the motor screening tasks compared with the CANTAB norms. In the current study Z scores were at or above zero and percentile scores ranged between 50th and 98th percentile of CANTAB norms.

In the Rapid Visual Information Processing Test, the current study had similar accuracy to the CANTAB norms but were faster to respond. On average fewer errors were made in the current study than the CANTAB norms in the Intra-Extra Dimensional Set-shift Test. In the Stockings of Cambridge Test the current study sample solved problems in fewer moves and although the initial thinking time was not very different to the normative values, thinking time for subsequent moves was shorter suggesting that overall the current study participants were more accurate and faster than the CANTAB norms. The current study participants were faster and more accurate on all measures on the Spatial Recognition Memory and Spatial Working Memory Tests. Finally, in the current study participants were more accurate in the Delayed Matching to Sample Test. There were no neuropsychological variables in which the current study mean scores were below the 50th percentile of the CANTAB norms. This suggests that participants in the current study had a higher level of neuropsychological functioning overall.

4.4 Eating Disorder Psychopathology

Differences in eating disorder psychopathology among the groups are reported in Table 4.11. Significantly more of the BN group had a history of anorexia nervosa compared with the BED and HC groups. The BED group had a significantly longer duration of any eating disorder compared with those in the BN group. The BN group scored more highly on the EDI Total score than the BED group but this was not statistically significant. The BN and BED groups had lower GAF scores than the HC group indicating a lower level of overall functioning in the eating disorder groups.

Table 4.11 Comparison of eating disorder psychopathology by diagnostic group.

	BN <i>n</i> =58 mean(sd) or n(%)	BED <i>n</i> =54 mean(sd) or n(%)	HC <i>n</i> =48 mean(sd) or n(%)	F χ^2 or t	p	d	Post Hoc (LSD)
History AN	9 (15.5%)	1 (1.9%)	0	13.48^b	0.001		
Duration of any ED (years)	12.16 (10.13)	18.56 (14.45)	—	2.73^c	0.01	0.51	
EDI-2 Total	94.40 (32.71)	84.67 (27.46)	—	1.70 ^c	0.09		
GAF	54.2 (5.3)	56.1 (3.7)	82.4 (9.0)	32.8^a	<0.001	3.82 3.83	BN<HC*** BED<HC***

^a = ANOVA df = (2,156),; ^b = Chi square (χ^2); ^c = t test (t); d = Cohen's d; *** = p<0.001; AN = anorexia nervosa; BN = bulimia nervosa; BED = binge eating disorder; ED = eating disorder; EDI-2 = Eating Disorder Inventory-2; HC = healthy controls; GAF = Global Assessment of Functioning.

The associations between neuropsychological variables and measures of eating disorder severity, and global functioning for the BN and BED groups combined (n=112) was investigated with Pearson's product-moment correlation coefficients. Results of the analysis are reported in Table 4.12. There were no significant correlations between the number of binges in the four weeks before testing and any of the neuropsychological variables analysed.

Table 4.12 Correlations between measures of eating disorder psychopathology and neuropsychological variables in the binge eating sample (n=112)

Test	Binges past 4 weeks	Duration of ED (years)	EDI Total	GAF
NART IQ	-0.05	0.34**	0.28**	0.09
Motor function				
MOT mean error	-0.09	-0.04	0.07	0.01
MOT mean latency (ms)	-0.021	0.16	-0.12	-0.05
Visual Attention				
RVP total hits	-0.08	-0.19*	0.01	0.06
RVP total misses	0.08	0.19*	-0.01	-0.07
RVP mean latency (ms)	-0.12	0.21*	-0.11	-0.15
Memory				
VRM free recall	0.13	-0.28**	0.16	-0.04
VRM recognition	0.05	-0.19*	0.04	0.01
VRM recognition delayed	0.15	-0.17	0.08	0.07
SRM number correct	-0.09	0.10	-0.03	0.11
SRM mean correct latency (ms)	0.07	0.14	-0.04	-0.10
DMS % correct	0.09	-0.17	-0.16	-0.02
DMS mean correct latency (ms)	0.13	0.31**	-0.20*	0.04
DMS A'	0.30	-0.35	0.29	-0.20
DMS B''	-0.10	-0.11	0.16	0.06
SWM between errors	0.01	0.28**	0.10	-0.03
SWM within errors	-0.04	0.21*	0.17	0.01
SWM total errors	0.00	0.29**	0.11	-0.03
SWM strategy	-0.02	0.17	-0.06	-0.04
Set-shifting				
IED total errors adjusted	-0.10	0.19*	-0.05	0.09
IED stages completed	0.11	-0.11	0.03	-0.13
IED total trials adjusted	-0.11	0.19	-0.05	0.10
TMT proportional score	0.01	0.09	-0.00	-0.10
Inhibitory control				
AGN SP mean correct latency (ms)	0.02	0.16	-0.14	-0.23*
AGN SN mean correct latency (ms)	0.07	0.10	0.03	-0.15
AGN SP commissions	-0.01	0.22*	-0.01	0.15
AGN SN commissions	-0.09	-0.15	0.03	0.04
AGN SP omissions	0.00	-0.21*	0.05	-0.18
AGN SN omissions	-0.04	-0.06	0.17	-0.17
Problem solving				
SOC problems in min moves	0.07	-0.18	0.00	0.07
SOC mean moves	-0.03	0.15	-0.13	0.07
SOC mean initial thinking time (ms)	0.01	0.11	-0.00	0.02
SOC mean subsequent thinking time (ms)	0.10	0.21*	0.06	0.01

* = $p < 0.05$; ** = $p < 0.01$; ED = eating disorder; EDI = Eating Disorder Inventory-2; GAF = Global Assessment of Functioning; AGN SN = Affective Go/No-go Shift Negative; AGN SP = Affective Go/No-go Shift Positive; BCLC = Big Circle/Little Circle; DMS = Delayed Matching to Sample; FMPS = Frost Multidimensional Perfectionism Scale; IED = Intra-Extra Dimensional Set-Shift; NART = National Adult Reading Test; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; TMT = Trail Making Test; VRM = Verbal Recognition Memory.

A number of small correlations that reached statistical significance were found between duration of any eating disorder and some of the neuropsychological variables. Longer duration of illness was correlated with poorer accuracy and slower response times on Rapid Visual Performance tests, lower recall on tests of verbal memory both in free recall and recognition conditions, increased errors on the Intra-Extra Dimensional Set-Shift, longer subsequent thinking time on Stockings of Cambridge 5-move problems, and increased errors on both between and within conditions on Spatial Working Memory. Contrary to this trend was the significant, moderate sized correlation between duration of illness and higher NART IQ scores. Two of the shift positive Affective Go/No-go variables had small correlations with duration of illness, with illness duration associated with a higher rate of commission errors and a lower rate of omission errors. No significant correlations were found between any of the other neuropsychological test variables and duration of eating disorder.

As duration of any eating disorder was significantly correlated with age ($r = 0.77$, $n = 112$, $p < 0.001$), a partial correlation between duration of eating disorder and neuropsychological variables controlling for age was conducted to investigate this association further. Results of these analyses are reported in Table 4.13.

When age was controlled for, there was no longer a significant association between illness duration and neuropsychological performance other than a significant modest negative correlation with verbal recall.

Table 4.13 Partial correlations between duration of eating disorder and psychometric test performance controlling for the effects of age in the binge eating sample (n=112).

Test	Duration of ED (years) r	p	Duration of ED age covariate r	p
RVP total hits	-0.22	0.02	-0.17	0.08
RVP total misses	0.21	0.02	0.17	0.09
RVP mean latency (ms)	0.21	0.02	0.09	0.09
VRM free recall correct	-0.28	0.002	-0.22	0.03
VRM recognition total correct	-0.19	0.04	-0.12	0.22
AGN SP total commissions	0.22	0.03	0.01	0.91
AGN SP total omissions	-0.21	0.03	-0.18	0.07
IED total errors adjusted	0.19	0.001	0.08	0.42
DMS mean correct latency (ms)	0.31	0.001	-0.08	0.42
SWM between errors	0.28	0.001	0.17	0.08
SWM within errors	0.21	0.02	0.11	0.26
SWM total errors	0.29	0.001	0.13	0.20
NART IQ	0.34	0.001	0.12	0.24

r = Pearson's r; * p<0.05; ED = eating disorder; AGN SN = Affective Go/No-go Shift Negative; AGN SP = Affective Go/No-go Shift Positive; BCLC = Big Circle/Little Circle; DMS = Delayed Matching to Sample; IED = Intra-Extra Dimensional Set-Shift; NART = National Adult Reading Test; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SP = shift positive; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; VRM = Verbal Recognition Memory

The EDI Total score, an overall measure of eating disorder severity, did not show any significant correlations with any of the neuropsychological variables other than a small negative correlation with latency to respond on the DMS task and a small positive correlation with NART IQ scores.

GAF scores were not significantly correlated with any neuropsychological variables other than a small negative correlation with latency to respond in the shift positive condition on the AGN.

4.5 Comorbidities: Depression and Anxiety

Prevalence of lifetime depression and depression in the past month, measured by the criteria in the SCID-I were significantly higher in the BN and BED groups than the HC group as reported in Table 4.14.

Table 4.14 Comparison of current and lifetime depression on SCID-I by diagnostic group

	BN <i>n</i> =58 n (%)	BED <i>n</i> =54 n (%)	HC <i>n</i> =48 n (%)	χ^2	p	Post Hoc (χ^2)
Depression lifetime (SCID-I)	35 (60.3%)	39 (72.2%)	21 (43.8%)	8.58	0.01	BED>HC** BED>HC*
Depression past month (SCID-I)	17 (29.3%)	13 (24.1%)	1 (2.1%)	13.62	0.001	BN>HC*** BED>HC**
Anxiety past month (SCID-I)	30 (51.7%)	23 (42.6%)	3 (6.3%)	25.94	<0.001	BN>HC*** BED>HC***
Anxiety lifetime (SCID-I)	35 (60.3%)	27 (50.0%)	10 (20.85%)	17.39	<0.001	BN>HC*** BED>HC**

** = $p < 0.01$; *** = $p < 0.001$ BN = bulimia nervosa, BED = binge eating disorder, HC = healthy controls; SCID-I = Structured Clinical Interview-I

Prevalence of lifetime anxiety and anxiety in the past month, measured by the SCID-I were significantly higher in the BN and BED groups than the HC group as reported in Table 4.14.

The binge eating sample (BN and BED groups combined) were divided into those than had comorbid current depression and those that did not have co-morbid depression and compared in neuropsychological performance. Results of the analyses (t-tests) are reported in Table 4.15. No differences were found between the groups for any neuropsychological variable other than on the Delayed Matching to Sample DMS B”.

A comparison of neuropsychological functioning in women with binge eating with and without comorbid anxiety disorders in shown in Table 4.16. Women with co-morbid

anxiety scored fewer hits on the Rapid Visual Processing Test compared to women who did not have co-morbid anxiety. Women with co-morbid anxiety had fewer correct responses on both the Spatial Recognition Memory Test and Delayed Matching to Sample Test compared with the women without co-morbid anxiety. No other significant differences were found between the groups for any other neuropsychological variable.

Table 4.15 Comparison of neuropsychological function in women with binge eating with and without comorbid depression.

Test	Binge eating with depression <i>n</i> =30 mean (sd)	Binge eating without depression <i>n</i> =82 mean (sd)	t	p	d
NART IQ	104.57 (7.15)	105.05 (7.79)	0.29	0.78	
Motor function					
MOT mean error	9.09 (2.23)	9.30 (2.61)	0.40	0.69	
MOT mean latency (ms)	893 (254)	901 (231)	0.15	0.88	
Visual attention					
RVP total hits	18.27 (5.01)	17.90 (4.85)	0.35	0.73	
RVP total misses	8.73 (5.01)	9.09 (4.85)	0.34	0.74	
RVP mean latency (ms)	417 (78)	418 (89)	0.03	0.98	
Memory					
VRM free recall	7.83 (2.00)	8.17 (1.67)	0.90	0.37	
VRM recognition	23.13 (1.04)	23.27 (0.98)	0.63	0.53	
VRM recognition delayed	22.67 (1.83)	23.17 (1.03)	1.84	0.07	
SRM number correct	18.33 (2.17)	18.48 (1.66)	0.37	0.71	
SRM mean correct latency (ms)	2254 (762)	2226 (519)	0.23	0.82	
DMS % correct	88.44 (8.92)	87.48 (10.75)	0.44	0.66	
DMS mean correct latency (ms)	3881 (1583)	3823 (1221)	0.21	0.84	
DMS B"	-0.96 (0.18)	-0.75 (0.47)	2.08	0.04	0.59
SWM between errors	21.77 (17.53)	21.93 (15.61)	0.06	0.96	
SWM within errors	1.33 (2.26)	1.23 (2.46)	0.19	0.85	
SWM total errors	22.30 (17.88)	22.52 (15.89)	0.06	0.95	
SWM strategy	31.67 (6.13)	31.86 (5.17)	0.16	0.87	
Set-shifting					
IED total errors adjusted	24.97 (19.01)	23.60 (20.54)	0.32	0.75	
IED stages completed	8.77 (0.63)	8.59 (0.80)	1.12	0.27	
IED total trials adjusted	96.23 (33.10)	94.07 (37.11)	0.28	0.78	
TMT proportional score	34.58 (23.19)	31.49 (13.99)			
Inhibitory control					
AGN SP mean correct latency (ms)	552 (72)	524 (66)	1.95	0.05	
AGN SN mean correct latency (ms)	546 (67)	515 (62)	2.20	0.03	
AGN SP total com	3.40 (2.42)	3.46 (3.08)	0.12	0.92	
AGN SN total com	2.03 (1.99)	2.11 (2.15)	-0.17	0.87	
AGN SP total omissions	3.17 (4.02)	2.53 (1.95)	1.43	0.15	
AGN SN total omissions	2.07 (2.97)	1.40 (1.68)	1.49	0.14	
Problem solving					
SOC problems in min moves	9.07 (1.91)	9.41 (1.59)	0.97	0.33	
SOC mean moves	6.20 (1.43)	6.39 (1.33)	0.59	0.56	
SOC mean initial thinking time (ms)	12626 (7856)	13166 (8467)	0.30	0.71	
SOC mean subsequent thinking time (ms)	1534 (2921)	1661 (3269)	0.19	0.85	

d = Cohen's d; AGN SN = Affective Go/No-go Shift Negative; AGN SP = Affective Go/No-go Shift Positive; BCLC = Big Circle/Little Circle; DMS = Delayed Matching to Sample; IED = Intra-Extra Dimensional Set-Shift; NART = National Adult Reading Test; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; TMT = Trail Making Test; VRM = Verbal Recognition Memory

Table 4.16 Comparison of neuropsychological function in women with binge eating with and without comorbid anxiety disorders.

Test	Binge eating with anxiety <i>n</i> =53 mean (sd)	Binge eating without anxiety <i>n</i> =59 mean (sd)	t	p	d
NART IQ	105.02 (7.39)	104.84 (7.84)	0.12	0.91	
Motor function					
MOT mean error	9.51 (2.55)	9.01 (2.46)	1.05	0.30	
MOT mean latency (ms)	895 (220)	901 (251)	0.14	0.89	
Visual attention					
RVP total hits	16.92 (4.15)	18.97 (4.44)	2.25	0.03	0.32
RVP total misses	10.06 (5.15)	8.03 (4.44)	2.23	0.03	
RVP mean latency (ms)	426 (85)	410 (87)	1.04	0.30	
Memory					
VRM free recall	7.92 (1.57)	8.22 (1.91)	0.89	0.38	
VRM recognition	23.21 (1.03)	23.25 (0.98)	0.25	0.81	
VRM recognition delayed	23.17 (1.28)	23.92 (1.32)	1.03	0.30	
SRM number correct	18.06 (1.90)	18.78 (1.65)	2.16	0.03	0.40
SRM mean correct latency (ms)	2242 (692)	2226 (487)	0.14	0.89	
DMS % correct	85.41(11.48)	89.83 (8.61)	2.32	0.02	0.43
DMS mean correct latency (ms)	3781 (1335)	3891 (1316)	0.44	0.66	
DMS B"	-0.74 (0.47)	-0.89 (0.35)	1.61	0.11	
SWM between errors	23.73 (16.36)	20.31 (15.77)	1.12	0.26	
SWM within errors	1.83 (0.76)	0.76 (1.13)	1.42	0.20	
SWM total errors	24.58 (16.71)	20.59 (15.97)	1.28	0.20	
SWM strategy	32.56 (4.98)	31.14 (5.74)	1.39	0.17	
Set-shifting					
IED total errors adjusted	24.55 (21.07)	23.44 (19.28)	0.29	0.77	
IED stages completed	8.61 90.78 0	8.47 (0.90)	0.95	0.34	
IED total trials adjusted	95.13 (37.82)	94.22 (34.49)	0.13	0.89	
TMT proportional score	34.01 (18.57)	30.79 (15.24)	1.00	0.32	
Inhibitory control					
AGN SP mean correct latency (ms)	531 (66)	533 (71.3)	0.15	0.88	
AGN SN mean correct latency (ms)	520 (67)	527 (63)	0.59	0.56	
AGN SP total com	3.75 (2.76)	3.17 (3.02)	1.07	0.29	
AGN SN total com	2.30(2.27)	1.89 (1.93)	1.01	0.31	
AGN SP total omissions	2.98 (3.19)	2.20 (2.06)	1.55	0.12	
AGN SN total omissions	1.85 (2.38)	1.34 (1.82)	1.28	0.20	
Problem solving					
SOC problems in min moves	9.06 (1.84)	9.56 (1.49)	1.59	0.11	
SOC mean moves	6.43 (1.38)	6.23 (1.33)	0.78	0.44	
SOC mean initial thinking time (ms)	13213 (8218)	12850 (8395)	0.23	0.82	
SOC mean subsequent thinking time (ms)	1930 (3217)	1354 (3125)	0.96	0.34	

d = Cohen's d; AGN SN = Affective Go/No-go Shift Negative; AGN SP = Affective Go/No-go Shift Positive; BCLC = Big Circle/Little Circle; DMS = Delayed Matching to Sample; IED = Intra-Extra Dimensional Set-Shift; NART = National Adult Reading Test; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; TMT = Trail Making Test; VRM = Verbal Recognition Memory

4.6 Neuropsychological Performance and Impulsivity

A comparison of Barratt Impulsivity Scale (BIS) subscale scores among the groups are presented in Table 4.17. The BN group scored more highly on the Motor subscale compared with the HC group. Both the BN and BED groups scored more highly for impulsiveness on the BIS Cognitive subscale than the healthy control group.

Table 4.17 Impulsivity measured by the Barratt Impulsiveness Scale Subscales by diagnostic group

	BN <i>n</i> =58 mean (sd)	BED <i>n</i> =54 mean (sd)	HC <i>n</i> =48 mean (sd)	F	p	d	Post Hoc (LSD)
BIS non-planning	18.8 (8.3)	19.7 (7.6)	19.7 (6.8)	0.3	0.77		
BIS motor	18.4 (6.7)	16.2 (6.5)	14.6 (6.2)	4.8	0.01	0.59	BN>HC
BIS cognitive	14.0 (5.9)	13.5 (5.2)	11.3 (3.9)	4.1	0.02	0.54 0.48	BN>HC BED>HC

d = Cohen's d; BN = bulimia nervosa, BED = binge eating disorder, HC = healthy controls; BIS = Barratt Impulsivity Scale.

The association between neuropsychological functioning and impulsivity was investigated using Pearson product-moment correlation coefficients. Results of these analyses are reported in Table 4.18. The Non-planning subscale was not significantly correlated with any neuropsychological variable. The Motor subscale had a small correlation with Spatial Recognition Memory percent correct, Spatial Recognition Memory mean correct latency, Delayed Matching to Sample percentage correct, Delayed Matching to Sample mean correct latency and NART IQ. The Cognitive subscale had one moderate negative association with verbal free recall. For all of these significant associations, higher BIS

scores were associated with faster or less accurate performance on these neuropsychological tasks.

Table 4.18 Correlations between the Barratt Impulsivity Scale and neuropsychological variables in the eating disorder sample (n=112).

Test	Non-planning	Motor	Cognitive
NART IQ	-0.08	-0.24*	-0.18
Motor function			
MOT mean error	0.11	-0.02	-0.06
MOT mean latency (ms)	0.00	0.05	0.06
Visual attention			
RVP total hits	-0.10	-0.09	-0.08
RVP total misses	0.10	0.09	0.08
RVP mean latency (ms)	0.17	-0.01	-0.03
Memory			
VRM free recall correct	0.02	-0.11	-0.22*
VRM recognition total correct	-0.04	-0.09	-0.09
VRM recognition total correct delayed	0.05	-0.02	-0.09
SRM number correct	-0.02	-0.10	-0.11
SRM mean correct latency (ms)	-0.14	-0.22*	-0.03
DMS % correct	-0.12	-0.21*	-0.04
DMS mean correct latency (ms)	-0.11	-0.22	-0.05
DMS A'	-0.04	0.31	0.38
DMS B''	0.06	0.14	-0.05
SWM between errors	0.17	0.16	0.11
SWM within errors	0.14	0.05	0.06
SWM total errors	0.18	0.16	0.11
SWM strategy	-0.03	0.03	-0.01
Set-shifting			
IED total errors adjusted	-0.11	0.01	0.06
IED stages completed	0.10	0.03	0.02
IED total trials adjusted	-0.13	-0.01	0.04
Trails proportional score (B-A/A)	-0.01	0.02	0.00
Inhibitory control			
AGN SP mean correct latency (ms)	0.04	-0.12	-0.00
AGN SN mean correct latency (ms)	0.12	0.01	0.06
AGN SP total commissions	0.15	0.08	-0.00
AGN SN total commissions	0.09	0.13	0.08
AGN SP total omissions	-0.04	-0.10	0.10
AGN SN total omissions	-0.07	-0.04	0.04
Problem solving			
SOC problems solved in minimum moves	0.04	-0.15	-0.15
SOC mean moves	0.07	0.17	0.18
SOC mean initial thinking time (ms)	-0.01	-0.18	-0.02
SOC mean subsequent thinking time (ms)	0.01	0.01	0.08

AGN = Affective Go/No-go; DMS = Delayed Matching to Sample; IED = Intra-Extra Dimensional Set-Shift; NART = National Adult Reading Test; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; VRM = Verbal Recognition Memory.

4.7 *Summary of Key Neuropsychological Findings*

- Key findings from the neuropsychological functioning section of the current study including consideration of demographic group differences and confounding factors are summarised below:
- The binge eating disorder group were significantly older and of higher mean weight compared with the bulimia nervosa and healthy control groups. No significant differences were found among the groups for ethnicity, years of education or premorbid intellectual functioning.
- Caffeine use was higher in the binge eating groups; however there were no differences found for any of the neuropsychological variables between participants that had coffee on the day of the testing and those that had not.
- No differences were found among the groups for ingestion of alcohol or cannabis. Current illness and medication use was higher in the binge eating group than the other two groups.
- No differences were found in accuracy of motor function among the groups; however the binge eating group had faster response times compared with the bulimia nervosa and healthy control groups.
- No differences were found among the three groups on tests of visual attention.
- Learning and memory was found to be intact in the binge eating groups other than a significant reduction in verbal recall in the binge eating group.
- The bulimia nervosa group had superior function in one measure of the Intra-Extra Dimensional Set-shifting test compared with the healthy control group; however there were no other differences among the groups on other measures of set-shifting.

- No differences were found among the groups on measures of inhibitory control, although there was a non-significant trend towards a negative response bias in both the binge eating groups compared with a positive bias in the healthy control group.
- No differences were found among the groups on tests of planning.
- The total sample of the current study consistently performed at a higher level than CANTABeclipse computerised neuropsychological battery norms.
- Duration of any eating disorder was correlated with poorer performance on tests of visual attention, verbal recall and spatial working memory; however, these associations were not found when the effect of age was accounted for.
- The bulimia nervosa and binge eating disorder groups were more likely to meet criteria for both lifetime and current depression and anxiety than the healthy control group. However, very few significant associations were found between depression or anxiety and neuropsychological performance for the eating disorder sample.
- Levels of impulsivity on the Motor and Cognitive subscales of the Barrett Impulsivity Scale were found to be higher in the binge eating groups compared with the healthy control group. Very few significant associations were found between levels of impulsivity and neuropsychological performance in the eating disorder sample with no obvious pattern emerging from the analyses.

5. DISCUSSION: NEUROPSYCHOLOGICAL FUNCTIONING

5.1 Demographics

Analysis of demographic variables showed that the three groups did not significantly differ in levels of education, premorbid intelligence or ethnicity. The ethnic makeup of study participants reflected the female population of Christchurch. The majority of participants (85.6%) identified as New Zealand European which is very similar to the proportion found in the latest census in which 76.8% of Christchurch females identified as New Zealand European (Statistics New Zealand, 2016). The proportion of the sample that identified as Maori was 8.8% compared with 7.3% in the local population and 5.6% were Asian compared with 8.0% of the local population. These similarities suggest the results of the current study can be generalised to the general Christchurch population.

The groups differed in age and BMI and as expected the binge eating disorder group were older with higher BMIs than both the bulimia nervosa and healthy control groups. These differences in age and BMI were taken into account when analysing neuropsychological differences among the groups.

5.2 Potential Confounding Factors on Neuropsychological Functioning

One of the strengths of the current study is consideration taken of a number of potential confounding factors that have not always been taken into account in previous studies. Significant differences were found in caffeine intake on the day of testing, with the binge

eating groups having a higher intake. The binge eating groups also reported higher daily intake of caffeinated drinks. Caffeine is known to improve performance, particularly on tests requiring speed and attention (Haskell et al., 2005). No differences were found between those that had consumed caffeine before the testing and those that had not for any of the neuropsychological test variables. It is possible that the amount of caffeine consumed was not large enough or was not consumed close enough in time to the testing to affect the results. The strength of the caffeine drinks or the time consumed was not recorded in the present study so this question remains unanswered. Previous studies have shown that the dose of caffeine is an important consideration (Haskell et al., 2005; Rees, Allan & Lader, 1999) as is the time of ingestion before testing.

No differences were among the groups in the use of alcohol in the 24 hours before testing, although there was a trend towards more participants in the bulimia nervosa group using cannabis in the previous 24 hours. Three of the bulimia nervosa group had used cannabis compared with none in the binge eating disorder or healthy control groups. Increased use of cannabis in binge eating has been reported previously (Jordan et al., 2014). Although this difference was not statistically significant in the current study, this trend suggests that information on cannabis use should be collected before neuropsychological testing in future studies of binge eating.

The proportion of participants needing visual aids (glasses, contact lenses) was higher in the binge eating disorder group which is likely to be a reflection of the older mean age of this group. All participants who required them were wearing glasses or contact lenses for testing so this is unlikely to be an important factor in interpreting differences in neuropsychological functioning among the groups. No differences were found in the incidence of previous head injury among the groups and all affected individuals reported

incidences of mild seriousness. Although the binge eating group reported more current illnesses, on inspection these seemed unlikely to significantly influence performance on the testing.

5.3 *Motor Function*

Motor function was not impaired in bulimia nervosa or binge eating disorder groups in terms of accuracy or speed of motor response. Unexpectedly, the binge eating disorder group responded significantly faster than the bulimia nervosa and healthy control groups. This result suggests that on timed tests, motor function is not likely to have a negative effect on neuropsychological test performance. In contrast to this result, several studies have reported some degree of motor slowing in bulimia nervosa (Bosanac et al., 2007; McKay et al., 1986) and binge eating disorder (Aloi et al., 2015). However, the current study's finding is consistent with Darcy et al. (2012) who found no motor slowing in a group of adolescents with bulimia nervosa. As the majority of studies investigating neuropsychological functioning in binge eating have not reported measures of motor function it is difficult to make any conclusions about the role of motor functioning in neuropsychological functioning in binge eating.

Although motor functioning was not impaired in women with binge eating in the current study it remains an important component of any comprehensive neuropsychological test battery, regardless of whether motor function impairment is predicted or not. In computerised batteries it is essential that the ability of each participant to use a mouse or touch screen is assessed before proceeding to the remaining tests.

5.4 *Attention*

Sustained attention appears to be unimpaired in women with binge eating. Results of the Rapid Visual Information Processing Task showed no impairment in accuracy or speed of responding. This result is consistent with the majority of previous studies which have also reported no impairment in sustained attention in either bulimia nervosa (Alvarez-Moya et al., 2009; Beatty et al., 1990; Brand et al., 2007; Darcy et al., 2012; Murphy et al., 2004; Weider et al., 2015) or binge eating disorder (Kelly et al., 2013; Manasse et al., 2015).

The ability to sustain attention is important to understand in the context of examining complex neuropsychological performance, as it is required for some of the more complex executive function skills such as set-shifting. As attention is not impaired in women with binge eating this allows interpretation of executive performance independent from attention.

5.5 *Memory and Learning*

Immediate recall of verbal information was relatively impaired in the binge eating disorder group compared with the bulimia nervosa group, even after accounting for the difference in mean age and BMI among the groups. In contrast to this result immediate verbal recognition was not impaired in the binge eating disorder group. This is not surprising as recall of verbal information is a more cognitively demanding task than recognition. This is reflected in results of the current study with the mean percentage of words recalled ranging from 65% in binge eating disorder to 73% in the healthy control group, compared with rates of over 95% for verbal recognition. There may have been a ceiling effect in the recognition conditions as the mean rate of recall was 95% or more in all three groups. It is

possible that a more cognitively demanding test of recognition may have revealed differences among the groups.

Memory for verbal information in the delayed condition also appears to be unimpaired for both bulimia nervosa and binge eating disorder; however there was an interesting finding of higher rates of false positive responses in the binge eating disorder group. This pattern may suggest a tendency towards impulsivity in responding in this group.

Overall results from the current study suggest that there may be some reduction in performance on cognitively demanding tasks of verbal memory, such as recall, in individuals with binge eating disorder; however on less demanding tasks, such as verbal recognition, there appears to be no relative impairment in verbal memory compared with either the bulimia nervosa or healthy control groups.

Previous research has not found a consistent pattern of verbal memory impairment in binge eating. Some previous studies have found impairment in verbal memory in bulimia nervosa (Bosanac et al., 2007; Weider et al., 2015), whereas others have not reported verbal memory impairment (Degortes et al., 2015; Pendleton Jones et al., 1991). There are problems interpreting previous findings as many studies have not reported whether verbal memory impairments were in recall or recognition, or immediate or delayed conditions.

Research on verbal memory in binge eating disorder has not been reported to date so although the results of the current study suggest there may be some relative impairment compared with women without binge eating. Further investigation is required before any conclusions can be drawn regarding the verbal memory in women with binge eating disorder.

The current study did not assess verbal learning; however, this may be an interesting area to explore further. Brand et al. (2007) used an auditory verbal learning test in women with bulimia nervosa and although they found no differences in memory on the first trial, they found reduction in learning the fifth trial in the bulimia nervosa group compared with the control group. This is further support for the need to use cognitively demanding tasks to investigate neuropsychological function in binge eating as if differences are present, they are likely to be found only at more challenging levels.

Visual memory was not impaired in either the bulimia nervosa group or the binge eating disorder group measured on the Delayed Matching to Sample Test. This task requires the ability to perceive and retain information about complex combinations of objects, which differ in shape and colour, in order to recognise the same combination among four choices. Despite this complexity, many participants were able to identify a high percentage of object combinations accurately. As with the tests of verbal memory, there may have been a ceiling effect on this test, particularly as it is a test of recognition rather than recall, in that participants had a choice of four options and did not need to recreate the object combinations. This test was designed as part of the wider CANTAB battery to differentiate between those with brain injury and dementia (Robbins et al., 1994) however it has been shown to differentiate other mental health populations as previously discussed.

Ability to recall spatial position information using the Spatial Recognition Memory Task appears to be intact in bulimia nervosa and binge eating disorder. However, this task may not be as cognitively demanding as other tests of visual memory used in some other studies. The Spatial Recognition Memory test does not have a copy component and so is not influenced by drawing ability as with complex figure tasks (such as the Rey Osterrieth Complex Figure Test). Because the participant is not required to physically reproduce

spatial information it is a test of recognition only, requiring memory of *position* rather than *shape* or *design*, this task is less challenging than the complex figure tasks. The outcome variable on this task is the number of correct responses. Many participants in the current study scored close to the maximum score of 20 on this task and it seems likely there was a ceiling effect. It is possible that a more complex task may have found differences among the groups. This should be considered when planning future studies investigating spatial memory.

Previous research has reported conflicting findings regarding visuo-spatial ability in individuals with binge eating. Most studies investigating spatial ability in bulimia nervosa have used the Rey Osterrieth Complex Figure Test. A number of studies reported impairment in the copy and recall of conditions (Kim et al., 2011; Roberts et al., 2013; Weider et al., 2015), whereas others have not found impairment (Darcy et al., 2015; Degortes et al., 2015; Murphy et al., 2004). Impairment in copy and recall on the Rey Osterrieth Complex Figure Test was found in one study of women with binge eating disorder (Aloi et al., 2015). Although the results of the current study do not suggest impairment in this domain, the test used may not have been demanding enough to detect differences in visuo-spatial perception and memory. As some existing research has found evidence of impairment in visuo-spatial perception and memory, further research using more challenging tasks is required, particularly in individuals with binge eating disorder.

Working memory does not appear to be impaired in women with binge eating in the current study. Those with bulimia nervosa and binge eating disorder did not make more errors or nor was there evidence of poor strategy on the Spatial Working Memory test compared with healthy controls. Two studies have also reported no impairment in working memory in bulimia nervosa (Bosanac et al., 2007; Brand et al., 2007). In contrast, another

study (Weider et al., 2015), found working memory was impaired in bulimia nervosa.

However, Weider et al.'s study (2015) reported a composite score of working memory and did not report individual tests, making it difficult to compare with other studies.

In summary, memory for verbal and visuo-spatial information appears to be unimpaired in women with bulimia nervosa. If impairments are present, they would appear to be on more cognitively demanding tasks. There may be a greater degree of memory impairment in binge eating disorder for recall of verbal information indicated by fewer words recalled and more false positive responses on tests of recognition. Again impairments are only evident on more cognitively demanding tasks. Overall it seems unlikely that impairment in memory significantly affect individuals with binge eating.

5.6 Inhibitory Control and Attentional Bias

No differences were found in the ability to inhibit responses in emotionally neutral conditions suggesting that inhibitory control is unimpaired in both bulimia nervosa and binge eating disorder when there is no emotional component to the task. This is consistent with previous studies in bulimia nervosa (Degortes et al., 2015; Galimberti et al., 2012 and binge eating disorder (Kittel, Brauhardt, & Hilbert, 2015; Mole et al., 2015; Wu et al., 2013); however at least one study has found inhibitory control to be lower in bulimia nervosa than controls for neutral stimuli (Wu et al., 2013).

Tests of inhibitory control which include conditions containing emotional targets measure not only inhibitory control but also attentional bias. Responding more quickly to a specific valence (positive or negative) suggests attentional bias towards that valence. Women with binge eating did not differ from healthy controls in either the latency to respond, number of commissions (impulsive response) or number of omissions (lack of attention) in the

positive or negative valence conditions. This result suggests the absence of an emotional bias in women with binge eating. However, results from the emotional bias index, although not significant, suggest that further exploration of this area is warranted.

A positive Emotional Bias Index suggests a positive processing bias, that is, a faster response to a word with a positive valence than a word with a negative valence.

Conversely a negative Emotional Bias Index suggests that a respondent has a negative bias, that is, a faster response to a word with a negative valence. Although those in the binge eating groups had a tendency towards a negative emotional bias, this was not statistically significant, probably due to the large variance in responses within the groups. It is possible that some women with binge eating process emotional targets differently from some others, which suggests that these women may be more vulnerable to negative experiences overall.

Harrison et al. (2010) found a significant bias towards negative social stimuli in their study and suggest that this bias may play a role in the development and maintenance of eating disorders. It is possible that a negative bias may pre-date the development of an eating disorder as attention bias to negative social stimuli was reported in twin sisters of women with eating disorders including bulimia nervosa and binge eating disorder. (Kanakam et al., 2013).

Attentional bias using the Stroop Test paradigm (Stroop, 1935) has been reported in individuals with bulimia nervosa (for a review see Dobson & Dozois, 2004)). The Stroop Test paradigm measures the interference in processing stimuli in which the printed colour of a word is different from the meaning of the word to be read, resulting in longer reaction times and increased errors. The Stroop Test has been modified to assess processing of eating disorder specific words including food and body-related categories. Reaction time

to neutral or colour words appear not to be different from those of healthy controls but women with bulimia nervosa are slower to respond to words that are body or food related (Carter et al., 2000; Jones-Chesters, Monsell, & Cooper, 1998; Lovell, Williams, & Hill, 1997). It is thought that the processing of these words results in interference from emotions elicited from the eating disorder related words (Lovell et al., 1997). The only study investigating attention bias using Stroop tests in binge eating disorder found no difference between binge eating disorder and control groups (Duchesne et al., 2010).

In summary, inhibitory control in emotionally neutral conditions appears to be relatively unimpaired in women with binge eating and this finding is consistent with previous research. In tests of inhibitory control that included an emotional component, although there was no significant difference among the groups in the current study, there was a non-significant pattern of a negative attention bias in both binge eating groups. Attentional bias towards negative stimuli has been previously reported in eating disorders. Overall, if inhibitory control impairments are present in women with binge eating it seems more likely that this may be due to interference from attentional biases related to stimuli that have a negative emotional valence (affecting the ability to shift to positive valence stimuli) or are eating disorder-related (where body or food related words are disrupting attention resulting in slower responses).

5.7 Set-shifting

The Trail Making Test and the Intra-Extra Dimensional Set-shifting Test were used to investigate set-shifting in the current study but results were inconsistent. The proportional score on the Trail Making Test accounts for differences among participants' motor skills and is thought to more accurately measure set-shifting than the score from Part B alone. No differences were found among the groups on this test suggesting that there is no

impairment in set-shifting in women with bulimia nervosa. Although the Trail Making Test is commonly used as a test of set-shifting, it does not explore the concept of set-shifting in as much complexity as other tests such as the Wisconsin Card Sorting test or the Intra-Extra Dimensional Set-shift test which was administered in the current study.

All groups made a similar level of errors in the Intra-Extra Dimensional Set-shift Test; however, the bulimia nervosa group completed more stages on average than the healthy control group, and both the bulimia nervosa and binge eating disorder groups had a greater proportion complete all nine stages of this test. This suggests that in some conditions women with binge eating show superior set-shifting compared with women without binge eating. This was unexpected, as overall existing research has found either no difference in set-shifting or poorer performance in set-shifting when using the Trail Making Test and Wisconsin Card Sorting Test in women with bulimia nervosa (Roberts et al., 2007; Wu et al., 2014) or binge eating disorder (Kittel et al., 2015). In the only study to use the Intra-Extra Dimensional Set-shift Test in bulimia nervosa no differences in set-shifting were found in bulimia nervosa compared with healthy controls (Galimberti et al., 2012). No studies that have used the Intra-Extra Dimensional Set-shift Test in individuals with binge eating disorder.

The Wisconsin Card Sorting Test is considered to be a more difficult task than the Intra-Extra Dimensional Set-shift Test as the number of choices on the Intra-Extra Dimensional Set-shift Test are fewer (Oh et al., 2014). Therefore, tests of set-shifting in the current study may not have been of sufficient difficulty to show differences between individuals with binge eating compared to those that do not binge eat. However, the Intra-Extra Dimensional Set-shift Test may be more complex in other ways as it requires the participant to pay attention to small details in the irregular shapes and lines of only two

colours (pink and white) which are novel and cannot be simply described. This is compared with the Wisconsin Card Sorting Test, which uses recognisable shapes such as diamonds, circles and triangles, which are boldly coloured in yellow, red, blue or green, and are able to be categorised in more simple terms (e.g. yellow stars). The Intra-Extra Dimensional Set-shift Test may tap into detail and global processing (central coherence), as this test requires substantial focus on small details of visual information. If this is the case, the finding of superior performance by the bulimia nervosa group in the current study would be consistent with previous findings of weak central coherence in bulimia nervosa with enhanced detail processing (Lopez et al., 2008). Central coherence was not specifically investigated in the current study so this interesting finding cannot be related to the central coherence characteristics of the eating disorder groups in this study.

In summary, although previous research suggests that there may be some set-shifting difficulties in women with bulimia nervosa, the results of the current study do not support this finding. It is possible that the test used in the current study was not of sufficient difficulty to be able to detect differences among the groups, although differences have been found using this test in some previous studies. However, in the only significant difference found, the bulimia nervosa group completed more stages of the Intra-Extra Dimensional Set-shift Test compared with healthy controls. It could be speculated that the Intra-Extra Dimensional Set-shift Test may tap into the central coherence with the bulimia nervosa group showing skill in detail processing, as has been found in some previous research into central coherence in binge eating (see Lopez et al., 2009).

5.8 Eating Disorder Psychopathology

As previously noted there is significant movement among diagnostic groups within eating disorders (Agras, 1997; Sullivan et al., 1998). In the current study 15.5% of women with

bulimia nervosa had a history of anorexia nervosa, compared with 1.9% of those with binge eating disorder and none of the healthy control group. Agras et al. (1997) found 24% of 220 women recruited for a large treatment study of bulimia nervosa had a previous history of anorexia nervosa. A history of anorexia nervosa has been associated with higher levels of psychopathology (Monteleone et al., 2011; Vaz-Leal et al., 2011) and a poorer outcome in treatment studies (Eddy et al., 2007). There is some evidence that individuals who have recovered from anorexia nervosa may not completely recover neuropsychological functioning (Degortes et al., 2015; Tenconi et al., 2010). This has implications for understanding neuropsychological function in women with bulimia nervosa with a history of anorexia nervosa. The current study did not find a significant difference in neuropsychological function in women with bulimia nervosa with or without a history of anorexia. This section of the study was statistically under-powered with only nine women having a previous history of anorexia nervosa and therefore conclusions regarding the lasting impact of anorexia nervosa cannot be drawn. Longitudinal studies, rather than cross sectional as in the current study would have greater utility in understanding whether a history of anorexia nervosa has a negative impact on women who have moved into a bulimia nervosa diagnosis.

Duration of eating disorder was significantly associated with a number of neuropsychological variables including poorer performance on some measures of attention, verbal memory (recall and recognition), visuo-spatial recognition memory, spatial working memory, inhibitory control, and set-shifting. However, there was a significant positive correlation between duration of eating disorder and age. When age was used as a covariate in the analyses, only one variable, verbal free recall memory, retained a significant association with duration of eating disorder. This suggests that duration of illness does not

impact on neuropsychological functioning in women with binge eating. This pattern has been found in previous studies (Laessle et al., 1990; Roberts et al., 2013).

Illness severity, rather than illness duration, is more likely to impact on neuropsychological function. In the current study eating the Eating Disorders Inventory-2 (EDI-2), an eating disorder specific measure of illness severity, was not associated with neuropsychological functioning in women with binge eating. A more global measure of illness severity, the Global Assessment of Functioning, was also not associated with neuropsychological function. The sample size for these analyses was sufficient to detect a difference among the groups if there was one present. In the current study at least, eating disorder severity does not seem to be associated with neuropsychological functioning in women with binge eating. This is in contrast to findings reported by some other studies, for example, Roberts et al. (2013) found weak central coherence was associated with higher eating disorder severity in women with bulimia nervosa. Roberts et al. (2013) used a clinician-rated measure of illness severity (SCID-I) in contrast to the self-rated EDI-2 measure used in the current study. It would be useful to consider other ways of measuring illness severity other than a self-report measure such as clinician-rated methods. Consideration of biological markers of illness severity in future studies would also be interesting, particularly those that measure nutritional status. BMI has also been used as a measure of illness severity, particularly in studies of women with anorexia nervosa or bulimia nervosa, however, this is not seen as a reliable estimate. More promising measures of nutritional status could include measures of glucose availability and vitamin levels.

Although many studies have reported measures of illness severity, few have specifically investigated this as a factor in neuropsychological function. Further research in this area is needed.

5.9 *Depression and Anxiety*

On assessment the SCID-I revealed that 29% of the bulimia nervosa group and 24% of the binge eating disorder group met criteria for depression in the past month compared with only 2.1% of the healthy control group. Rates of lifetime depression have been reported to be as high as 55% in bulimia nervosa and 42% in binge eating disorder (Kessler et al., 2013). When lifetime prevalence was included rates rose to 60% of the bulimia nervosa group and 72% of the binge eating groups. The healthy control group had a lifetime prevalence of 44%. Depression is therefore a substantial comorbidity for a large majority of women with binge eating in the current study.

Depression is known to be associated with specific impairments in neuropsychological functioning (Snyder, 2013), particularly executive function (Castaneda et al., 2008), including set-shifting, planning and verbal fluency (Rogers et al., 2004). Although little if any impairment was found in individuals with binge eating compared with healthy controls it is possible that there may be some association between depression and neuropsychological functioning within the binge eating disorder sample. However, the results of the current study does not indicate this to be the case.

This suggests that although depression is prevalent in women with binge eating, it does not appear to negatively impact on overall neuropsychological functioning. Alternatively it is possible that the neuropsychological tests used were not of sufficient difficulty to detect small differences among the groups if they were present. One of the limitations of this section of the research is that a continuous measure of depression was not used in the analysis.

Another limitation is the lack of a measure of mood state at the time of testing. As discussed in a previous section, a recent study (Dingemans et al., 2015) examining mood and set-shifting in women with binge eating disorder found that negative mood state was associated with poorer set-shifting ability.

Lifetime prevalence of anxiety disorders in the current study was 60% in bulimia nervosa and 50% in binge eating disorder. This is comparative to that reported by Kessler et al. (2013) of 65% in bulimia nervosa and 56% in binge eating disorder. Anxiety is therefore a significant comorbidity in women with binge eating. Anxiety may affect neuropsychological function by increasing attentional bias to negative stimuli (Bauer et al., 2016) and creating interference in processing information (Mathews & Mackintosh, 1998; Singhal et al., 2012). Pallister & Waller, (2008) have found women with eating disorders display attentional bias and interference effects which are associated with anxiety.

As few significant associations were found in the current study between anxiety and neuropsychological functioning it seems unlikely that there was interference in processing stimuli as would be expected if anxiety was affecting performance on these tasks. It may be that a current of an anxiety disorder diagnosis may not be a good measure of anxiety in test-taking situations. A measure of state anxiety may be more useful to explore this further.

5.10 Impulsivity

Levels of impulsivity appear to be higher in women with binge eating disorders. In the current study the bulimia nervosa group had significantly higher motor impulsivity and cognitive impulsivity. Previous studies have also reported increased impulsivity using the Barratt Impulsiveness Scale (BIS) in bulimia nervosa. For example, Galimberti et al.

(2012) reported higher scores in the Cognitive subscale in women with bulimia nervosa compared with healthy controls but did not report a difference in Motor impulsivity. Other studies have not reported BIS subscale scores, but have used the BIS total score with some studies reporting higher total scores in bulimia nervosa (Kemps & Wildon, 2010; Rosval et al., 2006); and others no difference between individuals with bulimia nervosa and healthy controls despite having sufficient power to detect such a difference (Claes et al., 2006; Liao et al., 2009).

In the current study the binge eating disorder group did not show the same elevation in Motor impulsivity as the bulimia nervosa group but were higher on the Cognitive impulsivity subscale than healthy control group. Previous studies in binge eating disorder have not reported on individual subscale scores; however, one study found elevations in the BIS total score (Danner et al., 2012) with another finding no elevation (Svaldi et al., 2010). As with many study investigating neuropsychological functioning in binge eating, sample sizes were likely to have been insufficient to detect even a large effect size.

It could be expected that both motor and cognitive impulsivity may be associated with impulsive responding on neuropsychological tests. Faster responding with increased errors on neuropsychological tests would be consistent with impulsivity. Results from the current study did not find this pattern for Non-planning impulsivity which is thought to measure the ability to think ahead. Motor impulsivity showed a small, yet significant correlation with faster responding and increased errors on the Delayed Matching to Sample Test, which measures of visuo-spatial memory. The one other significant correlation found with Motor impulsivity was with faster responding on another visuo-spatial test, Spatial Recognition Memory. A single small negative correlation was found in the current study between cognitive impulsivity and recall of verbal information. The sample size

(n=122) was large enough to be able to detect significant associations if they were present. However, given the large number of analyses (uncorrected) here and no other findings supporting this result, the possibility that it is a spurious finding cannot be discounted. Hypothetically, the mechanism of such a relationship might be that cognitive impulsivity could be interfering with either storage or retrieval of verbal information however further research is required to determine whether this result has any validity.

Overall, results did not find that impulsivity in women with binge eating was associated with neuropsychological functioning, although further exploration of recall of verbal information and visuo-spatial memory may be warranted. The current study did not include tests of decision-making ability which may be more sensitive to an impulsive response style than some of the tests administered in the CANTAB battery.

5.11 Strengths and Weaknesses

A broad recruitment strategy was a strength of the current study as it drew participants from a range of sources ranging from referrals from the South Island Eating Disorders Service, a specialist eating disorders treatment unit, through to advertisements in the community. This gives greater confidence in the ability to generalise results to the wider binge eating population. The large sample size allowed the study sufficient statistical power to detect differences among the diagnostic groups. The range of potential confounding variables considered in the analyses was a strength that allows greater confidence in the results.

The use of a computerised neuropsychological testing battery was a strength of the study as it allowed improved accuracy, particularly on timed tests and a constancy in

administration among participants. The battery covered a wide range of neuropsychological domains in one testing session so it is time efficient.

However, the use of a computerised test battery also presents some limitations. CANTAB tests have not been well validated against standard non-computerised versions and recent factor analyses found the computerised versions did not always measure the same construct as the traditional versions (Lenehan et al., 2016; Smith et al., 2013). These studies suggested that although CANTAB is able to discriminate healthy adults from those with mild cognitive impairment, it is more a measure of general neuropsychological functioning rather than a measure of distinctive domains. For example, as already discussed in section 5.6 above, the current study the computerised tests of visual spatial memory, the Delayed Matching to Sample and Spatial Recognition Memory Tests, do not test the ability of the participant to learn and reproduce the target shape in a physical way as required by the possibly more challenging Rey Osterrieth Complex Figure Test. As such they are likely to be measuring different visuo-spatial constructs. Both computerised and traditional formats are likely to have a role in understanding neuropsychological functioning and it would be useful if validation studies comparing these two formats were undertaken. Note that one of the measures of set-shifting used in the current study was a pen and paper administered test, the Trail Making Test, and this format did not show any difference in performance between those with binge eating and those without. Overall it seems unlikely that the findings of little or no impairment in neuropsychological functioning in women with binge eating in the current study would be solely due to the test battery selected.

It also seems likely that some of the tests selected were not of sufficient difficulty as there appeared to be a ceiling effect on some tests. This problem has previously also been reported in studies of neuropsychological functioning in obesity (Fitzpatrick et al., 2013).

The neuropsychological test battery required the participant to focus on the testing for a reasonably prolonged period (average of 109 minutes). This could have led to fatigue, particularly on tests towards the end of the battery. However, as the tests were administered in the same order in both the eating disorder and control groups, participants were exposed to the same conditions so this should not have influenced the results when comparing neuropsychological functioning among the different groups.

The current study did not include tests of decision-making, or central coherence, two areas of executive function that have been found to be impaired in some studies of binge eating and should be included in future studies.

5.12 Future Research

Future research would benefit from recruitment of larger samples to give greater power to detect difference in studies investigating neuropsychological functioning in binge eating. It seems likely that more demanding tasks are required to explore relative differences in neuropsychological functioning in individuals with binge eating compared with healthy controls. Care should be taken to account for potential factors such as drug use and caffeine intake prior to testing as these factors have not commonly been accounted for in previous studies, yet are known to influence neuropsychological performance. Although these factors were found not to be a significant factor in the current study, this result does not preclude them from potentially influencing neuropsychological functioning in other

samples given the high rates of caffeine, alcohol and drug use in not only those with binge eating but also the general population.

Some areas of neuropsychological functioning have been under-researched including those focusing on learning and memory, and planning ability. It may be important to explore learning and memory tasks in the context of eating disorder salient stimuli such as food and body related stimuli as there is evidence of impairment in such tasks.

Binge eating disorder is under-researched compared with bulimia nervosa and more studies are necessary to understand neuropsychological functioning in those individuals with binge eating disorder. Most studies investigating neuropsychological functioning have not accounted for movement of individuals between different eating disorder diagnostic categories. A longitudinal approach to studying this would be challenging yet useful in understanding whether neuropsychological changes occur over the course of an eating disorder as an individual moves between diagnostic categories.

It may be that other factors such as nutritional status may be more important than diagnostic category. Nutritional status is well known to significantly impact on neuropsychological functioning as famously reported in the Minnesota Starvation Study (Keys et al., 1950). Within eating disorders there is some evidence that nutritional status may be a factor in neuropsychological function, for example, Laessle et al., (1990) found that intermittent starvation in people with bulimia nervosa negatively affected performance on tests of sustained attention. It is important to separate out BMI from nutritional status for example, weight gain did not always restore normal set-shifting performance in women with anorexia nervosa (Tchanturia et al., 2004). Potential biological mechanisms include the availability of glucose to fuel neuronal activity, but also the effects of poor nutrition on neuronal pathways that are dependent on the availability of certain vitamins and effects on

membrane fluidity (Gibson & Green, 2002). The impact of nutritional status in neuropsychological functioning in women with binge eating is an area yet to be fully explored.

5.13 Summary

Overall there were very few significant findings of neuropsychological impairment in the current study. This suggests that neuropsychological functioning as measured here is not significantly impaired in women with binge eating, and if relative impairments are present they are unlikely to have a major impact on overall functioning. Co-morbid depression and anxiety was not associated with neuropsychological functioning in women with binge eating. Furthermore, despite elevated levels of impulsivity on the Barratt Impulsiveness Scale, neuropsychological function was not associated with measures of impulsivity.

In eating disorders neuropsychological investigations are generally looking for relatively small and subtle impairments in neuropsychological functioning and this is particularly likely to be the case in the binge eating groups as they do not exhibit the more extreme starvation state of some of those with severe anorexia nervosa. Consequently the selection of neuropsychological tests is an important consideration when planning these studies. The appropriateness of the tests selected in the current study has already been discussed in section 5.11 above.

Although neuropsychological tests used in the current study may not have been of sufficient difficulty, the same tests have been used in other studies to detect neuropsychological problems in other mental health conditions including depression (Lee et al., 2015), schizophrenia (Patel et al., 2010; Pantelis et al., 2009) and obsessive compulsive disorder (Nedeljkovic et al., 2009) amongst others. The CANATBeclipse

neuropsychological battery has been found to be moderately correlated with other commonly used neuropsychological tests (Smith et al., 2013). Despite this, the CANTABeclipse neuropsychological battery may not be a suitable test battery for use with individuals with binge eating disorders, as the one published study with individuals with binge eating using the CANTABeclipse also did not find significant differences compared with a healthy control group (Galimberti et al., 2012).

Problems in the methodologies of some existing studies into neuropsychological functioning include small sample sizes resulting in statistically underpowered studies, varying methodologies including the reporting of different variables even on the same neuropsychological test batteries, and limited consideration of potential confounding factors. This makes it difficult to draw clear conclusions about the nature and magnitude of neuropsychological impairment in individuals with binge eating disorder and bulimia nervosa. Future research would benefit from ensuring samples sizes are sufficient to be able to detect differences. Areas warranting further research include executive function and verbal memory, with more studies investigating binge eating disorder in particular. The consideration of nutritional status and the potential mechanisms by which this factor could impact on neuropsychological performance should also be investigated further.

PART C

This section of the thesis examines the role of ghrelin in those with binge eating disorders. Chapter six will review current knowledge of ghrelin and present the research questions to be addressed. Chapter seven presents the methods for this section. The results are presented in Chapter eight and the key findings are discussed in Chapter nine.

6. LITERATURE REVIEW: GHRELIN

This chapter will describe the biochemistry of ghrelin, how ghrelin fits into body regulatory systems including the gut-brain axis of neurohormones that control appetite, feeding behaviour and energy homeostasis, and how ghrelin interacts with other hormones involved in appetite. Normal patterns of ghrelin secretion will be described. Research about ghrelin in eating disorders, the role of ghrelin in the reward system and the role of ghrelin in exercise and obesity will be reviewed. Finally, methodological issues that must be considered in ghrelin studies will be discussed.

6.1 *Ghrelin Structure and Function*

Ghrelin, was first described in 1999 (Kojima et al., 1999). The receptor for ghrelin, growth hormone secretagogue receptor (GHS-R), had been identified some years before (Guan et al. 1997), and so the existence of a hormone to activate the receptor had been predicted, as had the possibility that it played a role in growth hormone stimulation. It was therefore an important discovery when the ghrelin molecule was identified and found to be the first appetite hormone that promoted feeding behaviour (orexigenic) as all previously known appetite hormones were involved with pathways that suppressed feeding (anorexigenic). Ghrelin remains unique in that it is the only orexigenic hormone found to

date. Unsurprisingly ghrelin and its role in feeding behaviour and energy regulation has been of interest to eating disorder researchers.

Ghrelin is a 28-amino-acid peptide produced from preproghrelin, a 117 amino acid precursor. In mammals the majority of ghrelin production occurs in the X/A-like cells in the gastric oxyntic glands of the stomach (Alvarez-Castro, Pena, & Cordido, 2013) but smaller amounts are secreted by other areas of the body including intestines (Sakata et al., 2002), pituitary (Korbonits, et al., 2001), pancreas, kidney, lung, ovary and brain (Ueberberg et al., 2009). Ghrelin is present in two different molecular forms; acyl-ghrelin and des-acyl ghrelin. Acyl ghrelin is relatively unstable in this form and easily converts to des-acyl ghrelin (Rauh, Groschl, & Rascher, 2007). The half-life of acyl-ghrelin is around 10 minutes compared to 35 minutes for des-acyl ghrelin (Tong et al., 2013). In stomach tissues, acylated ghrelin makes up approximately a third of total ghrelin (Hosoda et al., 2000) whereas in circulation acyl ghrelin makes up between 10% and 25% (Ariyasu et al. 2001; Bang et al., 2007). It was initially thought that the acylated form was the most biologically active but there is increasing evidence that des-acyl-ghrelin is also biologically active across a number of different roles depending on where in the body it is active; as an agonist to acyl-ghrelin, in support of acyl-ghrelin, and actions independent from the acylated form (Delhanty, Neggers, & van der Lely, 2014; Pemberton & Richards, 2007).

Ghrelin is implicated in the modulation of a range of metabolic pathways in which cell growth is vital (Pradhan, Samson, & Sun, 2013) including bone growth (Delhanty, van der Eerden, & van Leeuwen, 2014), the reproductive system (Rak-Mardyla, 2013), cardiovascular function (van der Lely et al., 2004; Mao, Tokudome, & Kishimoto, 2014;

Nagaya et al., 2001) including repair of heart muscle after myocardial infarction (Frascarelli et al., 2003) and in the growth of tumour cells (Chopin et al., 2011).

The primary role of ghrelin has been found to be involved with energy homeostasis, appetite and body weight regulation across a number of vertebrates including mammals, birds (Kaiya et al., 2002) and amphibians (Kaiya, et al., 2001). Ghrelin is able to cross the blood-brain barrier (Asakawa et al., 2001; Banks, Burney, & Robinson, 2008) where it activates the site of the hypothalamic neuropeptide signalling pathway that is involved with feeding initiation, meal size and increasing body weight (Natalucci et al., 2005; Wren et al., 2001). Ghrelin receptors in the hypothalamus, specifically in the arcuate nucleus (ARC) and paraventricular nucleus (PVN), activate neurones which produce the orexigenic neuropeptide Y (NPY) and agouti-related protein (AgRP) and de-activate neurones involved in the production of the anorexigenic proopiomelanocortin (POMC) and cocaine-amphetamine-regulated transcript (CART). Ghrelin acts in opposition to the anorexigenic action of leptin, insulin and cholecystokinin (CKK).

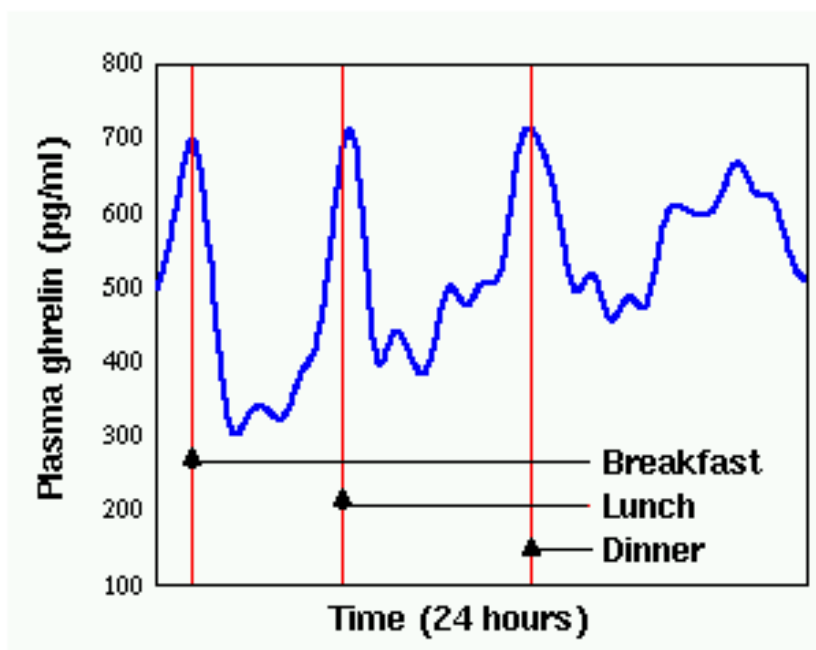
6.2 Normal Ghrelin Secretion Patterns

Ghrelin is not secreted evenly across the day but in a pulsatile manner. Ghrelin secretion peaks pre-prandially (before a meal) followed by reduced secretion after the ingestion of a meal. The timing of the peaks of ghrelin secretion appear to be related to the routine pattern of eating, for example sheep that are fed at regular times of the day show an increase in ghrelin before each meal time, but this increase is not seen when sheep have access to food ad libitum (Sugino et al., 2004). A study in rats also found the pattern of a ghrelin surge before an expected meal but not if there was an ad libitum feeding regime (Drazen et al., 2006). Ghrelin is secreted at higher levels in animals that are experiencing

conditions of food restriction compared with those that have sufficient food available (Carlini et al., 2008) apparently in an attempt to increase food ingestion.

In humans, ghrelin has also found to peak before eating and to decline afterwards (Callahan et al., 2004; Cummings et al., 2001; Drazen et al., 2006; Shiiya et al., 2002). The observed pattern of ghrelin secretion for people who eat three regular meals a day can be seen in Figure 6.1. It is not clear whether ghrelin increases sensations of hunger.

Increasing ghrelin levels have been associated with an increase in hunger ratings in some studies (Cummings et al., 2004); however, high ghrelin levels are not necessarily essential for hunger to be experienced (Di Francesco et al., 2006; Freka & Mattes, 2005; Frecka & Mattes, 2008) examined patterns of ghrelin secretion in 21 men and women who had a regular eating pattern and found the time of ghrelin peak was approximately 20 to 30 minutes before the regular time of lunch. Ghrelin fell post prandially (the period after a meal) with the nadir (lowest point) occurring between 40 and 60 minutes post breakfast and 60 to 85 minutes post lunch. Ghrelin showed a positive relationship with hunger and a negative relationship with ratings of fullness. Ghrelin secretion was likely to be entrained to regular eating patterns and peaked in anticipation of a meal rather than higher ghrelin triggering eating.



Adapted from Cummings et al., Diabetes 50:1714, 2001

Figure 6.1 The association between ghrelin secretion and meal ingestion over 24 hours

Higher ghrelin levels may increase the amount of food ingested during a meal. Wren et al., (2001) found that healthy individuals who had received an intravenous infusion of ghrelin consumed an average of 28% more while dining at a free-choice buffet than those who had not had a ghrelin infusion.

Ghrelin levels are known to rise when humans are placed on a restricted diet. Cummings et al., (2002) showed this clearly in a study of 13 obese participants, whose 24 hour pattern of ghrelin secretion was recorded before dieting and then again while dieting. In both the pre-dieting and dieting conditions the pre-prandial ghrelin peaks are clearly evident; however the area under the curve in the dieting condition is significantly higher. This indicates that the body resists conditions of food restriction by producing more ghrelin in an attempt to increase food ingestion back to pre-dieting levels. This finding aids understanding of the limited success of dieting for weight loss. In the second part of the study the same participants underwent gastric bypass procedures resulting in a significant

decrease in ghrelin secretion with little oscillation associated with meals suggesting that ghrelin suppression may be a factor in the success of weight loss after such surgery.

There appears to be no difference in ghrelin secretion between men and women (Bellone et al., 2003) or different ethnicities (Tschop et al., 2001). Patterns of ghrelin secretion change across the lifespan in accordance to energy needs. Ghrelin levels are higher in children than adults and do not show the same post-prandial fall (Misra et al., 2009). Ghrelin levels fall after puberty (Whatmore et al., 2003). Across adulthood ghrelin levels are fairly stable but are lower in older adults, reflecting reduced energy requirements in this group (Di Francesco et al., 2006). This pattern of higher ghrelin in children and lower levels in older adults seems to reflect the changes in need for nutrition to meet growth demands across the lifespan.

6.3 *Ghrelin and Insulin*

The association between ghrelin and insulin is complex. Ghrelin and insulin have been found to be negatively correlated in humans regardless of BMI or diabetic status (Tschop et al., 2001). An increase in acylated ghrelin has been found to reduce insulin secretion and increase insulin resistance (Barazzoni et al., 2007). Higher insulin levels as a result of increase in blood glucose seem to decrease ghrelin (Flanagan et al., 2003; Möhlig et al., 2002; Saad et al., 2002); however, it is thought that this is not a direct effect but is moderated through other mechanisms. The reduction of ghrelin in response to insulin has been found to be less in people with type 2 diabetes and this has been related to insulin resistance in this group (Anderwald et al., 2003). It appears that ghrelin moderates insulin secretion and vice versa due to some overlap in the signaling pathways involving the ghrelin receptor GHS-R (Chabot et al., 2014).

Insulin levels are typically low before a meal and rapidly rise on ingestion of food. It has been postulated that insulin may be involved in the post-prandial reduction of ghrelin; (Flanagan et al., 2003; Möhlig et al., 2002; Saad et al., 2002). Murdolo et al., (2003) investigated the association between ghrelin and insulin in humans by comparing healthy controls with a group of people with Type 1 diabetes who do not produce insulin in response to food. They found insulin was essential to trigger the post-prandial fall in ghrelin and suggested that the abnormal insulin response in the diabetes group could possibly explain hyperphagia in some individuals with uncontrolled type 1 diabetes. This result suggests that if the ghrelin system together with insulin may be involved in hyperphagia in diabetes, this could also be implicated in individuals who binge eat or are obese.

However, the mechanism by which ghrelin secretion is reduced post-prandially is contentious and may not depend entirely on insulin as the pulsatile pattern of ghrelin secretion across a day has also been found in conditions of fasting. In humans, despite no food intake to stimulate insulin, a fall in ghrelin was observed in accordance with the participant's regular meal time (Natalucci et al., 2005). Even sham feeding (where participants chew, smell and taste but do not swallow) has been found to decrease ghrelin secretion (Arosio et al., 2004). Both these studies indicate that ghrelin regulation is not solely determined by insulin and nutritional status measured in the gut, but suggest that the processes involving the brain are also likely to play a role in ghrelin secretion and the regulation of feeding behaviour.

6.4 *Ghrelin and Obesity*

Obesity is a significant factor in the development of a range of health problems including diabetes, cardiovascular disease and cancer (Haslam & James, 2005). It is also associated

with a number of metabolic conditions due to the role of body fat in many hormonal pathways (Ashburn & Reed, 2010; Kim, Cho, & Kim, 2014). As previously described, ghrelin plays a role in metabolic pathways involved in feeding and energy regulation. Therefore it is important to consider the association between obesity and ghrelin secretion.

It is well established that there is a negative association between obesity and ghrelin. Fasting ghrelin has been found to be lower in people who are obese (Blom et al., 2009; Shiiya et al., 2002; Tschop et al., 2001). The post-prandial fall is also less pronounced in this group (English et al., 2002). This suggests that the desire to eat following a meal may be impaired in individuals with very high weight, possibly due to reduced sensitivity to ghrelin. This pattern has also been found in rodents. Perreault et al. (2004) found ghrelin sensitivity was decreased in obese mice but that secretion levels returned to normal on weight loss. This suggests that the change in ghrelin secretion is related to increased weight, rather than causing weight gain because of altered secretion.

6.5 Ghrelin Secretion in Eating Disorders

A summary of research investigating ghrelin secretion in bulimia nervosa and binge eating disorder is presented in Table 6.1. Most studies have used only female participants, although three have included males, and either matched with controls for age and BMI or have corrected for any differences in age and BMI. All have used radioimmunoassays to measure total ghrelin after an overnight fast. Many have explored ghrelin secretion in response to either a standardised meal or glucose tolerance test.

Studies generally report altered fasting ghrelin secretion in individuals with bulimia nervosa but results are inconsistent as to how secretion is altered. Fasting ghrelin was found to be higher in women with bulimia nervosa than healthy controls in some studies

(Fassino et al., 2005; Kojima et al., 2005; Tanaka et al., 2003; Tanaka et al., 2006).

However, no difference in fasting ghrelin was found in a number of other studies (Devlin et al., 2012; Monteleone et al., 2003; Monteleone et al., 2005; Nedvidkova et al., 2011).

Troisi et al. (2005) is the only group to report that fasting ghrelin was lower in women with bulimia nervosa than controls. Fasting ghrelin is negatively correlated with both BMI and body fat in women with bulimia nervosa (Monteleone et al., 2003).

Area under the curve (AUC) measures the change in plasma ghrelin secretion over time and is often used to describe changes in secretion in response to a standardised meal or glucose drink. Devlin et al. (2012) used a liquid meal replacement to compare ghrelin secretion in 32 women with bulimia nervosa to that of 24 healthy control women. They found no difference in the pattern of secretion over time between women with BN and those with no eating disorder. This is in contrast to most other studies that have found the secretion of ghrelin in response to a standardised meal is reduced in women with bulimia nervosa even when BMI is taken into account (Kojima et al., 2005; Monteleone et al., 2005; Monteleone et al., 2003). This blunted response means that for women with binge eating, ghrelin reduces more slowly, and in some cases even rises before falling (Monteleone et al., 2003) and may not fall as much in women who do not binge eat.

Differences in ghrelin secretion in women who binge eating may be linked to eating disorder behaviours such as the frequency of bingeing and purging. Tanaka et al. (2003) found ghrelin had a positive correlation with the frequency of bingeing and purging in women with bulimia nervosa binge-purge and anorexia nervosa binge-purge subtypes. There is also some evidence that successful treatment results in a normalisation of ghrelin secretion in bulimia nervosa (Tanaka et al., 2006), possibly due to the restoration of more normal eating patterns. However, other groups have not found such an association

between binge/purge behaviours and ghrelin secretion (Monteleone et al., 2005; Troisi et al., 2005).

For women with binge eating disorder fasting ghrelin has consistently found to be lower than for healthy control groups (Geliebter, Hashim, & Gluck, 2008; Geliebter, Gluck, & Hashim, 2005; Geliebter et al., 2004) along with a blunted decrease in ghrelin secretion in response to a meal. This blunting effect is found even when comparing obese women with binge eating disorder to obese non-eating disordered women, which suggests that this change is not due to obesity alone. Munsch et al. (2009) is the only study of binge eating disorder which has not found this pattern of reduced fasting ghrelin and a blunted response to a test meal. As for individuals with bulimia nervosa, ghrelin secretion returns to normal levels fairly quickly after successful treatment (Geliebter et al., 2008).

Lower fasting ghrelin and a blunting of the post-prandial fall in individuals with binge eating may be a down regulation of the ghrelin system in an attempt by the body to reduce food intake. If this is the case, the presence of binge eating is in opposition to this and therefore requires an individual to over-ride the neurohormone signals to reduce energy intake. Alternatively feedback mechanisms including the ghrelin system could be impaired in this group but there is no evidence to support this.

In binge eating disorder there is no food energy deficit, although there may be periods of time (typically hours) without ingestion of food (for example in people with a pattern of fasting or restricted eating in the first part of the day who then consume the majority of the day's energy at the end of the day – often as part of a binge or objective over-eating episode) or individuals who are nutritionally deficient but not calorie deficient due to not eating a balanced diet.

Night eating syndrome has been the focus of one study (Allison et al., 2005). Ghrelin secretion was monitored over a 24 hour period in 15 women with night eating syndrome and 14 healthy controls. Women with night eating syndrome had lower total ghrelin in the early morning than the healthy control group which was attributed to suppression of ghrelin due to ingestion of food at night by the night eating syndrome group. As with binge eating disorder and bulimia nervosa it appears that the neuroendocrine profile is different in night eating syndrome and this is a result of eating patterns, not the cause of disordered eating. This finding is in contrast to a published case study of one woman with night eating syndrome who was treated with citalopram (Rosenhagen et al., 2005). Her ghrelin levels in the early morning were higher pre-treatment and during a relapse than they were during recovery. They concluded that higher ghrelin levels at this time may be promoting early morning eating in this woman.

Although anorexia nervosa is not a focus of the current study, an understanding of the patterns of ghrelin in this group is useful in understanding the role of ghrelin in binge eating. There is consensus among studies that circulating ghrelin is increased in anorexia nervosa (Tanaka et al., 2003; Troisi et al., 2005). The increase in ghrelin is likely to be influenced by not only by BMI, but also by both body composition and nutritional status, as women who are constitutionally thin have lower circulating ghrelin than BMI matched individuals with anorexia nervosa (Germain et al., 2007).

On weight restoration, ghrelin secretion reduces in women with anorexia nervosa (Nakahara et al., 2007; Tanaka et al., 2004). This suggests that any changes in ghrelin secretion in women with anorexia nervosa are at least in part due to the body attempting to improve nutritional status and fat composition rather than a malfunction of the ghrelin system.

Interestingly there is some support for the role of ghrelin administration as a component of treatment for anorexia nervosa to potentially increase appetite (Stoving, et al., 2009).

Human trials suggest it is safe to administer ghrelin with a low rate of side-effects reported (Alvarez-Castro et al., 2013).

To summarise, although not all studies are in agreement, it seems likely that changes in ghrelin secretion across eating disorders are related to the nutritional status of the individual. At one end of the spectrum, individuals with anorexia nervosa are in a nutritionally deprived state which leads to an increase in ghrelin secretion in an attempt to correct this. However while the eating disorder continues, these neurohormone signals are ignored and the individual engages in behaviours that are contrary to this signal such as food restriction and purging. At the other end of the spectrum are individuals with binge eating disorder, often with high weight, who engage in regular episodes of eating where a large number of kilojoules are ingested in the absence of purging behaviours. In this group fasting ghrelin levels are reduced and ghrelin secretion does not fall as quickly or to the same extent as in non-obese and non-bingeing people. Individuals are over-riding the neurohormone signals to reduce energy intake. This failure in ghrelin to drop quickly after eating may encourage continued consumption of food in this group.

The bulimia nervosa group falls somewhere in the middle and this may explain some of the conflicting results in this area. The bulimia nervosa group may or may not be overweight or obese and some studies have included participants diagnosed as having bulimia nervosa who are under a healthy BMI (less than 20), who may or may not purge by vomiting and who may or may not attempt to control their weight by other methods including exercise. They may or not be nutritionally compromised. However, despite these differences it seems that at least in individuals with bulimia nervosa of normal

weight there is a blunting of ghrelin secretion in response to a meal, possibly as a signal to reduce food intake, which as in binge eating disorder, is often ignored by the individual.

Table 6.1 Summary of studies investigating ghrelin secretion in binge eating

Study	Groups	Age	BMI	Sex	Method	Results	Fasting Ghrelin	Ghrelin AUC	Results Summary	Comments
Devlin et al. (2012)	32 BN 22 HC	24.0 26.1	22.4 22.8	F	Overnight fast, Ensure plus (600ml, 1.5kcal/g =6.3kJ), Blood samples - 20, -10, 0, 5,15, then 15 min intervals until 90 min.	mean (sd)	387.1 (185.1) 389.0 (205.3)	BNP = HC.	No differences in TG. No difference in rate of gastric emptying.	US. 75% Caucasian.
Fassino et al. (2005)	7 BN 9 HC	24.5 25.9	20.3 22.3	F	Overnight fast, IV administration of acyl-ghrelin (1.0µg/kg), blood samples at 15 min intervals up to 90 min.	mean (sd)	560.2 (97.2) 233.5 (87.5)		BN elevated TG at baseline. Response to AG no different from HC.	Italy
Kojima et al. (2005)	10 BNP 12 HC	24.7 24.8	20.0 20.2	F	Overnight fast, standardised breakfast (400kcal = 1674kJ). Blood samples at 0,30,60,120,180 min.	mean (sd)	265.0 (25.5) 199.3 (18.4)	BN < HC, p=0.04	BN fasting TG higher than HC. Lower ghrelin response post-prandially in BN than HC.	Japan
Monteleone et al. (2003)	9 BNP 12HC	24.2 24.5	21.7 21.5	F	Overnight fast, standardised breakfast 192 kcal = 803kJ ,standardised lunch 1217kcal = 5092kJ. Blood samples at 0,45,60,90,120,180 min.		Specific values not reported. BNP=HC	Specific values not reported. BN<HC	Fasting TG positive correlation with BMI and body fat%. Pre-prandial BN-P no different from HC. Post prandial TG blunted response in BN compared to HC.	Italy
Monteleone et al. (2005)	9 BNP 10HC	24.5 24.2	21.5 21.7	F	Overnight fast, standardised breakfast 840kJ, standardised lunch		Specific values not reported	Specific values not reported.	Pre-prandial BNP no different from HC;	Italy. Replication on previous

Study	Groups	Age	BMI	Sex	Method	Results	Fasting Ghrelin	Ghrelin AUC	Results Summary	Comments
					5460kJ, samples taken at times 0,45,60,90,120 and 180 min				"Blunted" response to food in BNP.	study published 2003.
Monteleone et al. (2005)	56 BN 13 BED 34 BEDO 28 HCO 51 HC	23.4 26.9 33.9 38.3 22.6 P<.001	21.9 25.8 39.8 38.1 21.7 p<.001	F	Overnight fast, fasting blood sample		Specific values not reported.	Specific values not reported.	BED, BEDO and HCO had lower TG than the normal weight HC and BN. TG negative correlation with BMI and % body fat. TG not correlated with binge or vomit frequency.	Italy. Separated obese and non-obese BED and HC into different groups
Nedvidkova et al. (2011)	7 BN 7 HC	24.3 25.8	20.6 20.0	F	Overnight fast, TG baseline, after exercise, after exercise + Aci,* 90 min post exercise, 90 min post exercise + Aci	mean (sd)	1099 (218) 1112 (273)	NA	No difference in fasting TG. Aci administration and exercise - BN < HC after 45 min exercise. Aci + exercise decreased ghrelin in both groups.	Czech Republic. Small sample, BMI low
Tanaka et al. (2003)	18 BNP 13 BNNP 21 ANR 10 ANBP 15 HC	22.7 22.7 21.8 24.6 22.1	20.0 21.2 13.9 14.4 21.4	F	Overnight fast, single blood sample	mean (sd)	286.9 (146.4) 121.2 (64.0) 256 (118.6)	NA	BN-P>BNNP, HC. ANBP>AN-R Frequency BP positive correlation	Japan

Study	Groups	Age	BMI	Sex	Method	Results	Fasting Ghrelin	Ghrelin AUC	Results Summary	Comments
							345 (151.4) 120.8 (20.4)		with TG in ANBP and BNP	
Tanaka et al. (2006)	24 BNP 25HC	23.6 23.1	18.5 21.4	F	Overnight fast, single blood sample	mean (sd)	301.7 (18.9) 150.3 (7.5)	NA	TG higher in BN than HC. After treatment TG levels fell in BN but not to the level of HC.	Japan. Very low BM., Regular binge/purge episodes after treatment (average 2x week).
Troisi et al. (2005)	15 AN 14 BN 22 BED 23 HC	26.7 29.2 38.0 25.6	16.0 26.1 33.0 21.2	F	Overnight fast, single blood sample, questionnaires: BULIT-R, EAT-26. Thyroid hormones T3, T4	mean (sd)	4624 (2182) 2357 (1133) 2405 (1453) 2897 (953)	NA	TG lower in women with binge-purge behaviours. No difference between BN-P and BN-NP. TG was correlated with lower BULIT scores. TG negative correlation with T3 and T4	Italy. Small sample sizes in groups. Self-report measures of ED behaviour. BN group made up of 6 BNP and 8 BNNP.
Rouach, et al. (2007)	8 BED 8 HCNW 8 HCO	49.7 32.6 50.2	36.7 21.2 35.2	16 F 8 M	Light breakfast, 2 hours later Trier Social Stress Test (TSST). Blood samples taken at -30, 0, 20, 40, 60 min.	mean (sd)	240 (40.8) 385.4 (79) 170.4 (15.7)		No change in ghrelin during stress test; however, when HC-NW grouped into cortisol responders	Israel. Limitations: stress test did not stress all participants.

Study	Groups	Age	BMI	Sex	Method	Results	Fasting Ghrelin	Ghrelin AUC	Results Summary	Comments
		HCNW < HCO, BED, p=0.03	HCNW < HCO, BED, p<0.001				HCNW > HCO, p=0.03 Baseline (not fasting)		and non-responders those at higher stress showed an increase in ghrelin. Suggested HPA axis involved. No correlation between urge to eat due to stress and ghrelin levels. Conclude that ghrelin levels reflect nutritional status rather than other factors such as stress.	Small sample. TG not fasting.
Munsch et al. (2009)	18 BEDO 20 HCO	50.2 48.6	32.4 34.3	14 F 4 M	Overnight fast, standardised breakfast (3337 kJ). Blood samples at -20, -5, 15, 30,45,60,90,120,180 min. Repeated after CBT treatment in BED group.		Specific values not reported. BED = HC	BED = HC	No differences between BED and controls. Treatment did not change ghrelin.	Switzerland. Larger breakfast than many other studies. Older age group, included 5 participants over 60 years.
Geliebter et al. (2008)	10 BED 9 HCO	29.9 30.3	36.5 35.8	F	Overnight fast, standardised liquid meal (1254kJ), samples taken at -15, 0,5,15,30,60,90,120 min.		Specific values not reported. BED<HC O, p=0.05	BED<HCO (trend, p=0.067)	Fasting ghrelin lower in BED, Blunted fall post-prandially, returns to normal levels after treatment.	USA

Study	Groups	Age	BMI	Sex	Method	Results	Fasting Ghrelin	Ghrelin AUC	Results Summary	Comments
					Compared pre-treatment to post-treatment in BED.					
Geliebter et al. (2005)	11 BED 14 BE 12 HCO	29.0 28.6 33.1 NS	36.6 35.9 35.3 NS	F	Overnight fast, standardised meal (1254kJ), samples taken - 15, 0,5,15,30,60,90,120 min.		Specific fasting values not reported. BED<HC	BED<HCO	BED lower baseline ghrelin compared to HC, lower AUC and smaller decline post meal. Sub threshold BED group intermediate but not significantly different from either BN or HC. No differences among groups for insulin or glucose. No differences in gastric emptying. After treatment baseline ghrelin increased as did AUC but not sig different from untreated group.	USA.to convert ghrelin from pg/ml to pmol/L multiply by 0.296. Conclude that BED down regulates ghrelin.
Geliebter et al. (2004)	11 BED 13 BE 13 HC	29 29 32	36.6 35.8 35.1	F	Overnight fast, liquid test meal (600ml, kJ not reported), blood samples at -15, 0,5,15,30,60,90 min.	mean (sd)	Specific fasting values not reported.	BED < HC p=0.03	Lower fasting ghrelin in BED, smaller decrease in ghrelin after meal. Measured	USA. Down regulation of ghrelin in BED due to over-eating.

Study	Groups	Age	BMI	Sex	Method	Results	Fasting Ghrelin	Ghrelin AUC	Results Summary	Comments
							BED < HC, p<0.05		gastric capacity with BED >HC.	
Allison et al. (2005)	15 NES 14 HC	40.8 38.6	36.1 38.7	F	3 day inpatient stay, food intake recorded, blood sampled on 3rd 2 hourly from 0800, then hourly from 2100-0900.	mean (sd)			NES Ghrelin lower in early morning hours than HC. Concluded lower ghrelin at night due to suppression due to ingestion of food. Neuroendocrine profile different in NES is a result of eating pattern not the cause.	USA, ethnicity approximately 50% Caucasian, 50% African-American.
Rosenhagen et al. (2005)	1 NES 3HC	27	23.5	F	Blood samples at 20 minute intervals overnight. 3 time points; before treatment, during treatment with citalopram, relapse, full remission			NA	Ghrelin levels were higher at pre-treatment and relapse compared to treatment and remission conditions. Suggested nocturnal ghrelin levels are elevated in NES.	Case study only
Schur et al. (2008)	24 HC	30.3	23.8	14 F 10 M	Overnight fast, single blood sample, Cognitive Restraint Scale, eating questionnaire. Grouped	mean (95% CI)	Low restraint scores had lower ghrelin	NA	Ghrelin negative correlation with BMI. Ghrelin had positive correlation with restraint scores.	USA

Study	Groups	Age	BMI	Sex	Method	Results	Fasting Ghrelin	Ghrelin AUC	Results Summary	Comments
					into tertiles based on restraint scores.		than higher restraint scores p=0.004		No differences between male and female.	
AN-R	Anorexia nervosa, restricting subtype					RIA	Radioimmunoassay			
AN-BP	Anorexia nervosa, binge/purge subtype					TG	Total Ghrelin			
BN-P	Bulimia nervosa purging subtype					AG	Acyl-ghrelin			
BN-NP	Bulimia nervosa non-purging subtype					INS	Insulin			
BED	Binge eating disorder					GLU	Glucose			
BED-HW	Binge eating disorder, normal weight					AUC	Area under the curve			
BED-O	Binge eating disorder, obese									
BE	Sub-clinical binge eating disorder					BULIT	Bulimia Test-Revised			
HC	Healthy control (no eating disorder)					TSSR	Trier Social Stress Test			
HC-NW	Healthy control, normal weight					HR	High restraint			
HCO	Healthy control, obese					MR	Medium restraint			
NES	Night eating syndrome					LR	Low restraint			

6.6 *Ghrelin and Food Reward*

Ghrelin may not only play a role in the gut-brain axis but may also have involvement in the hedonistic aspects of eating via dopaminergic action (Menzies et al., 2013). High levels of ghrelin receptors have been found in the ventral tegmental area (VTA) of the mesolimbic region of brain which is thought to be involved with mediating the reward properties of food (Schellekens, Dinan, & Cryan, 2013). Studies in mice have shown that direct injection of ghrelin into the VTA increases dopamine release (Jerlhag et al., 2007). In humans it has been shown that peripheral administration of ghrelin increases the activity as measured by f-MRI in the areas of the brain that are involved with reward in response to seeing pictures of food (Malik et al., 2008).

This increase in activity in the reward centres is relevant to binge eating as there is clearly a hedonistic aspect to bingeing for some individuals at least (Dalton, Blundell, & Finlayson, 2013; Murray et al., 2014). People with binge eating are more likely to have higher levels of other reward motivated behaviour such as alcohol consumption (Ferriter & Ray, 2011). This suggests shared neural pathways for binge eating and alcohol addiction (Leggio et al., 2011). Ghrelin may act as a reward amplifier, with highly palatable foods (Menzies et al., 2013), particularly foods high in sugar (Landgren et al., 2011).

6.7 *Ghrelin and Exercise*

Research on ghrelin and exercise is relatively recent and currently there is no clear association between ghrelin and exercise in healthy adults as findings differ depending on the type, intensity and duration of exercise (King et al., 2013).

A three month programme of diet and exercise in healthy women found that ghrelin increased relative to the control group; however this intervention induced a state of energy

deficit though diet restriction as well as exercise, so changes may be attributable to this rather than the exercise itself (Leidy et al., 2007).

There is some evidence that moderately intense exercise has the immediate effect of reducing ghrelin (Vestergaard et al., 2008), but this decline may be transitory with ghrelin levels returning to pre-exercise levels within 30 minutes (King et al., 2010; Schubert et al., 2014). Even low intensity exercise may reduce ghrelin secretion (Erdmann et al., 2007). However, other studies have not found a change in ghrelin secretion after intense exercise (Alajmi et al., 2016; Kraemer & Castracane, 2007).

In studies of longer term exercise programmes, results suggest that ghrelin secretion increases over a course of exercise; however, this is likely to be due to the resulting weight loss of the exercise regime rather than the exercise itself (Garcia et al., 2006; Leidy et al., 2007; Ravussin et al., 2001).

Exercise can be a component of bulimia nervosa and binge eating disorder as a method of weight suppression (Cook et al., 2015), and excessive exercise can be a purging method in bulimia nervosa (Stiles-Shields, Lock, & Le Grange, 2015). Therefore exercise could influence ghrelin secretion in both bulimia nervosa and binge eating disorder. To date there has been only one study that has specifically looked at the relationship between ghrelin and exercise in women with binge eating (Nedavidkova et al., 2011). Ghrelin levels decreased after exercise in women with bulimia nervosa but not in healthy controls. This decrease was considered most likely to be a reflection of poor nutritional status in bulimia nervosa rather than due to short term energy deficit due to exercise.

6.8 *Problems with Previous Research*

The ghrelin literature is a relatively recent, but fast moving area of research and as such there have been a number of studies publishing conflicting results. To help understand the possible reasons behind this, it is important to consider the methodologies when interpreting these studies as a number of different methodologies have been used. Such considerations include differences in ghrelin assays, participants, and methods of manipulating ghrelin to investigate its influences on different systems in the body.

The form of ghrelin that is measured is one such important consideration. Earlier studies did not differentiate between acyl and des-acyl forms of ghrelin and tend to report their findings as “total ghrelin”, “peripheral ghrelin” or “circulating ghrelin”; all different terms for the same thing. In studies that report only “ghrelin” it must be assumed that this is total ghrelin unless stated otherwise. In the current study the term “total ghrelin” will be used to refer to the total amount of ghrelin, inclusive of all forms, circulating in the blood. The growing recognition that different forms of ghrelin may have different functions together with development of ghrelin assay technology has resulted in the reporting of acyl and des-acyl forms, often along with total ghrelin, to give a more complete picture of how ghrelin acts in the body.

Human studies are of most relevance when considering the *in vivo* actions of ghrelin that are relevant to the topic of this thesis; women who binge eat. Methods used to explore patterns of ghrelin secretion in humans include monitoring ghrelin levels over a 24-hour period to describe the diurnal patterns, measuring ghrelin levels in response to fasting, test meals of known energy composition, oral glucose tolerance tests, and presenting meals of differing fat or carbohydrate compositions. Most studies control or match for age, gender and BMI.

6.9 *Summary of Literature and Research Questions:*

Ghrelin is the only orexigenic hormone found to date and has been shown to play a role in energy homeostasis. Some studies have found differences in ghrelin secretion in individuals with binge eating. It is unlikely that ghrelin is a contributor to the development of eating disorders whether restrictive, purging or bingeing in nature. Rather, it is likely that the disruption or alteration of the ghrelin system is likely as a result of these behaviours. In bulimia nervosa and binge eating disorder, the disruption in regular eating patterns changes the normal feeding regulation pathways which manage the initiation of eating, sensations of hunger, and body weight and composition. It appears that ghrelin may be down-regulated which may have implications for the many other systems of the body that it is involved in. These changes may also have implications for the maintenance and recovery from disorders of binge eating.

It is useful, therefore, to explore the changes in ghrelin in individuals with binge eating to further understand the associations between ghrelin and eating disorder behaviours, neurocognitive functioning, anxiety, depression, and addictive behaviours. In the next section of this thesis patterns of ghrelin secretion in women with bulimia nervosa and binge eating disorder will be compared with women who do not binge eat. The potential relationships between ghrelin and eating disorder behaviours will be explored.

The following questions will be addressed:

1. Are there differences in ghrelin secretion among women with binge eating and women who do not binge eat?
2. What are the associations between ghrelin and insulin in women with binge eating?

3. Is eating disorder pathology associated with ghrelin secretion in women with binge eating?

7. METHODS: GHRELIN

A description of the methodology of the overall study has already been given in Section 3. Methods for collection of age, ethnicity, BMI and percent body fat have previously been described in sections 3.5 and 3.6. The following section describes methodology specific to the neurohormone section of the current study.

7.1 *Biological Procedure*

All participants were required to fast overnight. The biological assessment was carried out by the research nurse. On arrival at the Clinical Research Unit they were measured for height and weight and BMI was calculated. An indwelling intravenous catheter was inserted and the participant was rested for 45 minutes before baseline bloods were taken at -15 and 0 minutes. An oral glucose load (75g glucose in 300mls, 1330kj) was given with blood samples taken at 15, 30, 45, 60, 120 and 150 minutes. Blood samples for hormones (total ghrelin, C-ghrelin and insulin) were centrifuged and frozen for later analysis. Glucose was measured at the same time points using finger prick testing kits.

At least some portion of the biological assessment was carried out in 144 study participants. However, of these, 26 participants were excluded from biological analysis: 16 participants were not able to sustain cannulation for obtaining blood samples, samples from 10 participants were lost due to the 2011 Canterbury earthquakes affecting freezer storage of samples, and two participants were excluded as they had fasting insulin levels more than two standard deviations from the mean suggesting either undiagnosed diabetes or failure to comply with fasting instructions.

7.2 Description of Neurohormone Variables

Ghrelin was assayed as total plasma ghrelin (including both acylated and des-acylated forms) and C-ghrelin measured in an assay for the C-terminus of the ghrelin molecule which is present in the acylated form of ghrelin and therefore is a measure of acylated ghrelin. A ratio of C-ghrelin to total ghrelin was calculated to allow investigation of possible changes in each form of ghrelin relative to the other. The higher the ratio, the more acylated ghrelin is present relative to total ghrelin. Not all participants have results for C-ghrelin as this assay was not carried out on the first 26 participants.

Fasting total ghrelin, C-ghrelin, insulin and glucose were measured at two time points (-15 minutes and 0 minutes) before oral glucose was given. Hormone and glucose levels at these time points were averaged to give a measure of mean fasting levels.

Area under the curve (AUC) was calculated for total ghrelin, C-ghrelin, insulin and glucose using the trapezoid method (Pruessner et al., 2003). Where there were up to two missing time points for any one participant these were estimated by averaging the time points either side, and adjusting proportionally for timing of the sample. If participants had more than one missing time point that could not be estimated their data were excluded from AUC analysis. Where missing data points were potentially the nadir (ghrelin and C-ghrelin) or peak (insulin and glucose) estimations were not calculated and so were not used to calculate nadir or peak levels or time to nadir or peak.

Homeostatic Model Assessment known as HOMA-IR is a commonly used index of insulin resistance (Wallace, Levy, & Matthews, 2004). HOMA-IR was calculated using the following equation:

$$\text{HOMA-IR} = [\text{glucose (mmol/L)} \times \text{insulin (pmol/L)}] / 135$$

The higher the HOMA-IR value the greater the insulin resistance. After an oral glucose tolerance test normal levels are below 3.82.

7.3 Description of Demographic and Psychological Variables

The number of binge-eating and vomiting episodes for the past month were obtained from the number of binges or vomits reported by each participant as part of the semi structured Eating Disorder Examination (EDE). EDI subscales Bulimia, Impulsivity and Perfectionism have also been used for this section of the study.

7.4 Statistical Analysis

Participants were grouped according to diagnosis (bulimia nervosa, binge eating disorder and healthy controls). The bulimia nervosa group was further divided into purging (BN-BP) and non-purging (BN-NP). This division was deemed to be meaningful as purging behaviour potentially has an influence on ghrelin secretion. The number of participants in each group for these analyses differs from analyses of neuropsychological data reported in Part B as not all participants were able to complete the biological assessment, usually due to difficulties with cannulation.

All analyses were performed using IBM SPSS Statistics version 23. Descriptive statistics were used to report sample characteristics. The associations of ghrelin, insulin and glucose levels and age, BMI, and body composition were explored using Pearson's product-moment correlations to identify possible confounders of ghrelin secretion patterns.

Differences in hormone secretion and glucose among diagnostic groups were investigated using ANOVA. Associations between psychopathology and ghrelin secretion were analysed using Pearson product-moment correlations for normally distributed variables, and Spearman's rho correlations were used for variables that were not normally

distributed. Results are reported as means and standard deviation or standard errors for continuous variables. Means and confidence intervals are reported in tables where at least one variable had been log transformed. Number and percentage are reported for categorical variables. Post hoc analyses were carried out using LSD analysis. All statistical tests were 2-tailed and level of significance was set as $p < 0.05$.

8. RESULTS: GHRELIN

8.1 *Description of the Total Sample*

Demographic variables and total ghrelin, C-ghrelin, insulin and glucose for the total sample are described in Table 8.1.

Table 8.1 Demographic and biological characteristics of the total sample.

	Number	Mean	sd
Age (years)	144	33.7	12.3
BMI	144	28.5	6.9
% Body fat	117	37.0	10.2
Fasting total ghrelin (pmol/L)	144	239	108
Fasting C-ghrelin (pmol/L)	100	90	49
Fasting insulin (pmol/L)	114	51	47
Fasting glucose (mmol/L)	134	5.6	1.1
Total ghrelin nadir (pmol/L)	116	145	57
C-ghrelin nadir (pmol/L)	83	50	28
Insulin peak (pmol/L)	92	554	558
Glucose peak (mmol/L)	129	10.6	2.9
Total ghrelin time to nadir (min)	116	96	39
C-ghrelin time to nadir (min)	83	89	34
Insulin time to peak (min)	92	68	31
Glucose time to peak (min)	129	59	29
Total ghrelin % change	116	-31	19
C-ghrelin % change	83	-42	12
Insulin % change	92	2173	7191
Glucose % change	129	92	53

% change is the difference at 120 min post glucose load compared to pre glucose load

Normality of distribution for all variables was examined. All were either normally distributed or approximated normal distributions with the exception of insulin variables which were strongly right skewed. Therefore natural log ($\log_e$) transformations were calculated for all insulin variables before statistical analyses were performed. Statistics

presented in subsequent tables are based on these analyses with back-transformed ($\exp(x)$) means and 95% Confidence Intervals (95% CI) reported to allow clinical interpretation.

As age, BMI and % body fat are potential confounding factors for biological variables, Pearson product-moment correlations were calculated between these variables and all fasting biological measures (total ghrelin, C-ghrelin, insulin and glucose). No significant association was found between age and total fasting ghrelin ($r = 0.08$, $n = 144$, $p = 0.36$), C-ghrelin ($r = 0.04$, $n = 100$, $p = 0.68$), or $\log_e$ insulin ($r = -0.10$, $n = 114$, $p = 0.31$). A small positive correlation was found for age with glucose ($r = 0.27$, $n = 134$, $p = 0.002$).

For BMI, moderate negative correlations were found with total ghrelin ($r = -0.37$, $n = 144$, $p < 0.001$), and C-ghrelin ($r = -0.42$, $n = 100$, $p < 0.001$). Positive correlations with BMI were found for $\log_e$ insulin ($r = 0.58$, $n = 114$, $p < 0.001$), and glucose ($r = 0.40$, $n = 134$, $p < 0.001$).

Percent body fat was also negatively associated with both fasting ghrelin ($r = -0.45$, $n = 117$, $p < 0.001$), and C-ghrelin ($r = -0.50$, $n = 87$, $p < 0.001$), and positively associated with $\log_e$ insulin ($r = 0.55$, $n = 88$, $p < 0.001$) and glucose ($r = 0.43$, $n = 108$, $p < 0.001$).

Across the total sample Body Mass Index and % body fat were very highly correlated ($r = 0.94$, $n = 117$, $p < 0.001$).

Pearson product-moment correlations were calculated to measure associations between fasting total ghrelin, C-ghrelin, insulin and glucose and are presented in Table 8.2 .

Fasting total ghrelin and C-ghrelin were highly correlated ($r = 0.69$, $n = 100$, $p < 0.001$).

$\log_e$ insulin was negatively associated with both total ghrelin and C-ghrelin. Glucose did not show any association with total ghrelin, C-ghrelin or insulin.

Table 8.2 Associations between total ghrelin, C-ghrelin, log_e insulin and glucose

	Total ghrelin	C-ghrelin	Insulin (Log_e)
C-ghrelin	0.69***		
Insulin	-0.35***	-0.48***	
Glucose	0.08	-0.12	0.24

Values reported are Pearson coefficient (r),

*** = $p < 0.001$ (two tailed).

A ratio of C-ghrelin to total ghrelin was calculated for the total sample and for the AUC as a measure of ghrelin secretion response to energy ingestion (glucose). The mean ratio for the total sample at baseline was 0.39, (SD = 0.17, $n = 83$). The ratio for the AUC was 0.46 (SD = 0.21, $n = 83$). A paired samples t-test found that the ratio at baseline was significantly lower than the ratio for the AUC ($t = 7.04$, $df = 82$, $P < 0.001$). This indicates that total ghrelin falls faster than C-ghrelin in response to ingestion of glucose.

8.2 Metabolic Disorders

Five of the total sample had been diagnosed with type 2 diabetes, of which three were taking the diabetes medication, metformin. None were insulin dependent. Of those with type 2 diabetes, two were from the BED group, two from BN-NP and one from BN-BP. None of the HC group had diabetes or took metformin. The mean age of those with type 2 diabetes or insulin resistance was 45.8 years and the mean BMI was 38.0.

A further five participants reported a diagnosis of polycystic ovary syndrome of which three were from the BED group and two from the BN-NP group. One of the BED participants with diabetes also reported a diagnosis of polycystic ovary syndrome. Two participants with polycystic ovary syndrome, both from the BED group, were taking metformin for this condition. None of the HC group reported a history of polycystic ovary syndrome. Of those with polycystic ovary syndrome, the mean age was 27 years and mean BMI was 33.6.

Five participants reported hypothyroidism (four from the BED and one from the HC group). All those with BED were taking thyroxine whereas the HC participant was not medicated. One participant from the BN-BP group reported hyperthyroidism but did not report being on any medication. Of those with hypothyroidism, the mean age was 38 and mean BMI was 24.5. None of those with hypothyroidism also had diabetes or insulin resistance. Thyroid stimulating hormone (TSH) was measured at baseline. Levels suggestive of hypothyroidism were found in three participants (2.1%), one from the BN-NP group and two from the BED group. One of these women had diagnosed hypothyroidism and was taking thyroxine whereas the remaining two did not report hypothyroidism and were not taking thyroid medication. A further three participants had TSH levels suggestive of hyperthyroidism. One of these women had a diagnosis of hyperthyroidism but did not report taking medication. The remaining two women did not report any medical diagnoses and were not taking any medication.

8.3 Age, BMI and Body Composition by Diagnostic Group

Results of a comparison of age, BMI and % body fat by diagnostic group are found in Table 8.3. Participants in the BED group were older and had higher BMIs than all other groups. There were no differences among the other three groups in age or BMI. Those in the BED group had a higher percentage body fat than all other groups. Of participants with BN, those who purged had lower body fat than those who did not purge.

As BMI and percentage body fat were significantly different among the groups, allowance for this was made in subsequent analyses. As reported in section 7.1 above, BMI and percentage body fat were highly correlated across the sample. BMI was chosen as a co-variate rather than percent body fat as BMI was available for the complete sample whereas percentage body fat was not available for 19 of the 46 healthy control group. Although

age was significantly correlated with glucose, as the groups did not differ with respect to age, it was not used as a co-variate in subsequent analyses.

Table 8.3 Results of ANOVA comparing age, BMI and body composition among women with bulimia nervosa, binge eating disorder and healthy controls.

	BN-BP <i>n</i> = 26 mean (sd)	BN-NP <i>n</i> = 25 mean (sd)	BED <i>n</i> = 47 Mean (sd)	HC <i>n</i> = 46 mean (sd)	F (df)	p	d	Post Hoc (LSD)
Age (years)	30.2 (12.8)	34.64 (11.3)	38.00 (13.0)	30.89 (10.6)	3.70 (3,140)	<0.05	0.66 0.67	BED>BN-BP BED>HC
BMI	25.1 (6.7)	27.4 (6.3)	33.0 (6.8)	26.4 (5.0)	13.07 (3,140)	<0.001	1.17 0.85 1.11	BED>BN-BP BED>BN-BP BED>HC
% Body fat	30.1 (10.6)	36.6 (8.6)	43.0 (8.0)	33.4 (8.8)*	13.70 (3,115)	<0.001	1.37 0.77 1.14 0.67	BED>BN-B BED>BN-NP BED>HC BN-NP>BN-BP

* % Body fat measured in only 19/46 HC

BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype;
BED = binge eating disorder; HC = healthy controls.

8.4 Fasting Ghrelin, Insulin and Glucose by Diagnostic Group

Comparisons of mean fasting total ghrelin, C-ghrelin, log_e insulin and glucose by

diagnostic group are found in Table 8.4. Those in the BED group had lower total ghrelin than those in the BN-BP and HC groups, but were not different from the BN-NP group.

There was no difference in C-ghrelin among the groups. Fasting insulin was significantly higher in the BED when compared with all other groups. Fasting glucose was higher in the HC group than in all other groups.

Table 8.4 Mean fasting total ghrelin, C-ghrelin, insulin* and glucose by diagnostic group.

	BN-BP <i>n</i> = 26 mean (95%CI)	BN-NP <i>n</i> = 25 mean (95%CI)	BED <i>n</i> = 47 mean (95%CI)	HC <i>n</i> = 46 mean (95%CI)	F (df)	p	d	Post Hoc (LSD)
Total ghrelin (pmol/L)	255 (205-305)	233 (192-275)	198 (172-224)	273 (241-305)	4.24 (3,140)	.01	0.52 0.76	BED<BN-BP BED<HC
C-ghrelin (pmol/L)	113 (91-136)	88 (62-113)	80 (63-96)	92 (75-110)	1.93 (3, 96)	.13		
C-ghrelin/total ghrelin	0.49 (0.36-0.61)	0.39 (0.33-0.46)	0.43 (0.32-0.53)	0.34 (0.32-0.37)	1.45 (3,96)	0.23		
Insulin (pmol/L)	23 (14-37)	27 (16-44)	48 (34-68)	39 (31-50)	3.40 (3,110)	.02	0.69 0.66 0.49	BED> BN-BP BED>BN-NP BED>HC
Glucose (mmol/L)	5.2 (4.8-5.6)	5.3 (4.9-5.7)	5.6 (5.3-5.8)	5.9 (5.5-6.4)	2.70 (3,130)	.05	0.61 0.53	BN-BP <HC BN-NP<HC

* All analyses of insulin were performed on log_e transformed variables. Insulin variables reported in this table have been back transformed (exp(x)).

BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls.

significant difference among the groups for fasting total ghrelin or C-ghrelin. There was no difference among the groups for the C-ghrelin/total ghrelin ratio. Fasting log_e insulin was significantly different among the groups with post hoc analysis indicating that the HC group had higher fasting insulin than the BN-NP group. The HC group also had higher fasting glucose than the BN-NP group. Insulin was significantly correlated with BMI across the total sample (Pearson product moment correlation, $r = 0.55$, $p < 0.001$, $n = 144$).

HOMA-IR is an index of insulin resistance. The majority of the total sample was in the normal range (HOMA-IR < 3.85); however 15.2% of the sample were above the cut off for insulin resistance. HOMA-IR distribution had a strong right skew and a log_e transformation was performed to achieve a normal distribution.

Table 8.5 Fasting ghrelin, C-ghrelin, insulin and glucose with BMI as co-variate by diagnostic group.

	BN-BP <i>n</i> = 26 mean (95%CI)	BN-NP <i>n</i> = 25 mean (95%CI)	BED <i>n</i> = 47 mean (95%CI)	HC <i>n</i> = 46 mean (95%CI)	Statistic F (df)	p	Post Hoc (LSD)
Total	236	227	222	261	1.21	0.31	
ghrelin (pmol/L)	(197-276)	(188-267)	(191-253)	(232-290)	(4,139)		
C-ghrelin (pmol/L)	104 (82-127)	85 (62-107)	88 (73-102)	88 (70-104)	0.69 (4,95)	0.56	
C-ghrelin/ total ghrelin	0.47 (0.35-0.60)	0.39 (0.26-0.51)	0.44 (0.36-0.52)	0.33 (0.24-0.42)	1.60 (3,95)	0.19	
Insulin* (pmol/L)	29 (21-41)	26 (19-37)	34 (25-47)	43 (35-55)	2.66 (4,111)	0.05	
Glucose (mmol/L)	5.4 (4.9-5.8)	5.4 (5.0-5.8)	5.3 (5.0-5.7)	6.0 (5.7-6.4)	3.83 (4,129)	0.01	BN-BP, BED, BN- NP<HC

ANCOVA reporting adjusted mean and 95% CI. F value for group interaction after adjusting for BMI. d = Cohen's d;

* Analyses of insulin were performed on log_e transformed variables. Insulin variables reported in this table have been back transformed (exp(x)).

BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls.

There was a significant difference in log_e HOMA-IR among the groups ($F=3.58$ (3,101), $P=0.017$). Women with BED had significantly higher HOMA-IR than women in the BN-BP (LSD, $p=0.007$) and BN-NP (LSD, $p=0.04$) groups but was not different from the HC group. The BN-BP group had lower HOMA-IR scores than the HC group (LSD, $p=0.014$).

HOMA-IR was significantly associated with BMI across the total sample ($r=0.56$, $p<0.001$, $n=105$). Comparison of the four groups with BMI as a co-variate revealed significant differences remained among the diagnostic groups ($F=0.65$, $df = (3,100)$, $p=0.015$). Post hoc comparisons showed that the BN-BP ($p=0.015$) and BN-NP ($p=0.007$) groups had significantly lower insulin resistance than the HC group but were not significantly different from the BED group.

Over the total sample HOMA-IR had a small to moderate negative correlation with fasting total ghrelin ($r=-0.29$, $p=0.002$, $n=105$) and with fasting C-ghrelin ($r=-0.43$, $p<0.001$, $n=71$).

8.5 Response to Oral Glucose Challenge by Diagnostic Group

Change in levels of total ghrelin over time in response to an oral glucose challenge can be seen in Figure 8.1. All three eating disorder groups had lower levels of total ghrelin secretion compared with the HC group as shown by the AUC and nadir. There were no differences among the groups in the time to reach nadir or the percentage fall from baseline as reported in Table 8.6.

The pattern of C-ghrelin secretion after the oral glucose challenge is shown in Figure 8.2. C-ghrelin secretion falls in all groups with no significant differences in AUC, nadir, time to nadir and the percentage fall from baseline (Table 8.7).

Insulin levels rise rapidly in response to the oral glucose in all four groups as shown in Figure 8.3. The AUC is significantly different among the four groups with post hoc analyses showing the BED group had a larger AUC than those in the BN-BP group. There were no differences among the groups for peak insulin, time to the peak or percentage rise from baseline as reported in Table 8.8.

Change in glucose in response to the oral glucose challenge is shown in Figure 8.4. There were no differences among the groups for AUC, peak glucose, time to reach peak glucose or the percent increase from baseline Table 8.9.

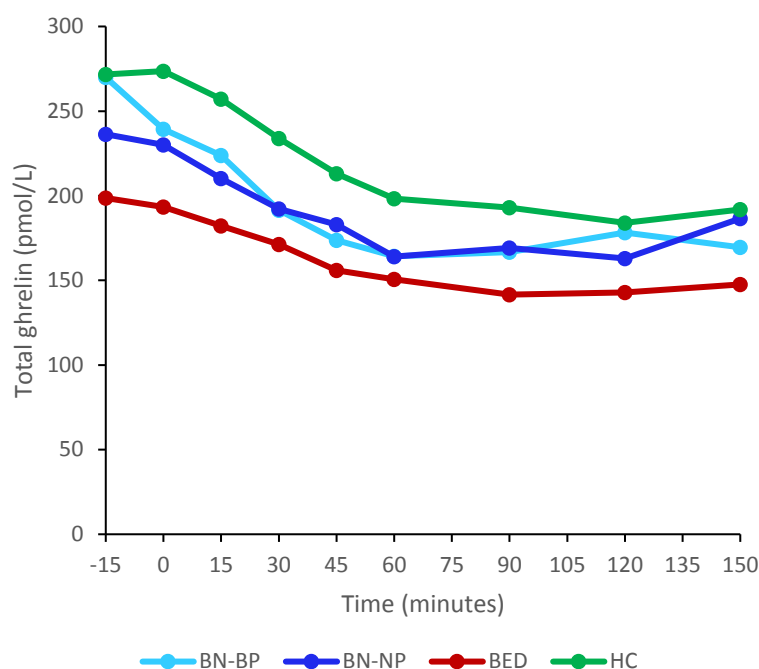


Figure 8.1 Change in total ghrelin in response to an oral glucose challenge by diagnostic group

Table 8.6 Change in total ghrelin (pmol/L) in response to an oral glucose challenge by diagnostic group

	BN-BP <i>n</i> = 18 mean (95%CI)	BN-NP <i>n</i> = 18 mean (95%CI)	BED <i>n</i> = 42 mean (95%CI)	HC <i>n</i> = 37 mean (95%CI)	F (df)	p	d	Post Hoc (LSD)
AUC	25299 (22715-27882)	26454 (22315-30592)	23391 (20565-26217)	30404 (27006-33802)	4.21 (3,111)	.007	.63 .31	BN-BP<HC BED< HC
Nadir	133 (116-150)	141 (116-166)	127 (109-144)	175 (155-194)	5.59 (3,112)	.001	.86 .61 .84	BN-BP<HC BN-NP<HC BED<HC
Time to nadir (minutes)	85.8 (63.7-108.0)	90.8 (72.5-109.1)	97.1 (85.5-108.8)	100.9 (87.8-114.1)	0.72 (3,112)	.55		
% Change from baseline	23.7 (12.0-35.5)	30.8 (16.0-45.7)	34.2 (29.5-39.0)	31.3 (28.0-34.5)	1.31 (3,112)	.27		

d = Cohen's d; BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

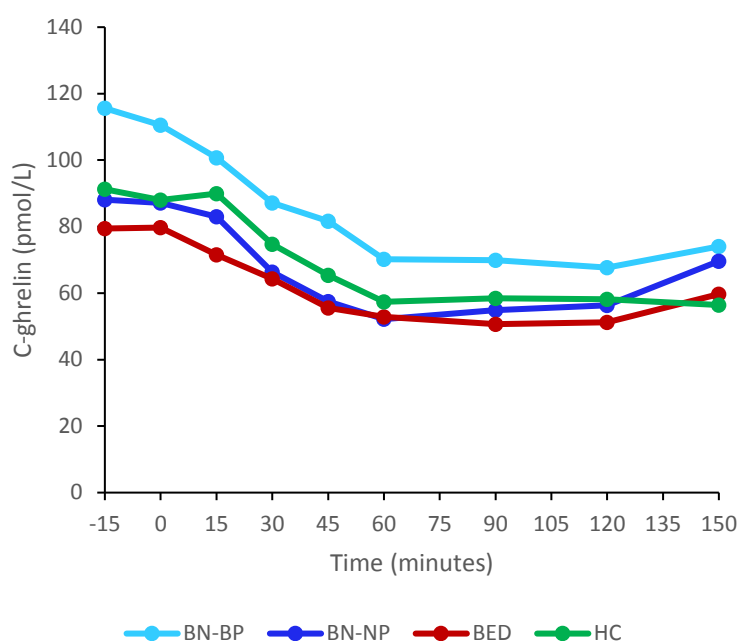


Figure 8.2 Change in C-ghrelin in response to an oral glucose challenge by diagnostic group

Table 8.7 Change in C-ghrelin (pmol/L) in response to an oral glucose challenge by diagnostic group

	BN-BP <i>n</i> = 11 mean (95%CI)	BN-NP <i>n</i> = 12 mean (95%CI)	BED <i>n</i> = 38 mean (95%CI)	HC <i>n</i> = 23 mean (95%CI)	F (df)	p
AUC	15421 (11290-19553)	12100 (8599-15601)	11108 (8592-13625)	12057 (10017-14094)	1.26 (3,80)	.30
Nadir	61 (44-79)	46 (31-62)	45 (35-56)	53 (43-63)	1.04 (3,79)	.38
Time to nadir (min)	102 (78-126)	74 (55-92)	91 (81-101)	88 (72-104)	1.39 (3,79)	.25
% fall from baseline	45 (40-50)	41 (29-53)	43 (39-47)	41 (37-45)	0.37 (3,79)	.77

BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

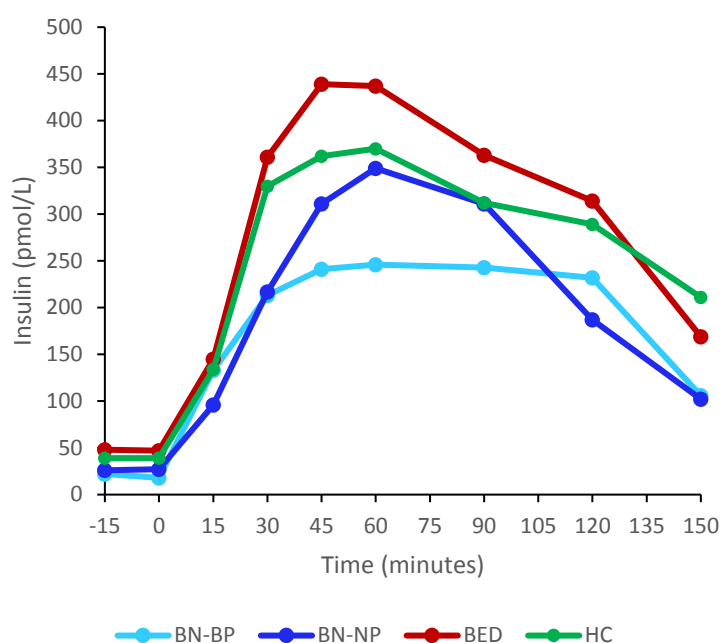


Figure 8.3 Change in insulin in response to an oral glucose challenge by diagnostic group

Table 8.8 Change in insulin* (pmol/L) in response to an oral glucose challenge by diagnostic group

	BN-BP <i>n</i> = 14 mean (95%CI)	BN-NP <i>n</i> = 15 mean (95%CI)	BED <i>n</i> = 25 mean (95%CI)	HC <i>n</i> = 39 mean (95%CI)	F (df)	p	d	Post Hoc (LSD)
AUC	33134 (25103-43734)	36634 (28053-47840)	51398 (36976-71444)	44678 (38701-51578)	3.30 (3,89)	.04	.76	BN-BP < BED
Peak	351 (265-465)	399 (284-561)	534 (382-747)	438 (377-509)	1.66 (3,88)	.18		
Time to peak (min)	56 (42-75)	67 (54-82)	60 (50-71)	61 (52-73)	0.35 (3,88)	.79		
% increase from baseline	1450 (789-2666)	1210 (590-2484)	977 (737-1295)	960 (740-1246)	0.88 (3,88)	.46		

* Analysis of insulin was performed on $\log_e$ transformed variables. Insulin values reported in this table have been back transformed ($\exp(x)$) to allow clinical interpretation. *d* = Cohen's *d*; BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

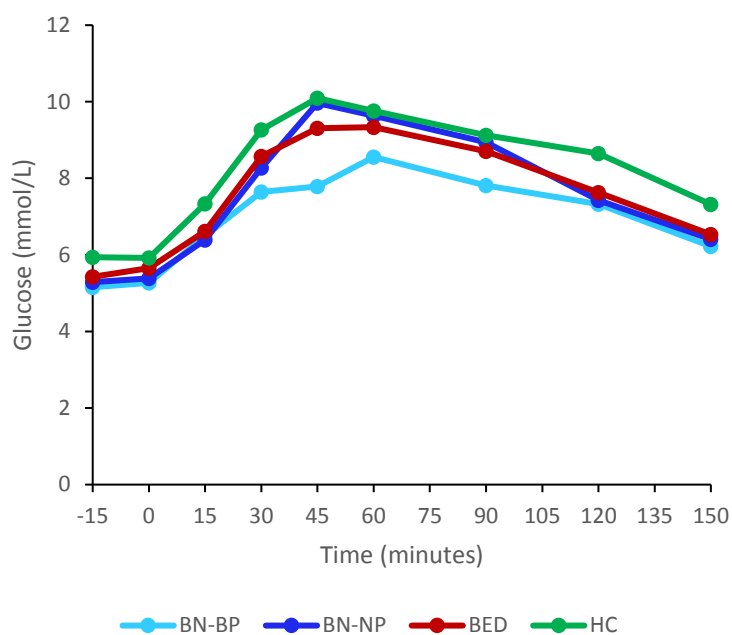


Figure 8.4 Change in glucose in response to an oral glucose challenge by diagnostic group

Table 8.9 Change in glucose in response to an oral glucose challenge

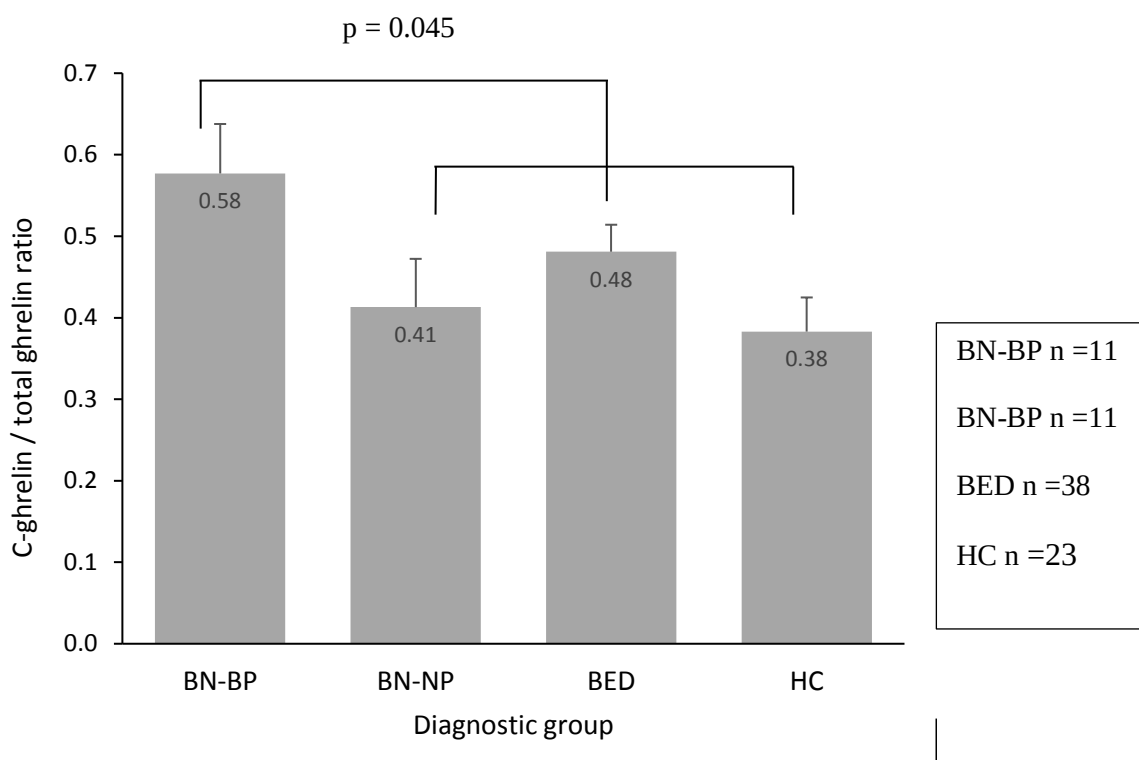
	BN-BP <i>n</i> = 20 mean (95%CI)	BN-NP <i>n</i> = 24 mean (95%CI)	BED <i>n</i> = 42 mean (95%CI)	HC <i>n</i> = 43 mean (95%CI)	F (df)	p
AUC (pmol/L.min)	1096 (956-1237)	1203 (1077-1329)	1195 (1097-1294)	1306 (1202-1409)	2.14 (3,121)	.10
Peak (pmol/L)	9.6 (8.3-11.0)	11.1 (10.0-12.3)	10.2 (9.4-11.1)	11.2 (10.3-12.2)	1.93 (3,125)	.13
Time to peak (min)	59 (46-73)	65 (52-78)	57 (48-65)	59 (49-68)	0.40 (3,125)	.75
% Increase from baseline	88 (60-117)	109 (91-128)	84 (66-102)	93 (78-107)	1.21 (3,125)	.31

BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

Comparisons of total ghrelin and C-ghrelin secretion in response to a glucose challenge when controlling for the effect of BMI is found in Table 8.10. For total ghrelin there was no difference in AUC among the four groups. The nadir was significantly higher in the BN-BP and BED groups compared to the HC group. There were no differences in the time to nadir or percent fall from baseline among the groups. There were no differences in C-ghrelin AUC, nadir, time to nadir or percent fall from baseline among the groups.

The C-ghrelin/total ghrelin ratio was significantly different among the groups ($F=2.75$, $df(3,79)$, $p=0.048$). Post hoc analysis showed that the C-ghrelin/total ghrelin ratio in the BN-BP group was significantly higher than all other groups. This suggests that total ghrelin is falling faster than C-ghrelin in response to the glucose challenge. This finding remains when the difference in BMI among the groups is taken into account. Adjusted means for each diagnostic group are presented in Figure 8.5.

Figure 8.5 C-ghrelin/total ghrelin ratio for AUC by diagnostic group with BMI as covariate. Adjusted means and standard errors reported.



Response to the oral glucose challenge for insulin and glucose when controlling for the effect of BMI is reported in Table 8.10. There were no differences in insulin AUC, peak insulin, time to peak insulin or percent change from baseline. For glucose, the AUC was significantly different among the groups, with the BN-BP and BED groups having smaller AUCs than the HC group. Peak insulin was also lower in the BN-BP and BED groups when compared with the HC group. There were no differences in the time to peak glucose and percent change from baseline among the groups.

Table 8.10 Total ghrelin, C-ghrelin, insulin and glucose levels in response to an oral glucose challenge by diagnosis controlling for BMI

	BN-BP mean (95%CI)	BN-NP mean (95%CI)	BED mean (95%CI)	HC mean (95%CI)	F (df)	p	Post Hoc (LSD)
Total ghrelin (pmol/L)	<i>n</i> = 18	<i>n</i> = 18	<i>n</i> = 42	<i>n</i> = 37			
AUC	23583 (19559-27606)	26278 (22356-30200)	25328 (22566-28091)	29124 (26308-31941)	2.14 (3,110)	.10	
Nadir	125 (100-151)	140 (116-164)	135 (118-153)	169 (151-187)	3.74 (3,111)	.01	BN-BP<HC BED<HC
Time to nadir (minutes)	83 (64-101)	90 (73-108)	101 (88-114)	99 (85-112)	1.02 (3,111)	.39	
% Change from baseline	21 (12-30)	31 (22-39)	37 (31-43)	29 (23-36)	2.78 (3,111)	.04	BED>BN-BP
C-ghrelin (pmol/L)	<i>n</i> = 11	<i>n</i> = 11	<i>n</i> = 37	<i>n</i> = 24			
AUC	13905 (10236-17575)	11926 (8490-15362)	12198 (10190-14206)	11074 (10190-14206)	0.57 (3,81)	.64	
Nadir	55 (39-71)	45 (29-61)	51 (42-60)	49 (38-59)	0.30 (3,80)	.83	
Time to nadir (minutes)	101 (81-122)	73 (53-94)	92 (80-103)	87 (73-101)	1.37 (3,80)	.26	
% Change from baseline	44 (37-51)	41 (34-48)	44 (40-48)	40 (35-45)	0.63 (3,80)	.60	
Insulin (pmol/L)	<i>n</i> = 14	<i>n</i> = 15	<i>n</i> = 25	<i>n</i> = 39			
AUC	37722 (28643-49631)	34752 (26762-45156)	43478 (35146-53804)	48436 (41078-57133)	1.90 (3,88)	.14	
Peak	399 (297-536)	380 (287-503)	454 (362-571)	474 (396-567)	0.78 (3,87)	.51	
Time to peak (minutes)	57 (44-73)	66 (52-85)	59 (48-72)	62 (53-72)	0.33 (3,87)	.80	
% Change from baseline	1283 (796-2065)	1259 (801-1979)	1137 (791-1633)	890 (664-1193)	0.93 (3,87)	.43	
Glucose (mmol/L)	<i>n</i> = 20	<i>n</i> = 24	<i>n</i> = 42	<i>n</i> = 43			
AUC	1135 (998-1272)	1225 (1102-1348)	1131 (1034-1229)	1340 (1247-1435)	3.68 (3,120)	.01	BN-BP<HC BED<HC
Peak	9.9 (8.6-11.2)	11.3 (10.1-12.4)	9.8 (8.8-10.7)	11.4 (10.6-12.3)	2.96 (3,124)	.04	BN-BP<HC BED<HC
Time to peak (minutes)	62 (49-75)	66 (54-78)	53 (43-63)	61 (51-70)	1.00 (3,124)	.40	
% Change from baseline	88 (64-112)	109 (87-103)	85 (67-102)	92 (76-108)	1.07 (3,124)	.37	

* Analysis of insulin was performed on log_e transformed variables. Insulin values reported in this table have been back transformed (exp(x)) to allow clinical interpretation. AUC = Area Under the Curve; BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls.

8.6 Association between Eating Disorder Psychopathology and Biological Measures

Eating disorder specific variables, exercise, BMI and percentage body fat by diagnostic group are described in Table 8.11. All eating disorder specific variables were strongly skewed to the right except for BMI, percentage body fat and minutes of exercise which approached a normal distribution.

Table 8.11 Description of eating disorder psychopathology variables across the total sample and by diagnostic group

	Total sample <i>n</i> = 144 mean (sd)	BN-BP <i>n</i> = 26 mean (sd)	BN-NP <i>n</i> = 25 mean (sd)	BED <i>n</i> = 47 mean (sd)	HC <i>n</i> = 46 mean (sd)
Binges past month	12.9 (13.3)	23.8 (15.1)	17.0 (9.7)	17.5 (10.6)	0 (0)
Vomits past month	-	26.4 (20.9)	-	-	-
Total purges past month	-	31.9 (22.5)	-	-	-
Exercise (min/week)	56.0 (44.4)	63.8 (37.3)	65.6 (36.9)	44.8 (33.1)	58.3 (58.1)
EDI Bulimia	7.0 (5.9)	11.3 (5.5)	10.1 (3.8)	9.6 (3.9)	-
EDI impulsivity	3.2 (4.2)	4.7 (4.7)	4.0 (4.4)	3.7 (4.3)	1.2 (2.9)
EDI Perfectionism	5.5 (4.5)	8.0 (4.8)	7.0 (4.7)	5.4 (4.1)	3.4 (3.5)
BMI	28.5 (6.9)	25.1 (6.7)	27.4 (6.3)	33.3 (6.8)	26.4 (5.0)
% body fat	37.0 (10.2)	30.1 (10.6)	36.6 (8.2)	43.0 (8.0)	33.4 (8.8)

BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

Associations between fasting total ghrelin and eating disorder variables are presented in Table 8.12. Spearman's rho was calculated to examine nonparametric data and Pearson's product-moment correlations were calculated for normally distributed variables. A moderate positive correlation was found with total ghrelin and the number of binges in the past month in BN-BP group but not in any of the other three groups. The BN-BP group also had the highest average number of binges of the three binge eating groups. A

moderate positive correlation was found between vomiting frequency and fasting ghrelin in the BN-BP group. A very strong correlation was found between the frequency of bingeing and purging over the past month in the BN-BP group ($r = 0.90$, $p < 0.001$, $n = 26$).

Across the total sample there was a small positive correlation found between the time spent exercising and fasting ghrelin. When examined by diagnostic group, this pattern was found in the HC group but not in any of the eating disorder groups.

A moderate to large negative correlation between both percentage body fat and BMI and fasting ghrelin was found in the BED group and not in the other three groups which had lower means for BMI and % body fat.

Table 8.12 Association between fasting total ghrelin and eating disorder psychopathology in the total sample and by diagnostic group.

	Total sample <i>n</i>=144	BN-BP <i>n</i>=26	BN-NP <i>n</i>=25	BED <i>n</i>=47	HC <i>n</i>=46
Binges past month ^a	0.24*	0.48*	0.15	-0.05	-
Vomits past month ^a	-	0.51**	-	-	-
Exercise (min/week) ^b	0.26**	0.19	-0.07	0.22	0.37**
EDE Bulimia ^a	-0.21*	0.04	-0.13	-0.05	-
EDE Impulsivity ^a	-0.04	0.29	-0.18	0.10	-0.02
EDE Perfectionism ^a	-0.01	-0.01	-0.05	0.27	-0.20
BMI ^b	-0.39**	-0.24	-0.26	-0.57**	-0.16
% body fat ^b	-0.43**	-0.29	-0.19	-0.62**	-0.20

* $p < 0.05$, ** $p < 0.01$; ^a Spearman's rank-order correlation (r_s); ^b Pearson's product moment correlation (r); BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

Associations between fasting total ghrelin and eating disorder variables are presented in Table 8.13. There was a large positive correlation between C-ghrelin and exercise in the bulimia nervosa group. Perfectionism on the EDI-2 also had a large positive correlation with C-ghrelin in the bulimia nervosa binge-purge group. There was a large negative

correlation for both BMI and percentage body fat with C-ghrelin in the binge eating disorder group.

Table 8.13 Association between fasting C-ghrelin and eating disorder psychopathology in the total sample and by diagnostic group.

	Total sample <i>n</i>=100	BN-BP <i>n</i>=16	BN-NP <i>n</i>=15	BED <i>n</i>=41	HC <i>n</i>=28
Binges past month ^a	-0.07	0.20	-0.34	-0.10	-
Vomits past month ^a	-	0.01	-	-	-
Exercise (min/week) ^b	0.19	0.50*	0.03	0.07	0.15
EDE Bulimia ^a	-0.09	0.01	-0.01	-0.05	-
EDE Impulsivity ^a	0.01	0.13	-0.29	0.11	-0.22
EDE Perfectionism ^a	0.18	0.52*	0.12	0.30	-0.31
BMI ^b	-0.42**	-0.17	-0.45	-0.53**	-0.19
% body fat ^b	-0.47**	-0.15	-0.38	-0.64**	-0.26

* $p < 0.05$, ** $p < 0.01$; ^a Spearman's rank-order correlation (r_s); ^b Pearson's product moment correlation (r); BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

The associations between fasting AUC total ghrelin and eating disorder psychopathology in the total sample and by diagnostic group are shown in Table 8.14. Total ghrelin AUC showed a positive correlation with both the number of binges and the number of vomits in the past month in the bulimia nervosa binge-purge group. Exercise was moderately correlated with total ghrelin AUC in the healthy control group.

Table 8.14 Association between fasting AUC total ghrelin and eating disorder psychopathology in in the total sample and by diagnostic group.

	Total sample n=115	BN-BP n=18	BN-NP n=18	BED n=42	HC n=37
Binges past month ^a	-0.18	0.30	-0.05	0.01	-
Vomits past month ^a	-	0.37	-	-	-
Exercise (min/week) ^b	0.29**	0.02	0.06	0.20	0.41*
EDE Bulimia ^a	-0.25**	0.19	-0.25	-0.02	-
EDE Impulsivity ^a	0.03	0.17	0.03	0.15	0.13
EDE Perfectionism ^a	-0.08	0.10	-0.43	0.24	-0.64
BMI ^b	-0.40**	-0.35	-0.22	-0.55**	-0.13
% body fat ^b	-0.42**	-0.29	-0.13	-0.65**	-0.26

*p<0.05, ** p<0.01; ^a Spearman's rank-order correlation (r_s); ^b Pearson's product moment correlation (r); BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

The associations between fasting AUC C-ghrelin and eating disorder psychopathology in in the total sample and by diagnostic group are reported in Table 8.15. Both BMI and percent body fat were negatively associated with AUC for C-ghrelin in the BED group.

Table 8.15 Association between fasting AUC C-ghrelin and eating disorder psychopathology in in the total sample and by diagnostic group.

	Total sample n=84	BN-BP n=11	BN-NP n=12	BED n=38	HC n=23
Binges past month ^a	-0.05	0.32	-0.25	-0.05	-
Vomits past month ^a	-	0.19	-	-	-
Exercise (min/week) ^b	0.16	0.23	0.13	0.11	0.09
EDE Bulimia ^a	-0.04	0.09	-0.04	-0.001	-
EDE Impulsivity ^a	0.12	0.36	-0.06	0.07	0.05
EDE Perfectionism ^a	0.11	0.19	-0.07	0.26	-0.26
BMI ^b	-0.42**	-0.14	-0.38	-0.53**	-0.22
% body fat ^b	-0.46**	0.04	-0.29	-0.65**	-0.42

*p<0.05, ** p<0.01; ^a Spearman's rank-order correlation (r_s); ^b Pearson's product moment correlation (r); BN-BP = bulimia nervosa binge-purge subtype; BN-NP = bulimia nervosa non-purging subtype; BED = binge eating disorder; HC = healthy controls

8.7 Summary of Key Findings

- Total ghrelin secretion was generally lower after an overnight fast in women with binge eating compared with women who do not binge eat.
- Total ghrelin secretion in response to a glucose load was blunted in women with binge eating compared with women who do not binge eat.
- C-ghrelin and total ghrelin were different in the rates of decline after a glucose challenge.
- The BN- BP group had a higher proportion of C-ghrelin after ingestion of glucose than all other groups.
- Insulin levels and insulin resistance were different in some groups of women who binge eat and these differences remained even after the effect of BMI is accounted for.
- Fasting glucose levels were lower in women with binge eating compared with women who did not binge eat and this difference was more evident after the effects of BMI had been accounted for.
- Some aspects of eating disorder pathology such as frequency of binges, frequency of vomiting, levels of exercise and psychological variables such as perfectionism and drive for thinness were correlated with total ghrelin.

9. DISCUSSION: GHRELIN AND OTHER

NEUROHORMONES IN WOMEN WITH BINGE EATING

This section will first compare how data from the current study compares to the general female population of New Zealand. Key findings highlighted in the previous chapter will then be discussed.

9.1 *Comparison of Sample Characteristics with the General Population*

9.1.1 Age

The mean age of the total sample at 33.7 years is older than many other comparative published studies (see Table 6.1) and is likely to be a reflection of recruitment strategies which were community based and not recruited from tertiary institutions or eating disorder treatment units which tend to have a younger population. In this study the range of ages of the women recruited is fairly wide, ranging from 16 years to 63 years, in comparison with studies which have a narrower age range.

Women in the binge eating disorder group were on average older than women in the bulimia nervosa group and those in the control group. This reflects the often later age of onset for binge eating disorder (Kessler et al., 2013) and the transdiagnostic nature of binge eating that some women with bulimia nervosa move into binge eating disorder over time (Stice et al., 2013). Despite age being significantly different among the groups in the current study, it is unlikely to have had a significant impact on understanding results as the biological variables of interest (ghrelin, C-ghrelin, and insulin) were found not significantly correlated with age. However, the inclusion of older participants is likely to

have increased the incidence of age-related metabolic illnesses including diabetes and hypothyroidism.

No association between age and ghrelin was found in the current study which is consistent with ghrelin secretion remaining relatively constant across middle adulthood (Di Francesco et al., 2006). There is evidence that ghrelin reduces in older people but the sample of the current study did not include children or adults above 63 years old.

9.1.2 Body Mass Index

The mean BMI of women in the current study is very similar to the mean BMI of the general population. The mean BMI of 28.5 across the total sample is similar to results reported from the New Zealand Adult Nutrition Study (University of Otago and Ministry of Health, 2011) which reported a mean BMI of 27.6 for adult women aged 15 years and over. This similarity suggests these results may be generalisable to the wider population.

Significant differences in BMI were found among the diagnostic groups. Women in the binge eating disorder group had significantly higher mean BMI than the other three groups which were all similar. Compared with other published studies investigating ghrelin in binge eating, BMI in this study tended to be higher for the bulimia nervosa group than many of the other studies. Reasons for this are likely to be that some studies were in Asian participants who tend to have lower BMI than other ethnicities. Some studies had a lower average age and BMI is known to increase with age. Sampling was likely to be more representative of the general population than in some other studies which included mainly college students. The inclusion of women with bulimia nervosa non-purging subtype may also have had an influence as some studies have included only bulimia nervosa binge-purge subtype. Other studies investigating BED had similar mean BMI to the current

study. The wide BMI range has implications for analysis of the neurohormone data as some of the sample had BMI related health problems including diabetes and insulin sensitivity, polycystic ovary syndrome, and thyroid conditions.

Significant negative associations between BMI and ghrelin and significant positive associations between BMI and both insulin and glucose were found. These patterns have been consistently found in previous research. This result highlights the importance of controlling for BMI in further analyses.

9.1.3 Prevalence of Metabolic disorders

In the current study 3.5% of the total sample had a diagnosis of type 2 diabetes. This compares to approximately 5.0% of adult women in New Zealand having diabetes although this figure combines both type 1 and 2 diabetes. The percentage of type 2 diabetes increases to 5.3% when suspected cases (undiagnosed) are included as reported in the National Health Survey (Ministry of Health, 2008; Ministry of Health, 2015b). It is likely that some of the participants in this study may also have had undiagnosed diabetes as 15% of the sample showed signs of insulin resistance using the accepted cut-off on the HOMA-IR index. It is possible that those with undiagnosed diabetes have skewed some of the neurohormone data, specifically insulin levels. Note that the two participants who were excluded from analysis due to outlying insulin levels did not report a diagnosis of diabetes. All abnormal blood results were reported back to the participant to allow them to address this with their family doctor.

The estimated prevalence of diagnosed polycystic ovary syndrome in New Zealand women is in the range of 5 to 10% of women of reproductive age (Farquhar et al., 1994). Results from the current study are consistent with the lower end of this estimation at 3.5%. When

healthy control participants are excluded the rate of polycystic ovary syndrome in the eating disorder sample rises to 5.1%. Polycystic ovary syndrome is known to be associated with changes in insulin and increased risk of developing diabetes (Balen, 2004; The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group., 2004). This association is found even in women with a BMI in the healthy range (Cattrall & Healy, 2004).

Five percent of the total sample reported thyroid conditions. The prevalence of thyroid conditions (both hypothyroid and hyperthyroid) for adult women in the general population in New Zealand is around 5.0% (Ministry of Health, 2008).

Hypothyroidism is associated with increased insulin resistance (Kapadia, Bhatt, & Shah, 2012) and higher rates of type 2 diabetes due to a complex chain of interactions between thyroid hormones which results in decreased insulin secretion (Wang, 2013).

Overall 9.7% of the combined eating disorder groups reported a diagnosis of diabetes, polycystic ovary syndrome or hypothyroidism. One participant (2.0%) in the healthy control group reported any of these conditions (hypothyroidism). Because of the inclusion of women with diabetes, polycystic ovary syndrome and hypothyroidism it could be expected that insulin secretion could be altered in the eating disordered groups more than in the healthy control group.

9.1.4 Fasting ghrelin, insulin and glucose

Studies with healthy female participants report mean fasting total ghrelin levels between 121pmol/L (Tanaka et al., 2003) and 385pmol/L (Rouach et al., 2007). The current study fell towards the middle of this range at 273pmol/L. C-ghrelin has not been reported in many studies and has not been reported in any studies of participants with eating disorders.

In the current study C-ghrelin was strongly correlated with total ghrelin as expected. It was found to be at a very similar level to that found by (Bang et al., 2007) who reported a correlation coefficient (r) between ghrelin and C-ghrelin 0.61 compared with 0.69 in this study.

Normal levels for fasting insulin (Canterbury Health Laboratories, 2016, retrieved from <http://www.labnet.health.nz/testmanager> 17/03/16) are 10-80 pmol/L, after overnight fast for individuals with a BMI lower than 25. The current study had a mean fasting insulin of 50.7 pmol/L which falls within this range. However 15.8% of the total sample had fasting insulin levels above 80 pmol/L. There was a significant correlation between BMI and insulin across the total sample. This suggests that high insulin could be due to the higher BMI in many of the participants. This is consistent with the known association, between BMI and insulin (Murray et al., 2014). It is also likely that some of the sample were insulin resistant or had undiagnosed diabetes. HOMA-IR results are consistent with 15% of the total sample having at least some level of insulin resistance. The positive correlation between BMI and HOMA-IR is consistent with individuals of higher BMI being more likely to have insulin resistance.

The normal range for fasting glucose is between 3.5 and 6.0 mmol/L (Canterbury Health Laboratories, 2016, retrieved from <http://www.labnet.health.nz/testmanager> 17/03/16). In the current study the mean fasting glucose was 5.6 and ranged between 3.2 and 11.7. Overall 26.1% of participants had elevated fasting glucose levels. This finding is consistent with the abnormal insulin levels in some of the sample as reported above. In response to the oral glucose challenge test (OGCT) a significant proportion of the sample showed elevated glucose (>7.8mmol/L) at 120 minutes post oral glucose and 12.9% exhibited glucose levels suggestive of diabetes (>11.0 mmol/L). As with the insulin

results, the elevated glucose was correlated with BMI which is consistent with current knowledge of the association between BMI, glucose, and insulin secretion.

9.2 *Discussion of Key Findings*

9.2.1 Total ghrelin is lower in binge eating

Fasting ghrelin levels were found to be lower in women with binge eating disorder compared with those who do not binge eat. This is consistent with finding from other studies which have also reported a lower ghrelin in binge eating disorder (Geliebter et al., 2008; Geliebter et al., 2005; Geliebter et al., 2004; Monteleone et al., 2005).

There is less clarity around fasting ghrelin levels in women with bulimia nervosa. Although both the bulimia nervosa groups had lower fasting total ghrelin than the healthy control group in the current study, these were not statistically significant. This finding is consistent with a number of published studies which found no significant difference in fasting total ghrelin in bulimia nervosa compared with women without an eating disorder (Devlin et al., 1990; Monteleone et al., 2003; Monteleone et al., 2005; Nedvidkova et al., 2011). In contrast, other studies have reported fasting ghrelin to be higher in women with bulimia nervosa than healthy controls (Fassino et al., 2005; Kojima et al., 2005; Tanaka et al., 2003; Tanaka et al., 2006). The characteristics of the sample may be an important consideration when trying to understand these different findings as studies differ on average BMIs, ethnicities and recruitment strategies. The current study sample is older and has a higher mean BMI than many previous studies. The current study is likely to be more representative of the general population as it was recruited from the community rather than university students or eating disorder clinics as in many other studies.

When BMI is taken into account, differences in total ghrelin by diagnosis reduce or become non-significant. It is well established that fasting ghrelin is lower at a higher BMI. This suggests that BMI has more influence over ghrelin secretion in a fasting state than having regular binge eating. As Monteleone et al. (2005) suggest, lower total ghrelin in women who binge eat could be due to the secondary effect of high BMI and may serve as a mechanism to reduce energy intake. Despite the reduction in strength of the association when BMI is taken into account, the pattern of lower total ghrelin in groups with binge eating remained which suggests that although BMI has a significant impact on ghrelin secretion there may be more subtle effects of binge eating that are harder to detect.

The reduction in ghrelin secretion in response to energy ingestion is less in women with binge eating. In the current study an oral glucose challenge test (OGCT) was used to observe the response to ingestion of energy after a period of fasting. The resulting AUC, an indication of the overall change in hormone secretion, together with the shape of this curve also gives information about the timing of response, duration of effect and change from baseline levels. The binge eating groups all had a lower AUC for total ghrelin compared to the healthy control group. The binge eating disorder group had the lowest AUC of all groups and the bulimia nervosa binge purge group and bulimia nervosa non-purging group fell in between the binge eating disorder and control groups.

Correspondingly the nadir was lower in all the eating disorder groups compared to the control group. This pattern suggests that ghrelin secretion is blunted in the eating disorder groups. Studies comparing binge eating disorder and healthy controls have generally found this pattern of a blunted ghrelin response to ingestion of energy whether it be from a liquid meal or a standardised breakfast of known energy content (Geliebter et al., 2005; Geliebter et al., 2008; Geliebter et al., 2004); however, one small study did not find differences between binge eating disorder and healthy controls (Munsch et al., 2009). As

most studies have been carried out by one research group the replication of this finding in the current study is an important contribution to the understanding of ghrelin secretion in binge eating.

The timing of the response to glucose ingestion appears to be the same regardless of eating disorder diagnosis. In the present study the time to nadir for total ghrelin was not different among the groups including healthy controls. The size of the response indicated by the percent fall from baseline levels was also not different among the four groups. This may reflect the pattern of secretion but may also be due to a floor effect as those groups with already lower secretion have less room to fall than those beginning at a higher level.

The strength of the differences in ghrelin secretion in response to oral glucose reduce when the effect of BMI is accounted for. This again suggests that the differences among the binge eating groups and healthy controls may be due to BMI rather than diagnosis. As with the fasting ghrelin results, the general trend of reduced secretion in the eating disorder groups remained but the differences were not statistically significant. It is possible that this section of the study was underpowered. The two bulimia nervosa groups had 18 participants each which may not have been a sufficient sample size to detect differences as there was a large amount of variance within each group.

It has been suggested that ghrelin is a stronger signal for meal initiation when the body is in need of energy such as in lower weight participants compared with higher weight (Blom et al., 2009). It seems that women who regularly binge eat, and particularly those with higher BMI may have lower levels of total ghrelin which in theory would result in lower levels of hunger and food ingestion. Reduction in ghrelin is more likely to be a response to high BMIs than to bingeing. This is supported by the finding when individuals without an eating disorder over eat, the resulting reduction in ghrelin secretion is the same as for a

normal sized meal (Votruba et al., 2009). It appears that binge eating is not driven by ghrelin levels and seems more likely to be driven by other mechanisms.

9.2.2 Changes in C-ghrelin levels are different to total ghrelin

The correlation between C-ghrelin and total ghrelin is high ($r=0.69$ $p<0.001$). This is expected as C-ghrelin makes up part of total ghrelin, being a combination of both acyl and des-acyl ghrelin. C-ghrelin is more unstable as it easily loses its serine ring to transform into des-acyl ghrelin and makes up a smaller proportion of total ghrelin than des-acyl ghrelin (Bang et al., 2007). Across the total sample C-ghrelin made up 39% of total ghrelin after an overnight fast. However in response to ingestion of glucose the proportion of C-ghrelin rose to 46%. This suggests that acyl and des-acyl ghrelin may be differently affected by ingestion of glucose and that total ghrelin falls faster than C-ghrelin.

When comparing the ratio of C-ghrelin to total ghrelin among the diagnostic groups it was found that there were no differences for this ratio in the fasting condition; however the groups differed after glucose ingestion with the bulimia nervosa binge-purge group having a significantly higher ratio of C-ghrelin to total ghrelin. This difference remained even after the effect of BMI was accounted for. However, C-ghrelin levels were not found to be different among the groups after the glucose challenge. This finding suggests that total ghrelin is falling faster compared to C-ghrelin in the bulimia nervosa binge purge group than other three groups. These two findings suggest that the des-acyl form of ghrelin is reduces more rapidly in response to glucose. This is a surprising result as acyl ghrelin is thought to be the more active form and is easily converted to des-acyl ghrelin. This suggests that in the bulimia nervosa binge-purge group acyl ghrelin is either continuing to be secreted by the stomach or is not degrading to des-acyl ghrelin at the same rate as the other groups. Therefore total ghrelin alone is not a good indicator of ghrelin secretion in

response to energy ingestion. If this is the case it is essential to measure both forms of ghrelin to understand ghrelin secretion in women with binge eating. Most studies have not done this to date.

However, caution must be taken when making conclusions from this result in the current study. The sample size for this analysis, particularly in the two bulimia nervosa groups, was smaller than in some of the other analyses. C-ghrelin was not being analysed for the first 26 participants who were mostly from the bulimia nervosa groups.

9.2.3 Insulin and insulin resistance are higher in binge eating

As expected, insulin increased in response to glucose ingestion in all groups. The size of this increase as measured by the AUC was greatest in the binge eating disorder group. This is consistent with a higher BMI, and increased insulin resistance. The higher insulin response may be involved in explaining the blunted ghrelin response in this group as insulin is thought to be involved in reducing ghrelin secretion (Chabot et al., 2014). The pattern of insulin secretion over time as indicated by the time to peak was not different among the groups indicating that it is the size of the response and not a delay in responding that is responsible for the differences among the groups.

This result suggests that those with binge eating and particularly those with higher BMIs such as the binge eating disorder group are at increased risk of developing diabetes and the health consequences of that diagnosis.

9.2.4 Glucose is lower in binge eating

Results of the current study suggest a state of comparative hypoglycaemia in women who binge eat compared to those that do not binge. All four groups exhibited increased blood

glucose levels after ingestion of a glucose drink as expected and there were no differences among the groups in the timing of the increase in blood glucose with all groups reaching peak glucose levels at the same rate. However, fasting blood glucose was significantly lower in the eating disorder groups compared with healthy controls when the effect of BMI was accounted for. Blood glucose levels remained lower in response to the oral glucose challenge in the eating disorder groups.

To understand this pattern it is important to consider the association between ghrelin, insulin and blood glucose. In healthy individuals increased ghrelin suppresses insulin release which results in increased blood glucose levels in both fasting conditions and glucose challenge tests (Yada et al., 2008). The current study has shown that women who binge eat have a blunted pattern of ghrelin secretion. Therefore in women with binge eating lower levels of ghrelin will result in relatively higher levels of insulin independent from BMI (which also increases insulin levels). The resulting increase in insulin levels results in reduced blood glucose levels even when BMI is taken into account. This is consistent with ghrelin playing a role in insulin release and glucose metabolism and again highlights the potential health consequences of a pattern of regular binge eating.

Interestingly, low glucose levels have been found to be associated with an increase in behaviours showing reduced self-control (Gailliot & Baumeister, 2007). Furthermore when glucose is restored to normal levels, self-control is also restored. This is of interest in individuals with binge eating as loss of self-control is central to defining binge eating. Further research on the association between low glucose and bingeing would be of interest.

9.2.5 Eating disorder psychopathology is associated with ghrelin

Eating disorder psychopathology is associated with ghrelin secretion in women with binge eating but different factors appear to be relevant for different diagnostic groups.

The frequency of bingeing was positively associated with ghrelin secretion but only within the bulimia nervosa binge-purge group. The frequency of bingeing was highest in this group with slightly lower levels in those with bulimia nervosa non-purging and binge eating disorder. Higher levels of bingeing were associated with higher fasting total ghrelin and a greater AUC for total ghrelin within the bulimia nervosa binge-purge group. There was a similar nonsignificant trend in the bulimia nervosa non-purging group but no association between total ghrelin and bingeing frequency in the binge eating disorder group. This finding of an increase in ghrelin with increased bingeing is interesting as overall the eating disorder groups had lower total ghrelin than the healthy control group. This pattern may be better understood by considering the frequency of vomiting.

Within the bulimia nervosa binge-purge group increased vomiting was linked to higher total ghrelin levels. Vomiting may reduce nutrient intake overall and although on average this group was of normal weight, they may be energy or nutrient deficient at times due to the binge-purge cycle. This result is consistent with that found by Tanaka et al., (2003) in women with bulimia nervosa and anorexia nervosa. They found that those with a binge-purge pattern had higher ghrelin secretion compared with those who followed the more restrictive pattern in anorexia nervosa or non-purging forms of bulimia nervosa. As there was a very strong correlation between bingeing and vomiting in the bulimia nervosa group in the present study ($r = 0.90$) it is likely that ghrelin secretion is related more to vomiting rather than bingeing per se.

When considering the association between eating disorder characteristics and C-ghrelin in the current study it is important to note that the sample sizes are small in some groups and this section of the study is likely to have insufficient sample sizes to detect a difference among the groups. There appears to be a similar relationship for C-ghrelin and bingeing and vomiting as that previously reported for total ghrelin. This adds further support to the importance of the binge-purge cycle in understanding ghrelin secretion in bulimia nervosa and reinforces the need to identify those with purging and non-purging form of this disorder.

The association between ghrelin secretion and exercise is complex. Exercise in healthy participants is known to increase ghrelin secretion (King et al., 2013) but is complicated by intensity and duration of exercise and the effect of weight loss. In women with binge eating, exercise can be an important compensatory or attempted weight loss behaviour, particularly in the non-purging form of bulimia nervosa. However, in the current study there was no difference in the number of minutes of exercise per week among the groups. There was a wide range of time spent exercising both across the total sample and within diagnostic groups with some participants exercising extensively and others doing little or no exercise. Across the total sample increased exercise was associated with higher fasting total ghrelin, supporting the concept that exercise creates a state of energy deficit resulting in an increase in ghrelin in order to restore this deficit. When the effect of exercise was explored within the diagnostic groups this association with exercise was only statistically significant in the healthy control group, although there was a non-significant trend for this pattern in both bulimia nervosa binge purge subtype and binge eating disorder. This pattern was not found in the bulimia nervosa non purging group which is surprising because of the importance of exercise as a way of compensating for bingeing in this group.

When examining ghrelin secretion in response to an ingestion of energy (glucose), women with a binge-purge pattern of bulimia nervosa who exercised more had higher total ghrelin secretion compared with women who binge but do not purge, and to healthy women who do not binge or purge. Overall this is a pattern of results which suggests that eating disorder behaviours such as vomiting and exercise are associated with increases in total ghrelin, particularly in those women with bulimia nervosa binge-purge subtype, but the frequency of bingeing may not be associated with increased total ghrelin. There are likely to be a number of factors involved in this association and further research is needed in order to understand this complexity.

One study has reported the impact of exercise in women who binge eat (Nedvidkova et al., 2011) finding that ghrelin levels reduced immediately after exercise in women with bulimia nervosa, but this study did not investigate the long term effects of exercise in this group and did not differentiate between purging and non-purging forms of bulimia nervosa. The current study did not investigate the immediate effects of exercise on ghrelin secretion in women with binge eating; however more research is needed to look at both the immediate and longer term influence of exercise in women with binge eating.

An interesting difference was found between total ghrelin and C-ghrelin when examining the amount of exercise in the current study. The bulimia nervosa binge-purge group had a significant association between exercise and fasting C-ghrelin. There was a similar trend which did not reach significance for the AUC. It appears that in women with bulimia nervosa binge-purge subtype, activities such as vomiting and exercise that affect energy balance in a negative way are associated with higher C-ghrelin, a measure of the form thought to increase eating in normal circumstances. Although this association was evident,

the levels of ghrelin remain lower overall than those that found in women who do not binge eat.

The EDI has commonly been found to differentiate between different diagnostic groups and healthy controls and has good reliability to assess both eating disorder specific behaviours and attitudes (e.g. Bulimia subscale), and also more general psychological characteristics that have been associated with eating disorders (e.g. Impulsivity and Perfectionism subscales) (Gleaves et al., 2014). Eating disorder samples frequently display higher scores on these subscales which can differentiate between eating disorder and healthy control groups. In the current study eating disorder groups scored significantly higher than healthy controls on the Bulimia, Impulsivity and Perfectionism subscales as expected.

No association was found between EDI Bulimia scores and total ghrelin in the current study despite the finding of a positive association between the number of binges and total ghrelin as discussed above. No association was found between ghrelin and either Impulsivity or Perfectionism across the total sample or within diagnostic groups. The EDI does not appear to be a useful instrument in understanding patterns of ghrelin secretion.

Higher Perfectionism scores were associated with increased C-ghrelin but not total ghrelin in the bulimia nervosa binge-purge group but this pattern was not in any of the other two diagnostic groups. Again the small sample size is noted and caution is required in making conclusions from this result other than it is an interesting finding that fits alongside the finding that C-ghrelin is associated with increased purging and exercise. Perfectionism may be a proxy for these variables or may be a factor in its own right. It is unclear at this point and further research is required.

As expected, BMI and percentage body fat was significantly negatively associated with total ghrelin in the binge eating disorder group but not in the other three groups, although trend was the same in the other groups. This reinforces the findings that body composition is one of the most important factors in understanding hormone secretion in eating disorders.

9.3 Strengths and Weakness of the Current Study

The current study differed from many other studies investigating ghrelin in women with binge eating as an oral glucose drink was used as an energy source compared with standardised breakfasts or liquid meal replacements used in many other studies. A glucose drink is not a usual breakfast food and is lacking some of the components of a meal such as texture and therefore the need to chew, and is made up of simple carbohydrates rather than a range of carbohydrate, protein, fats and fibre. However, Doubkova et al. (2010) found that ingestion of dietary fibre which provided volume but no energy did not change ghrelin secretion whereas fibre plus glucose did in both healthy women and women with bulimia nervosa, although sample sizes were very small. Their study did not use a typical meal which would have been an interesting comparison.

Regularity of breakfast eating by participants was not accounted for in the current study. (Frecka & Mattes, 2008) found that in healthy women, fasting ghrelin was higher in those who ate breakfast regularly compared with those who tended to eat their first meal later in the day. It is possible that in the current study the healthy control group ate breakfast more regularly which had the potential to elevate fasting ghrelin levels in the healthy control group.

Other weaknesses of the current study include some missing biological data. Care was taken to estimate values where appropriate using an established method (trapezoid) but to avoid estimating values where inappropriate, for example if the time of peak or nadir was not clear, or where there were more than three missing values in a row. Sample sizes in some groups, particularly for C-ghrelin, were compromised due to unavailability of samples for a number of reasons, including collapse of vein, unavailability of assay at the time of sampling and loss of some samples due to the effect of significant earthquakes in Canterbury resulting in power loss and subsequent failure of freezers in which samples were stored. The current study was largely observational and did not involve experimental manipulation of ghrelin to investigate effects of ghrelin on neuropsychological function. Future studies may be able to advance this area using methods to manipulate ghrelin secretion.

The current study had considerable strengths in study design. Care was taken to accurately place participants in diagnostic categories using the SCID-I semi-structured interview which is considered the gold standard for research. Particular care was taken to differentiate purging from non-purging bulimia nervosa and this proved essential when investigating differences in ghrelin and insulin secretion in these groups. The current study is one of few to include assays for both total ghrelin and a measure of the acyl form of ghrelin (C-ghrelin assay). This allowed identification of patterns of ghrelin secretion, particularly in the BN-BP group that would not have been evident otherwise.

Participants were recruited from both community and clinical sources which is important to enable generalisation of the results to a wide range of women with binge eating – not only those attending treatment clinics or tertiary institutions as in many other studies. The

recruitment strategy in the current study also allowed a large sample overall, and adequate sample sizes to detect differences among groups for most comparisons.

9.4 *Research for the Future*

Results from the current study suggest a number of areas for further research. Firstly, assays for both acyl and des acyl ghrelin need to be included in studies of ghrelin secretion as both appear to alter independently in binge eating, particularly when purging is present. It would be useful to compare ghrelin secretion in response to test meals of different nutritional characteristics. It seems clear that glucose ingestion results in a decrease in ghrelin; however, different meal compositions (those including fat, glucose, protein, fibre) could potentially affect ghrelin secretion in different ways that at present are unknown. It may be interesting to consider psychological variables, beyond hunger, such as subjective reports of satiety and the hedonistic qualities of the food.

Further exploration of eating disorder characteristics is needed. Inclusion of participants with purging disorder may be helpful to understand the contribution of bingeing as opposed to vomiting to ghrelin secretion. The role of exercise in ghrelin secretion both immediate and long term would also be helpful to aid in understanding the role of activities that create a negative energy balance. Other aspects potentially of interest include further examination of psychological traits associated with binge eating such as reward dependence and impulsivity.

The current study has not investigated changes in ghrelin secretion after treatment of binge eating. A small number of studies have found that ghrelin secretion levels normalise after treatment in women with binge eating disorder (Geliebter et al., 2008; Munsch et al., 2009) and in a case study of night eating syndrome (Rosenhagen et al., 2005). Future research in

changes to ghrelin secretion after treatment for bulimia nervosa and binge eating disorder would contribute to understanding this more fully.

9.5 *Summary of Ghrelin in Binge Eating*

Ghrelin is part of a complex relationship between systems regulating energy balance as well as other functions in the body, particularly those involved in growth. Results from the current study suggest that there is some disruption to the ghrelin system in women with binge eating. Ghrelin is blunted in women with binge eating and this is partially due to higher body fat/BMI. The reduction in ghrelin may be part of the system controlling insulin, resulting in higher insulin and lower blood glucose in women with binge eating leading to increases in insulin resistance and potential to develop diabetes.

The level of purging and other activities such as exercise that negatively affect energy balance may work in the opposite direction and act to increase ghrelin secretion, although not to a level that fully compensates for the reduced ghrelin overall. The bulimia nervosa binge-purge group also differs from the other groups in that C-ghrelin is higher, again suggesting a mechanism to improve energy balance in this group. In the bulimia nervosa non-purging group and binge eating disorder group the major influence on ghrelin secretion appears to be BMI, an indirect measure of body fat, rather than eating disorder behaviours.

Ghrelin is likely to be implicated in insulin secretion and may increase insulin resistance and risk of diabetes in women with binge eating, particularly when associated with high weight.

PART D

10. LITERATURE REVIEW: GHRELIN AND COGNITIVE FUNCTION

Ghrelin is known to play a role in regulating brain functions other than just energy metabolism and appetite and has been implicated in cognitive function, particularly in learning and memory through increasing neuronal density (Beck & Pourie, 2013). Increasing the number of neuronal connections, sometimes termed neuroplasticity, is thought to be a necessary for development of learning and memory, particularly in the hippocampus. The majority of studies investigating the relationship between ghrelin and cognitive functioning have been carried out in animals; however, as the hippocampus is structurally similar across species animal models can be reliably extrapolated to human hippocampus physiology and anatomy (Beck & Pourie, 2013).

A series of experiments by Diano et al., (2006) showed that peripherally administered ghrelin crosses the blood-brain barrier in rodents and is taken up by different areas of the brain including the hippocampus. The number of synapses in the hippocampus was found to increase with ghrelin administration suggesting neuroplasticity of this area is enhanced by ghrelin. They were able to demonstrate that administration of ghrelin improved learning and memory in both rats and mice. Furthermore, they found that ghrelin knock-out mice (those mice in which researchers have inactivated, or "knocked out", the ghrelin gene by replacing it or disrupting it with an artificial piece of DNA) which exhibited learning and memory deficits improved performance after administration of ghrelin. This comprehensive suite of studies reported in this single publication by this research group (Diano et al. 2006) suggests that ghrelin is involved with promoting neural plasticity in

rodents, which in turn is likely to have improved performance on tasks of memory and learning even in animals with learning and memory deficits. Similar findings of increased spatial memory and evidence of neuroplasticity in response to acyl-ghrelin administration have been reported by other studies (Chen et al., 2011; Carlini et al 2002; Carlini et al., 2004).

It is possible that there is some survival value if memory is improved when ghrelin levels are high when animals are in a starvation state as this could potentially improve food finding ability. To examine this Carlini, et al (2008) used a mouse model of food restriction in an attempt to mimic conditions of humans with anorexia nervosa. They compared mice on 50% food restriction with mice with ad lib feeding regimes. As expected total ghrelin levels in the food restricted group were almost three times that of the control group. Despite this, food restricted mice showed an impairment in memory using the Spontaneous Object Recognition Test and exhibited an increase in anxiety-like behaviours. Central administration of ghrelin to the food restricted mice improved memory to the level of the control group. This result does not support the theory that elevated ghrelin levels enhance learning and memory in food deprived animals as a way of increasing survival in times of food shortages. However, as the authors note, the novel stimulus task used might not be an ecologically valid test for learning and memory related to feeding opportunities and it may not have been advantageous for the hungry mice to expend energy on investigating non-food items. The increase in anxiety was not predicted in this study and it was suggested that it may have been due to the central administration of ghrelin rather than being administered peripherally. A similar result was also found by Carvajal et al., (2009) who found that ghrelin decreased memory retention and increased anxiety behaviours in recently hatched chicks.

Ghrelin may also have a neuroprotective effect by inhibiting apoptosis (cell death) after brain injury or stroke and reducing the impact of inflammation on neuronal loss (Spencer, Miller, & Andrews, 2013; Moon et al., 2009), and this effect is found irrespective of ghrelin acylation (Chung et al., 2008). This protective function is of interest in dementia research in humans.

In the only human study investigating ghrelin and cognitive function to date (Spitznagel et al., 2010) investigated the relationship between fasting ghrelin and cognitive function in 35 older healthy adults (age 60-85 years). In contrast with most animal studies they found a correlation between high ghrelin and lower cognitive performance on tasks of verbal memory, working memory and naming tasks. The authors suggested this effect may have been modulated by an association between ghrelin and disinhibition; however, this was not specifically examined.

In summary, ghrelin increases neural density in the hippocampus, an area of the brain associated with learning and memory. The increase in neural density, often described as neuroplasticity in these studies, has been shown to improve performance on tests of memory and learning in rodents when administered peripherally although studies using centrally administered ghrelin do not consistently show this pattern and have found ghrelin increases anxiety in rats and chickens. Ghrelin has also been found to have a neuroprotective function by decreasing the impact of neuronal loss after brain injury. Only one study to date has examined ghrelin and cognitive function in humans and unexpectedly found a correlation between ghrelin and decreased memory in older adults.

Table 10.1 Table of literature regarding cognitive function and ghrelin

Author	Participants	Method	Results	Comments
Carlini et al. (2002)	Rats	Injected ghrelin intracebrally, Open-field test (habituation), Elevated plus-maze anxiety behaviours), Step-down test (memory)	Single administration of ghrelin increased memory retention (positive relationship with ghrelin dose) and anxiogenic behaviour.	First to show ghrelin administration improves memory retention
Carlini et al. (2004)	Rats	Injected ghrelin intracebrally comparing 3 sites (hippocampus, amygdala, dorsal raphe nucleus). Open-field test (habituation), Elevated plus-maze anxiety behaviours), Step-down test (memory).	Single administration of ghrelin increased memory retention (positive relationship with ghrelin dose) and anxiogenic behaviour. Ghrelin receptors in hippocampus, amygdala, dorsal raphe nucleus. Hippocampus highest impact on memory retention.	Shows ghrelin increases hippocampal receptors
Diano et al. (2006)	Rats, mice	Series of experiments on rats, mice and ghrelin knock-out mice. Histology, memory testing (Spontaneous alternation plus-maze task, T-maze footshock avoidance and step-down inhibitory avoidance paradigms, Object recognition memory tests, peripheral administration of ghrelin	Ghrelin receptors present in hippocampus. Peripherally administered ghrelin can enter hippocampus. Spine synapse density increased with ghrelin. Evidence of increased neuroplasticity with ghrelin. Improved learning and memory performance in rats and mice. Restoration of learning and memory in ghrelin knock-out mice	Demonstrates that ghrelin increases neuronal plasticity in hippocampus and the relationship between this physiological change and memory improvement. Shows ghrelin can restore memory impairment in ghrelin depleted animals.

Carlini et al. (2008)	Mice	Compared memory performance in food restricted mice compared to unrestricted mice. Intracerebral administration of ghrelin.	Despite 3x normal ghrelin levels in food restriction found decreased memory function.	Does not support naturally high ghrelin improving memory in food restricted state but did show memory restoration on administration of ghrelin in food restricted state.
Chaung et al. (2008)				Both acylated and non-acylated ghrelin appear to have neuroprotective action.
Carvajal et al. (2009)	Neonatal chicks of domestic chickens	Injected ghrelin intracerebrally, Open-field test (habituation), One-trial passive avoidance task (memory retention)	No significant effect on memory retention, increase in anxiogenic behaviours.	Does not support relationship between ghrelin and improved memory.
Spitznagel et al. (2010)	Human (older adults 60-85 years)	Single fasting ghrelin sample, neuropsychological battery including tests of verbal memory, working memory and naming task	Negative correlation between ghrelin and verbal memory, working memory and naming	Only study investigating ghrelin and cognitive function in humans. Correlational study with no experimental manipulation of ghrelin levels.
Chen et al. (2011)	Rats	Measured intrahippocampal electrical activity following infusion of ghrelin to hippocampus, Spatial memory testing with Morris water maze	Single ghrelin infusion increased activity in the hippocampus in a way to suggest synaptic plasticity, and produced significant improvement in spatial memory	Ghrelin increases neuroplasticity in hippocampus and improves spatial memory.
Moon et al. (2014)	Mice	Ghrelin administered peripherally to mice with cognitive deficits and neuronal loss	Hippocampal neurogenesis improved after ghrelin administration.	Ghrelin increased neurogenesis in cognitively impaired mice.

11. GHRELIN AND NEUROPSYCHOLOGICAL FUNCTION IN WOMEN WHO BINGE EAT

11.1 Research Question

Animal studies suggest that ghrelin may affect neuropsychological functioning in animals as increased ghrelin levels appear to improve cognitive functions associated with food gathering. Conversely, low ghrelin levels potentially impair neuropsychological functioning related to food finding in animals. As ghrelin secretion is altered in humans with binge eating it is possible that ghrelin levels could be associated with neurocognitive functioning in this group. This section of the current study investigates associations between fasting total ghrelin and C-ghrelin, and neuropsychological function in women with binge eating compared with women who do not binge eat.

11.2 Methods

The methods for this section have been described in previous methods and can be found in Chapters 3 and 7. The participants in this section of the study differ slightly from the neuropsychological testing section as 14 eating disorder participants and two healthy control participants did not have neurohormone data available.

11.3 Results

Descriptive statistics for neuropsychological variables for the total sample and by diagnostic group are presented in Table 11.1.

Table 11.1 Mean and standard deviations for neuropsychological variables for the total sample and by diagnostic group.

	Whole sample n=144	BN-BP n=26	BN-NP n=25	BED n=47	HC n=46
RVP total hits	18.2 (4.6)	18.9 (3.9)	18.0 (5.0)	17.9 (4.6)	17.7 (5.4)
RVP total misses	8.8 (4.6)	8.1 (3.9)	8.9 (5.0)	9.1 (4.6)	9.3 (5.4)
RVP A	0.91 (0.04)	0.92 (0.04)	0.91 (0.05)	0.91 (0.04)	0.91 (0.05)
RVP B	0.94 (0.07)	0.94 (0.05)	0.94 (0.05)	0.95 (0.07)	0.93 (0.09)
RVP mean latency	418.9 (81.1)	423.6 (97.5)	412.9 (77.3)	414.7 (85.1)	415.0 (75.8)
VRM free recall	8.3 (1.7)	8.4 (1.8)	8.1 (1.6)	7.8 (1.8)	8.6 (1.5)
VRM recognition	23.3 (1.0)	23.2 (1.0)	23.5 (0.7)	23.1 (1.1)	23.3 (0.9)
VRM delayed recognition	21.2 (1.2)	23.2 (1.3)	23.2 (0.9)	22.9 (1.6)	23.3 (0.9)
SOC prob solved in min moves	9.3 (1.7)	9.3 (1.6)	9.3 (1.7)	9.2 (1.8)	9.6 (1.8)
SOC 5 moves	6.3 (1.3)	6.1 (1.0)	6.4 (1.3)	6.3 (1.5)	6.3 (1.4)
SOC thinking 1 st	12239 (8897)	14604 (9079)	12237 (8369)	12209 (7963)	13479 (10335)
SOC thinking sub	1449 (2867)	1096 (1297)	1552 (2013)	1964 (4064)	1375 (2870)
SRM %correct	87.3 (8.7)	88.1 (10.3)	86.6 (11.3)	85.6 (8.0)	87.5 (7.4)
SRM latency	2244 (577)	2178 (489)	2224 (612)	2315 (654)	2232 (553)
DMS % correct	90.6 (8.0)	91.5 (6.7)	89.0 (9.5)	90.5 (8.2)	90.8 (7.8)
DMS latency	3589 (1176)	3446 (792)	3512 (1298)	3682 (1272)	3707 (1336)
SWM total errors	21.1 (16.4)	22.6 (19.2)	20.2 (15.9)	21.3 (13.9)	22.4 (18.7)
SWM strategy	31.4 (5.6)	32.1 (5.2)	31.9 (6.2)	31.7 (5.4)	30.9 (5.9)
TMT proportional	1.2 (0.6)	1.4 (0.8)	1.3 (0.6)	1.3 (0.6)	1.1 (0.6)

BN-BP = bulimia nervosa binge-purge; BN-NP = bulimia nervosa non-purging, BED = binge eating disorder; HC = healthy controls; DMS = Delayed Matching to Sample; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; TMT = Trail Making Test; VRM = Verbal Recognition Memory

There were no significant differences among the four groups for any of the neuropsychological variables using ANOVA for normally distributed variables and Kruskal Wallis Tests for those variables without a normal distribution.

Associations between neuropsychological performance and fasting total ghrelin were examined using correlational analysis and are presented in Table 11.2. Pearson's product-moment correlations were used for normally distributed variables and Spearman's rank-order correlations were used for variables that were not normally distributed. There were no significant associations between ghrelin and neuropsychological performance for any of the variables across the total sample. When analysed by diagnostic group, there were no significant associations between ghrelin and neuropsychological performance other than a

significant moderate correlation ($r_s = 0.35$, $p < 0.05$) between fasting total ghrelin and RVP B (a measure of false alarm on a test of visual attention) in the BED group. This result showed increased ghrelin was associated with fewer false alarms as indicated by a higher RVP B score.

Table 11.2 Associations between ghrelin and neuropsychological variables for the total sample and by diagnostic group.

	Total sample n=144	BN-BP n=26	BN-NP n=25	BED n=47	HC n=46
RVP Total Hits	-0.05	-0.28	-0.17	-0.04	0.10
RVP Total Misses	0.05	0.28	0.17	0.04	-0.10
RVP mean latency	0.03	-0.10	0.11	0.29	-0.16
RVP A	-0.05	-0.25	-0.19	-0.02	0.09
RVP B [#]	0.03	0.06	-0.13	0.35*	-0.14
VRM free recall	0.09	0.07	0.24	-0.16	0.10
VRM recognition [#]	-0.13	0.12	-0.21	-0.26	-0.06
VRM delayed recognition [#]	-0.01	0.21	0.002	-0.17	-0.06
SOC problems solved min moves [#]	-0.16	0.07	-0.007	-0.27	0.12
SOC time 5 moves [#]	0.07	0.25	0.09	-0.10	-0.26
SOC thinking 1 st [#]	-0.02	0.26	-0.04	-0.03	-0.03
SOC thinking sub [#]	-0.07	0.07	-0.08	-0.06	-0.21
SRM %correct	-0.02	-0.02	0.11	-0.02	-0.24
SRM latency	-0.003	-0.06	0.22	-0.01	-0.03
DMS % correct [#]	0.01	-0.10	0.04	-0.06	0.21
DMS latency	-0.01	-0.07	0.13	0.08	-0.19
SWM errors [#]	0.003	0.07	0.32	-0.02	0.08
SWM strategy	0.03	0.09	0.18	-0.13	0.10
TMT proportional score	-0.02	-0.14	0.27	0.02	-0.02

* $p < 0.05$; Variables marked with [#] are reported as Spearman's rank-order correlations (r_s). All other variables reported are Pearson's product-moment correlations (r). BN-BP = bulimia nervosa binge-purge; BN-NP = bulimia nervosa non-purging, BED = binge eating disorder; HC = healthy controls; DMS = Delayed Matching to Sample; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; TMT = Trail Making Test; VRM = Verbal Recognition Memory

Associations between fasting C-ghrelin and neuropsychological performance for the total sample and by diagnostic group are presented in Table 11.3. There were no significant correlations between fasting C-ghrelin and neuropsychological performance across the

total sample. A significant moderate correlation ($r_s = -0.52$, $p < 0.05$) was found between fasting C-ghrelin and RVP B in the BN-NP group. This result indicates that there is an association between fasting C-ghrelin and a higher RVP B score indicating fewer false alarms on a test of visual attention. There were no other significant correlations found between fasting C-ghrelin and neuropsychological variables in any of the other diagnostic groups.

Table 11.3 Associations between neuropsychological performance and C-ghrelin in the total sample and by diagnostic group.

	Total sample n=100	BN-BP n=16	BN-NP n=15	BED n=41	HC n=28
RVP Total Hits	-0.10	-0.016	-0.20	-0.11	-0.08
RVP Total Misses	0.10	0.16	0.20	0.11	0.08
RVP mean latency	0.03	-0.17	-0.17	0.16	-0.04
RVP A	-0.11	-0.13	-0.20	-0.11	-0.10
RVP B #	0.05	0.13	-0.52*	0.19	-0.24
VRM free recall	-0.11	-0.21	-0.09	-0.09	-0.30
VRM recognition #	-0.11	0.12	-0.33	-0.06	-0.33
VRM delayed recognition #	-0.05	0.16	-0.28	-0.05	-0.12
SOC problems solved min moves #	-0.08	0.07	0.13	-0.16	-0.19
SOC time 5 moves #	0.03	-0.11	0.14	0.09	0.03
SOC thinking 1 st #	0.05	0.41	0.11	-0.05	-0.03
SOC thinking sub#	-0.07	-0.10	0.07	-0.07	-0.03
SRM %correct	-0.07	0.29	0.19	0.19	-0.26
SRM latency	0.05	0.44	-0.08	0.04	0.14
DMS % correct #	-0.07	-0.13	0.01	-0.03	-0.23
DMS latency	0.10	0.35	0.15	0.15	0.11
SWM errors #	0.11	-0.02	0.36	0.04	0.19
SWM strategy	0.07	0.02	0.01	0.04	0.19
TMT proportional score	0.07	-0.26	0.30	0.06	0.14

* $p < 0.05$; Variables marked with # are reported as Spearman's rank-order correlations (r_s). All other variables reported are Pearson's product-moment correlations (r). BN-BP = bulimia nervosa binge-purge; BN-NP = bulimia nervosa non-purging, BED = binge eating disorder; HC = healthy controls; DMS = Delayed Matching to Sample; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; TMT = Trail Making Test; VRM = Verbal Recognition Memory

11.4 Discussion

As previously reported in the neuropsychology section of this thesis there was no meaningful difference in neuropsychological performance between those with binge eating and those without binge-eating. Within the three binge eating groups there was also no differences in psychological function. There were however, some differences in ghrelin secretion among the groups with the binge eating participants having a lower fasting ghrelin and a blunted response to energy ingestion. Therefore if there were to be any association between neuropsychological function it would be expected that lower ghrelin would be associated with lower neuropsychological performance on tasks of learning and memory. This pattern was not found in this study. All but one of variables showed no association with ghrelin. Rapid Visual Processing RVP B'', a measure of false alarms in a task of visual attention, was associated with ghrelin. Higher total ghrelin was associated with better performance on this variable in the binge eating disorder group only. However, this could be a spurious result considering the relatively large number of tests carried out, and even if not, the mean score for this test was very close to the optimal score and even a relatively low score on this test may still indicate a high level of performance so would not be clinically meaningful.

Similarly there was no indication of any association between psychological function and C-ghrelin. There was only one significant finding of ghrelin having a negative association with Rapid Visual Processing RVP B'', indicating a poor performance was associated with higher ghrelin in the bulimia nervosa non-purging group only. Again it seems likely that this result is spurious. This result is contrary to that predicted by some animal models which predict that higher ghrelin should show increased performance (Diano et al. 2006). The animal model has ecological validity in that animals who have not eaten for a while

would have higher levels of circulating ghrelin which may help to increase attention to increase the likelihood of finding food . Overall it appears that in the current study at least, there is no relationship between ghrelin secretion and neuropsychological function in women with binge eating.

There are a number of problems with the design of this part of the study which make it difficult to draw meaningful conclusions. Firstly there were no neuropsychological impairment reported in the binge eating groups which makes it unlikely that differences in ghrelin would impact on performance. Sample size in some groups was lower than ideal and the C-ghrelin section was likely to be underpowered. This was a study by observation and did not include any experimental manipulation of ghrelin.

It would be more useful to investigate the influence of ghrelin on neuropsychological function in women with anorexia where there is more evidence of neuropsychological functioning changes. It may be that ghrelin plays a more significant role when the body is in a state of energy deficit rather than adequate energy balance as in most women who binge eat.

12. CONCLUSION

This study has reported on neuropsychological functioning and ghrelin secretion in a group of women with binge eating who were recruited as part of the Binge Eating Psychotherapy Study. The recruitment of 112 women with binge eating and a comparison group of 50 healthy women who did not binge eat allowed sufficient power to detect meaningful differences in neuropsychological functioning and ghrelin secretion for many of comparisons made.

The five hypotheses explored in this study are revisited below:

- **Women with binge eating will have poorer neuropsychological performance compared to women who do not binge.**

Overall the current study did not find a consistent pattern of neuropsychological impairment in women who binge eat, regardless of a diagnosis of bulimia nervosa or binge eating disorder. The binge eating participants on average performed at a level that would be expected of healthy women with similar demographic characteristics including educational level. This result suggests that if neuropsychological changes/impairments are present in individuals with binge eating they are likely to be small and would seem unlikely to adversely affect the general functioning of those with binge eating. This is in contrast to some previous studies which have reported impairment in neuropsychological function in binge eating but is in agreement with other studies which have found neuropsychological functioning to be comparable to healthy control groups.

- **Depression and anxiety will be associated with poorer neuropsychological performance in women with binge eating.**

Although depression and anxiety might be expected to negatively affect neuropsychological functioning in the binge eating groups, the current study did not find this pattern. A substantial proportion of the sample (29% with bulimia nervosa and 24% with binge eating disorder) met criteria for a major depressive episode in the past month using the SCID-1. However, no measurement of mood was made at the time of neuropsychological testing and this should be included in future studies. Similarly state anxiety was also not measured at the time of testing and again should be included at the time of testing as a way of looking at state anxiety rather than a clinical diagnosis of an anxiety disorder.

- **The severity of eating disorder symptoms will be associated with poorer neuropsychological test performance in women with binge eating.**

The current study did not show consistently support this hypothesis. There was a wide range in duration of illness with the average duration of longer than 10 years which could be assumed to be long enough to affect functioning. Despite this, duration of illness was not associated with poorer performance once the effect of age had been taken into account. Illness severity was also found not to be associated with poorer neuropsychological functioning. This is a surprising result as the relationship has been reported in previous studies in women with binge eating (Roberts et al. 2013). The Eating Disorders Inventory-2 (EDI-2) was used to assess illness severity in the current study. This measure focuses on eating disorder behaviours and cognitions which are self-reported. In their study, Roberts et al. (2013) used the clinician administered SCID-I as a measure of eating disorder illness severity. It would be useful to consider other ways of measuring illness severity other than a self-report measure such as clinician-rated methods. Consideration of biological markers of illness severity in future studies would also be interesting, particularly those

that measure nutritional status. For example, the impact of glucose availability and vitamin levels may be worthy of future exploration in the binge eating population.

As with any study, there are strengths and weakness in the current study that need to be considered with regard to investigating neuropsychological functioning. It is possible that the CANTAB computerised neuropsychological test battery used in the current study may not have been of sufficient difficulty to detect differences in neuropsychological functioning in women with binge eating compared with healthy controls; however, the same battery has been used to demonstrate impairment in neuropsychological functioning in individuals with other mental health diagnoses such as depression and social phobia, some of which have been carried out within the same research unit as the current study (Bourke et al., 2012) as well as mild cognitive impairment in brain injury and dementia (Robbins et al., 1994). Even if more challenging tests were to demonstrate such differences in neuropsychological functioning in individuals with binge eating, it is uncertain whether differences would be an important factor affecting overall functioning in individuals with binge eating. Further research into the very few statistically significant differences (of very small magnitude) found here is necessary to determine their replicability and if replicated, the real life significance of such subtle differences on life functioning in this group.

There is also a lack of consistency in the neuropsychological domains have been tested with a focus recently on set-shifting and decision-making but there is a lack of consensus around the assessment of some of the more basic executive functions, particularly learning and memory. This is in contrast to some other mental health disorders which have established protocols to examine neuropsychological functioning, for example in schizophrenia (Nuechterlein et al., 2008; Kern et al., 2008) Although there has been an

attempt to standardise neuropsychological testing in anorexia nervosa with the development and testing of the Ravello Profile test battery (Rose et al., 2011; Stedal et al., 2012). The development of a test battery specific to binge eating may be a useful approach to standardise testing in this area to be able to directly compare studies in order to get a more cohesive understanding of the neuropsychological profile in this group.

It should also be noted that the difficulty in publishing null results may also have skewed the published studies towards those that have found differences. This highlights the importance of publication of null results and the contribution that the current study can make towards a fuller picture of neuropsychological function in binge eating.

The strengths of this section of the current study include the emphasis given to assess diagnostic categories by using structured clinical interviews and peer review before confirmation of final categorisation. The use of a computerised battery is a strength as it improves accuracy, particularly in timed tests and provides confidence that the assessment has been administered in a consistent way across participants. The lack of sufficient samples sizes has plagued many of the published studies in the binge eating literature; however, in the current study group sizes were of sufficient size to be able to detect differences among the groups.

The neuropsychological results from the current study support a transdiagnostic approach in that as a group, there does not seem to be significant neuropsychological differences between women with bulimia nervosa and those with binge eating disorder. Although as a group there were no strong patterns of neuropsychological changes or impairment in women with binge eating, some individual participants did show lower neuropsychological functioning. Identification and greater examination of subgroups with impairment is important to better understand why some with binge eating are affected and others appear

to retain normal functioning. This highlights the importance of understanding individual differences when formulating treatments rather than a one-size-fits-all approach based solely on diagnostic category.

Overall the results from the current study have contributed to increased understanding of binge eating. Neuropsychological functioning may not be an important factor in differentiating individuals with binge eating from healthy individuals without binge eating. This finding does not support the use of cognitive remediation as a broad treatment approach, other than possibly for those with a history of anorexia or who are exhibiting clear impairments in specific domains such as set-shifting and decision-making. However, exploration of negative attention bias may be useful to explore further in binge eating, and may be particularly relevant for treatment strategies which use cognitive techniques such as CBT-E.

- **Ghrelin levels will be altered in women with binge eating compared to women who do not binge eat.**

Results from the current study suggest that ghrelin secretion is blunted in women with binge eating and this is partially explained by higher levels of body fat. Reduction in ghrelin may be associated with insulin regulation, resulting in elevated insulin and lower blood glucose levels in women with binge eating. The current study has also highlighted the importance of measuring both acyl ghrelin and des-acyl ghrelin as the ratio of these two forms of ghrelin may be important in understanding changes in ghrelin which are associated with eating disorder behaviours such as vomiting.

High weight appears to be the most significant factor in the current study that may influence ghrelin secretion in women with binge eating. High weight was associated with

reduced ghrelin levels. Frequency of bingeing was not associated with ghrelin secretion in any group but vomiting frequency was associated with increased ghrelin in the bulimia binge purge group. Activities that negatively affect energy balance such as vomiting and excessive exercise appear to be associated with higher ghrelin levels in women with binge eating. This is consistent with the mechanism of ghrelin in driving appetite to ensure organisms gets sufficient food.

Alterations in ghrelin secretion may have significant implications for the long term health of women with binge eating. The current study suggests that lower ghrelin levels are associated with higher insulin levels and increased insulin resistance. This would increase the probability of the development type 2 diabetes, particularly in those of high weight.

The pattern of lower ghrelin levels in women who binge eat is potentially a mechanism to reduce food consumption which is being over ridden possibly by psychological mechanisms such as those in Fairburn's theory of binge eating that emphasises the role of cognitions around food and body as well as difficulties with emotion regulation.

- **Higher ghrelin levels will have a positive association on some aspects of neuropsychological functioning, particularly an improvement in memory, whereas lower ghrelin levels will be negatively associated with neuropsychological performance in these area.**

Despite evidence of neuropsychological changes in animals with respect to ghrelin levels, this finding was not replicated in the current study in humans. Although ghrelin levels were lower in women with binge eating no significant association was found between ghrelin levels and neuropsychological functioning. This result could have been influenced by a number of factors including the sensitivity of the neuropsychological test battery as

already discussed the above sections. The ecological validity of the tests being selected is an important consideration and it is possible that the tests in the neuropsychological battery did not tap into the neuropsychological domains used when in a state of hunger or food seeking. Selecting neuropsychological tests that have been modified with eating disorder salient stimuli, such as those that are food and body related, may also be more powerful in examining neuropsychological functioning in individuals with binge eating.

The current study did not involve manipulation of ghrelin levels and did not measure ghrelin levels during neuropsychological testing. An experimental design which manipulates ghrelin levels may be necessary in order to explore this potential association more fully, for example, comparing neuropsychological functioning during low and high ghrelin conditions. The addition of a group of women with anorexia nervosa would also be a valuable addition to a study of this kind to be able to cover the range of disordered eating as ghrelin levels are known to be elevated in this group (Germain et al. 2007; Tanaka et al. 2003).

The finding that ghrelin is blunted in binge eating suggests that normalising eating patterns in women who binge eat in order to restore normal ghrelin secretion could be an important part of treatment. Treatment trials are needed to further examine whether and how quickly ghrelin secretion returns to normal patterns on successful treatment of binge eating. The more that is known about the impact of binge eating, the more likely it is that treatments can be designed to meet individual specific characteristics in order to improve the lives of those who do not currently recover using established treatments.

It remains unclear whether a transdiagnostic approach is appropriate when considering ghrelin secretion as there were significant differences found between those with bulimia nervosa and those with binge eating disorder. Although there may be benefits in terms of a

transdiagnostic psychological treatment approach, the transdiagnostic model may have limited applicability in relation to consideration of biological differences given the differences found between bulimia nervosa and binge eating disorder were related to higher weight in binge eating disorder. There is a need to adapt treatments to take into account the extra biological risk factors for those with binge eating disorder.

This area of research is at a very early stage in the eating disorders field and future studies need to be carefully designed to take into account the many potential confounding variables which could affect ghrelin secretion.

In conclusion, although the results of the current study suggest that targeting neuropsychological functioning may be unlikely to significantly benefit this group, it is clear that carefully designed research is needed to be able to understand the influence of ghrelin in those individuals with binge eating and how this might inform treatment in the future.

13. APPENDICES

APENDIX A: Participant Information Sheet

A comparison of three psychotherapies for binge eating
Ver 18.08.06

Contact: Sarah Rowe, ph 372 0400



Canterbury DHB
District Health Board
Te Pōari Hauora o Waitaha

The Christchurch School of Medicine & Health Sciences

DEPARTMENT OF PSYCHOLOGICAL MEDICINE

Telephone (03) 372 0400

Fax (03) 372 0407

Clinical Research Unit
Terrace House
4 Oxford Tce
Christchurch

A comparison of three psychotherapies for binge eating

Information Sheet

Introduction

You are invited to take part in a clinical treatment trial of psychotherapies for women who have problems with binge eating, being conducted by Virginia McIntosh, Jenny Jordan, Janet Carter, Jan McKenzie, Kathryn Taylor, Chris Frampton, Andrea Bartram, Sarah Rowe, Caroline Bray, Katrina Light and Peter Joyce.

The major focus of this study is to compare the effectiveness of three psychotherapies (talking therapies) for binge eating problems. The three types of psychotherapy to be investigated in this study are: cognitive-behavioural therapy (CBT), Schema Therapy and Appetite focused CBT. Cognitive-behaviour therapy helps people to understand and change cues that lead to binge eating, including unhelpful patterns of thinking, feeling and behaving, particularly those that relate to nutrition, food and eating. Schema therapy focuses on long-standing beliefs and patterns of behaving that contribute to binge eating. Appetite focused CBT uses many of the same approaches as standard CBT, and emphasises the role of appetite, hunger, and fullness in problems with binge eating.

All three therapies will be conducted approximately weekly for six months (with the exact number of sessions in the range of 15-30), followed by approximately monthly sessions for 6 months. We would like to follow participants after the end of treatment to obtain a clear picture of the extent of the improvement and whether or not this is maintained. This will involve being interviewed and completing questionnaires at regular follow-up intervals.

Your participation in this study is completely voluntary (your choice). If you agree to take part you may withdraw at any time for any reason and this will in no way affect your future health care.

More about this study

What are the aims of this study? We hope to determine whether there are differences between the three types of therapy: cognitive-behaviour therapy, schema therapy, and appetite focused CBT in the treatment of binge eating problems.

Who can participate in this study? If you are suffering from significant problems with binge eating, are medically well and above a body mass index (BMI, weight (kgs)/height (m)²) of 17.5 (ie, not severely underweight), 16 years or over and not taking psychotropic medications or receiving other treatments for binge eating, you may participate in this study.

What is binge eating? This is when you eat a large amount of food in a short time and feel out of control while doing so. This may or may not be followed by attempts to counteract the effects of the binge eating, including fasting, self-induced vomiting, taking laxatives or other substances to try to get rid of the food or to prevent weight gain, or over-exercising. The binge eating may have been present for months or even years.

How will participants be selected for this study and who will select them? If you meet the above inclusion criteria, you may be referred to the study by your general practitioner, psychiatric emergency service or other mental health services, or you may contact the Clinical Research Unit yourself if you think you are suffering this kind of problem with binge eating.

How many participants will be involved? We hope to study at least 200 women.

Where will the study be held? This study will be held in Terrace House, near Christchurch Hospital, Cnr. Antigua Street & Oxford Terrace.

What is the time span for the study? Your psychotherapy will occur over one year, approximately weekly for the first 6 months then approximately monthly for 6 months. We would also like to follow your progress after completion of treatment so you will be contacted one, two and three and four years after treatment ends.

What will happen during the study? Your participation in this study first involves an assessment by a clinical psychologist. At this time the researcher will explain the study in more detail and answer any questions you have. If you feel that you may benefit from our treatment and there is no reason why our treatment would not be appropriate, the researcher will obtain your written consent to participate in the study.

After you have given consent to participate we will organize with you:

- A time to complete a more detailed structured assessment with your therapist.
- A neuroendocrine assessment to examine certain of your body's hormones (including insulin, glucagon, cholecystokinin, leptin and ghrelin) that are potentially related the regulation of appetite and satiety. This assessment will involve coming to the clinical research unit for a morning (from 8.30am), without having eaten breakfast. During this assessment we will take a series of blood samples while you will be resting comfortably with a needle inserted in a vein. After the first blood samples you will be given a glucose drink, to be drunk within a 5 minute period. We are also interested in your report of hunger, fullness, depression and anxiety over this time.
- A series of tasks to be completed on a computer, which assess abilities such as planning, thinking and memory. This will take approximately two hours and will be done at the clinical research unit.
- To complete a booklet containing questions about your binge eating symptoms, current relationships, and aspects of your childhood and personality. This takes approximately an hour to complete.

Following the assessment you will be randomly allocated to receive one of the three psychotherapies and begin treatment with your therapist. Randomly allocated means that neither you nor the therapist will choose which psychotherapy you will receive, but that it is chosen "by the flip of a coin". All therapists in this study are clinical psychologists, senior psychiatric registrars or consultant psychiatrists. You will have six months of weekly psychotherapy sessions, followed by monthly sessions for 6 months. All treatment is free of charge. If at any stage your binge eating is not improving or is getting worse, there is the opportunity to consider other treatments.

You will be asked if you consent to having therapy sessions audiotaped. This is to ensure a high quality of treatment. Some audiotapes may be heard by other members of the research team. You have the option of stopping the taping or having the tapes destroyed at any time.

The Clinical Research Unit is jointly funded by the Canterbury District Health Board (CDHB) and Otago University. Therefore all clinical notes are the property of the CDHB and are subject to their regulations.

You will also be asked to complete a questionnaire before each therapy session so we can record any changes in your symptoms and functioning. These questionnaires take only about 5 to 10 minutes of your time.

There is no obligation for you to take part in this study. If you choose not to participate we will refer you back to your general practitioner or other appropriate health professional.

Will my GP know I am in the study? We prefer to advise your GP that you are involved with this treatment programme, however, this is your decision.

Why the detailed research assessment? The detailed research assessment is for a number of reasons. The questionnaires you complete will help us to assess how clinical factors (e.g. severity or subtype of binge eating, and other problems, such as mood or anxiety) and personality influence how people progress during and after treatment. Similarly, the computer assessment will enable us to examine the association between how

people with binge eating perform on tasks measuring such things as memory, planning and attention and the relationship of that performance to progress in treatment.

Some of the blood tests are to check that you are currently physically healthy (e.g. blood count, thyroid tests). We also wish to extract and store DNA (genetic material). Each person has a DNA make-up (their genes) that is different from that of everybody else – except in the case of identical twins. This genetic make-up is a mixture of the genes of the individual's mother and father. The precise way they are mixed varies from child to child within the same family, so having the same parents does not mean that two children will have exactly the same genes. The research you are invited to participate in will investigate how genes are related to binge eating, to specific eating disorder symptoms and behaviours such as self-induced vomiting, and to personality traits, such as impulsiveness, tendency to worry and perfectionism, and to related factors such as depression and anxiety.

DNA samples will be identified only with a code and as with all other material gathered in this research will be confidential and will not be disclosed or used in any way without your informed consent. In particular the researchers will not claim any right, ownership or property in your individual genetic information or that of your kinship group, hapu or iwi, without you having first sought or obtained informed consent to the transfer of any such right, ownership or property. Your consenting to participate in DNA sampling for the proposed study will not be construed as creating any right or claim on the part of the researchers to your genetic information. Occasionally, when genetic analyses are completed it is necessary to introduce your DNA into a laboratory bacterium (*E. coli*.)

DNA samples will be retained for 5 years after completion of the study. If you decide to withdraw your consent to the storage of your DNA samples during this storage period, you may do so by contacting the Clinical Research Unit, Ph 372 0400, or by writing to the address at the end of this Information Sheet.

Risks and Benefits

The major benefit for participants is that they will receive free high quality psychotherapy for binge eating over a period of one year. This is a therapeutic study using treatments specifically designed to help individuals with binge eating problems. Without treatment it is possible that binge eating may persist for months or even longer.

There may be some discomfort associated with talking about personal issues in psychotherapy. With the taking of blood, there may occasionally be, as with any blood tests, slight bruising. Participants in this study will not receive any payment or reimbursement of expenses.

If you choose to participate in this study, there may be repercussions from your whanau/family because you have given away genetic information. Whilst the sample given is from you, it will contain information shared by other whanau/family members and they may consider you do not have the right to give that information to others. Te Runanga O Ngai Tahu does not support genetic research.

Participation

- Your participation in this study is entirely voluntary (your choice).
- If you agree to take part, you are free to withdraw from this study at any time, for any reason.
- If you choose not to take part or to withdraw, this will not affect any of your future care or treatment. We will refer you back to your general practitioner or other health professionals as appropriate.
- You may have a friend, family or whanau support to hear about the study, including the risk and/or benefits and any other explanations you require.
- While we anticipate that most people participating in this study will be treated as outpatients, if your eating disorder or other problems indicated the need for inpatient care or alternative treatments then these would be organised.

If you have any queries or concerns about your rights as a participant in this study you are free to contact a Health and Disability Services Consumer Advocate, Ph. (03) 377 7501.

Confidentiality

We will take all precautions to maintain confidentiality. All forms and computer files will be marked with numbers only, not names. No material that could personally identify you will be used in any reports based on this study. The data from this study will be available only to the study investigators. All data will be stored in secure areas.

You do not have to answer all questions and you may stop an interview at any time.

This programme is conducted within the Clinical Research Unit, in a collaboration between the Christchurch School of Medicine (University of Otago) and the Canterbury District Health Board. Two types of information will be collected from you – *research* information and clinical information. Research information is kept in a non-identifying form as described above. Usual CDHB policies and procedures are followed for confidentiality of clinical information.

Results

How can I obtain results of this research? When this study is over you may have a summary of the key results. Detailed results will be published in international scientific journals.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not receive any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

This study has received ethical approval from the Upper South A Ethics Committee

Where can I get more information about the study? Sarah Rowe or Andrea Bartram may be contacted by telephone or by letter: 'Psychotherapy for Binge Eating', Clinical Research Unit, University Department of Psychological Medicine, Terrace House, 4 Oxford Terrace, Christchurch, Ph. 372 0400.

APPENDIX B: Consent Form

18.08.06



Canterbury DHB
District Health Board
 Te Puni Hauora o Waitaha

The Christchurch School of Medicine & Health Sciences

DEPARTMENT OF PSYCHOLOGICAL MEDICINE

Clinical Research Unit
 Terrace House
 4 Oxford Terrace
 Christchurch

Telephone (03) 372 0400

Fax (03) 372 0407

A comparison of three psychotherapies for binge eating

You are invited to take part in a clinical treatment trial of psychotherapies for people who have Binge Eating Disorder or Bulimia Nervosa, being conducted by Gini McIntosh, Janet Carter, Jenny Jordan, Jan McKenzie, Kathryn Taylor, Martin Kennedy, Chris Frampton, Andrea Bartram, Sarah Rowe, Caroline Bray, Katrina Light and Peter Joyce.

I have read and I understand the information sheet dated 18th August 2006 for those taking part in this study.

I have been given the opportunity to discuss this study. I am satisfied with the answers I have been given.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.

I understand that my participation in this study is confidential and that no material that could identify me will be used in any report on this study.

I understand the compensation provisions for this study.

I have had time to consider whether to take part.

I know whom to contact if I have any questions about this study.

I consent to the researchers storing a specimen of my blood for its later use as part of this study. YES / NO

I consent to blood samples being destroyed at the end of the study. YES / NO

I consent to my therapy sessions being audio-taped. YES / NO

I wish to receive a copy of the results of this study. YES / NO

I understand there will be a significant delay between the information I provide and receiving the results.

I agree to my GP being informed of my participation in this study. YES / NO

GP's name _____ Address _____

I would be willing to be contacted to discuss participation in future research in this area. YES / NO

Genetic study:

I am aware that the proposed study will involve analysis of my genetic makeup. I consent to such an analysis being performed. YES / NO

I understand that if I consent to such analysis, no rights will be created for the researcher to my genetic information. YES / NO

I am aware that the proposed study may involve storage of my genetic makeup and give my consent. YES / NO

I _____ (print full name) hereby consent to take part in this study.

Date: _____

Phone number: _____

Signature: _____

Signature of witness: _____

Project explained by: _____ Role: _____

Contact phone numbers: Andrea Bartram or Gini McIntosh (03) 372 0400

A comparison of three psychotherapies for binge eating

APPENDIX C: The Global Assessment of Functioning

GAF

	ID#					
	Test #					

	Current GAF Score		
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Code

91-100-----**Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.**

81-90-----**Absent or minimal symptoms** (e.g., mild anxiety before an exam), **good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g., an occasional argument with family members)

71-80-----**If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g., some occasional urge to binge or some occasional thoughts of dissatisfaction with body size/weight but no preoccupation, difficulty concentrating after family argument); **no more than slight impairment in social, occupational, or school functioning** (e.g., temporarily falling behind in schoolwork).

61-70-----**Some mild symptoms** (e.g., occasional bingeing and/or regular compensatory behaviour (restriction/exercise/purging), depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g., occasional truancy or theft within the household), **but generally functioning pretty well, has some meaningful interpersonal relationships.**

51-60-----**Moderate symptoms** (e.g., regular bingeing and/or regular compensatory behaviour (restriction/exercise/purging), flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g., few friends, conflicts with peers or co-workers).

41-50-----**Serious symptoms** (e.g., frequent bingeing and/or frequent or severe compensatory behaviour, suicidal ideation, severe obsessional rituals, -frequent shoplifting) **OR any serious impairment in social, occupational, or school functioning** (e.g., no friends, unable to keep a job).

31-40-----**Some impairment in reality testing or communication** (e.g., Meets full criteria for Anorexia Nervosa-preoccupation's or rituals interfere with functioning, speech at times is illogical, obscure, or irrelevant) **OR major impairment in several areas, such as work or school, family relations, judgement, thinking or mood** (e.g.,

depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).

21-30-----**Behaviour is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgement** (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) **OR inability to function in almost all areas** (e.g., stays in bed all day; no job, home or friends).

11-20-----**Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears faeces) **OR gross impairment in communication** (e.g., largely incoherent or mute).

1-10-----**Persistent danger of severely hurting self or others** (e.g., complete non compliance with treatment, recurrent violence) **OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.**

Cigarettes / tobacco:	yes	no	No. per day:	
No. of years smoking:			No. of pack years:	
	(packs per day x years: 1 cig. = 0.05 pack x no. of years) e.g., 15 cig. = 0.75 pack x 5 yrs smoking = 3.75 pack years			
How many today		Time of last cigarette.....		

Have you had any alcohol in the past 24 hours?	yes	no
If yes, how much?		(standard drinks)
Over how many hours?		
Approximate time of last drink?		

Have you smoked cannabis in the past 24 hours?	yes	no
How much?		
Over how many hours?		
Approximate time finished smoking?		

Have you taken any other substances in the past 24 hours?	yes	no
If yes, which substance(s)?.....		
Approximate time taken?		

Time testing started _____ Time finished: _____ Total time: _____
Tester: _____

Observations: _____

13. LIST OF REFERENCES

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